Correspondence

Letters to the Editor should not exceed 500 words.

Oral Contraceptives and Liver Damage

SIR,—The nature of the liver damage associated with oral contraceptives is not clear. Histological examination has apparently been performed only in one case,¹ and a second case is presented here.

A previously healthy quadriparous woman of 38 years gave no history of alcohol or gall-bladder disease. In autumn 1963 (and also during the last months of her pregnancies) she experienced generalized itching. Simultaneously she had started ethinyloestradiol 0.05 mg. + norethisterone acetate 4 mg. daily with regular breaks. No other drugs. In April 1964 episodic eczema (? Besnier's prurigo), increased itching, and finally acholuric jaundice occurred. Serum transaminase, alkaline phosphatase, and bilirubin

(about 35% nonglucuronized) were raised, but not the amylase (Fig. 1). The gamma-globulins were high (1.5 g./100 ml.) and the prothrombin time low (but became normal after parenteral vitamin K). Haemolysis tests and skin tests (scratch test and intracutaneous test) for ethinyloestradiol + norethisterone acetate were negative. An eosinophilia (8–18%) was found.

The drug was discontinued and ten days later the transaminases had fallen to normal levels and the itching gradually decreased in intensity. Two months later liver-function tests, including the bromsulphthalein test, were normal.

To exclude the possibility of a malignant tumour a laparotomy was performed (R. Karlsson). The gall-bladder was thin-walled and contained a solitary stone the size of a pigeon's egg. There were no indications of biliary obstruction. The bile ducts were not dilated, no stones were palpable in the common bile duct, and cholangiographs of the cystic duct at two sessions showed a normal biliary tract. The histology is shown in Fig. 2.

Among 8,919 patients in 27 reports* of treatment with different oral contraceptives no jaundice was reported. But although the incidence thus appears to be less than 1:9,000 caution is indicated. It would naturally be a great advantage if one could detect among the population those women that are possibly prone to liver damage from contraceptive steroids, but this is difficult until we understand how the side-reactions arise. Of the possible mechanisms that have been discussed three may be mentioned:

(i) *Allergy*.—The possibility of inducing rises in transaminase levels in all persons using the pills²; the absence of oedema, eosinophilia, and inflammatory cells in the liver; the negative skin tests, all suggest that allergy is not the cause. A piece of evidence in favour is the eosinophilia in our patient.

(ii) *Toxicity*.—This possibility cannot be ruled out, but the low incidence suggests that it is unlikely.

(iii) *Congenital enzyme defect*.³—This would be a parallel phenomenon to the rather uncommon haemolytic anaemia found after use of antimalarial agents and due to a congenital hereditary intracellular enzyme deficiency. The histological picture, with large amounts of intracellular bile pigment in the absence of signs of biliary thrombi or dilated bile ducts could be in agreement with such a hypothesis.^{4–5} If this were the case, the solution would be to avoid prescribing oral contraceptives for persons with idiopathic jaundice of pregnancy or who have suffered from itching during pregnancy (as this patient had)—a condition that might also be ascribed to the congenital enzyme defect—and to find a method of diagnosing the defect beforehand.—We are, etc.,

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* References sent on request.

Thrombosis in Women of Child-bearing Age

SIR,—Thrombotic disease occurs occasionally in young women of child-bearing age. It is therefore to be expected that it will occur in women who happen to be taking oral contraceptives. Some cases of arterial thrombotic or thrombo-embolic episodes in women taking oral contraceptives have been reported to the Committee on Safety of Drugs. It may well be that these do no more than reflect the normal incidence of such conditions in women of child-bearing age, and the committee wish to stress that there is no evidence of a relationship between the use of oral contraceptives and these events.

In accordance with their usual procedure for following up reports of suspected adverse reactions to drugs, the committee are seeking to establish the relative frequencies of such incidents in women who are taking oral contraceptives and women of the same age who are not. To help the committee in their study doctors are requested in cases of arterial or venous thrombosis or pulmonary embolism in women of child-bearing age to take a careful drug history, including whether or not the patient has been taking an oral contraceptive, and to notify the Committee on Safety of Drugs if an adverse reaction to any drug is suspected.—I am, etc.,

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FIG. 1.—Serum concentrations of glucuronized and nonglucuronized bilirubin and alkaline phosphatase.

FIG. 2.—Liver section, eosin-haematoxylin $\times 600$. The architecture is microscopically normal; there is no cirrhosis, cholangiolitis, or proliferation of bile ducts, but fairly severe biliary stasis with marked intracellular bile pigment centrally in the lobules. No biliary thromboses are seen. No fat is present. (J. Wägermark, B. Thorell.)