Her blood-pressure was 120/80. Investigation showed a haemoglobin of 12.3 g./100 ml. and a total white cell count of 9,700/c.mm. The E.S.R. was 18 mm. in the first hour. Cerebrospinal fluid examination showed two lymphocytes per c.mm. and a protein of 40 mg. per 100 ml. X-ray examination of the skull and chest was normal. A left carotid angiogram was normal. A lumbar air encephalogram was also normal. An electroencephalogram showed delta activity at 2½ cycles per second in the left fronto-temporal area. She improved rapidly over the course of the next four weeks, although she still showed some nominal dysphasia when last seen on 5 July 1963. A written report about her on 7 April 1964 revealed that she had then made a complete recovery.

Oral contraceptive regime.—The patient started taking Enavid on 19 April 1963. She took two tablets daily from 19–23 April. She then had heavy menstrual bleeding lasting from 24 to 28 April. From 29 April to 17 May she took one tablet of Enavid daily. Because she developed very slight vaginal bleeding from 7 May she was advised to discontinue the tablets on 17 May. On 5 June, with her menstrual period two weeks overdue, she took two Enavid tablets. The next day she became ill on the flight to London. She stopped taking the tablets and her periods returned to normal in July.

Case 2.—Mrs. X. Y., aged 26, was seen at the West Middlesex Hospital on 27 December 1963 by Mr. Douglas Langley. She complained that six weeks previously she noticed that "something was wrong with her vision" on waking. Examination revealed a congruous left upper quadrantic field defect. She was seen in the neurological clinic on 17 January 1964. There were no abnormal physical signs apart from the field defect; in particular the pulse was regular, there was no cardiac murmur, no bruit to be heard over the cranium, and no tenderness of the calves. The field defect was unchanged when she was seen again on 10 April 1964. In her past history she had epileptic seizures at the age of 17 years, was taking phenobarbitone, and had no further seizures since the age of 19 years.

Oral contraceptive regime.—The patient had had two normal pregnancies in 1959 and 1961. She started taking Ortho-Novin (norethisterone 2 mg., mestranol 0.1 mg.) in June 1963. She took one tablet daily for 20 days of each menstrual cycle. She stopped taking them after the visual disturbance in December 1963.

The most likely explanation of the clinical picture in both cases is that they had a small cerebrovascular episode. There was no obvious source for an embolus. It is, of course, true that even young people can, rarely, have cerebrovascular lesions from no apparent cause. However, both cases were young women taking oral contraceptives. Lorentz⁴ reported the case of a 41-year-old woman who developed a left parietal lesion whilst taking 20 mg. of Enavid daily for three months, for painful symptoms associated with menstruation. A presumptive diagnosis of cortical venous thrombosis was made and she had residual neurological signs. In her case the dose of Enavid was of course many times higher than that recommended for contraceptive purposes.

It is noted that two private reports (one of a conference on thromboembolic phenomena in women, held in Chicago in September 1962; and one on Enavid submitted to the Food and Drug Administration in September 1963) failed to demonstrate any significant increase in the risk of thromboembolic death from the use of Enavid.

While final judgment about the relationship of progestagens to thromboembolic incidents must be reserved, it is apparent that these cases should be reported and that

medical practitioners should be aware of the possible hazards of the use of these drugs.

I am indebted to Dr. Macdonald Critchley for permission to report Case 1 and Mr. Douglas Langley, F.R.C.S., for Case 2.

—I am, etc.,

London W.C.1.

K. J. ZILKHA.

REFERENCES

- ¹ *Brit. med. J.*, 1962, 2, 315.
- ² McIntyre, N., Phillips, M. J., and Voigt, J. C., *ibid.*, 1962, 2, 1029.
- ³ Egeberg, O., and Owren, P. A., *ibid.*, 1963, 1, 220.
- ⁴ Lorentz, I. T., *ibid.*, 1962, 2, 1191.

Oral Contraceptives and Liver Damage

SIR,—The report on hepatic impairment during the intake of contraceptive pills by Dr. A. Eisalo and his colleagues (15 August, p. 426) is interesting and we would like to make some comments. Our observations lend support to the view that the oestrogens in the pills may be the most important constituents causing liver damage.

Many similarities can be found when steroid-induced jaundice¹ and idiopathic or recurrent jaundice of pregnancy^{2–4} are compared. Both the clinical picture and the laboratory results suggest impairment of the excretory function of the liver and also some damage to the liver cells which causes elevation of serum transaminases. Of all hormonal steroids the oestrogens show the most augmented excretion during pregnancy. Both the oestrogens and bilirubin are excreted in conjugated form in the bile. However, in recurrent jaundice of pregnancy the excretion of bilirubin into the bile is impaired as well as that of oestrogens.⁵ In the Dubin-Johnson syndrome bilirubin conjugation is normal, but excretion into the bile is impaired, and the excretion of oestrogens into the bile of these patients also seems to be disturbed.⁶ In the Bongiovanni-Eisenmenger syndrome only synthetic oestrogens give rise to jaundice.⁷ It should also be mentioned that some of the anabolic steroids which have been reported to cause jaundice are converted to a small extent into oestrogens. All these observations suggest a close connexion between the metabolism of bilirubin and of the oestrogens.

We have observed three cases of jaundice due to contraceptive pills. Ikonen⁸ has described the case history of a woman who had jaundice during two successive pregnancies and after this a third time following administration of Anovlar (norethisterone acetate + ethinyloestradiol). The clinical symptoms as well as the laboratory findings were very similar. Adlercreutz⁹ reported two cases. The first woman had severe pruritus (which is said to be a prodrome of jaundice) during the end of her second pregnancy (first pregnancy interrupted). Half a year later she developed jaundice following intake of Conovid (norethynodrel + 3-methoxy-ethinyloestradiol). Two years later she received Lyndiol (ethinyloestrenol + 3-methoxy-ethyl-oestradiol), but had to stop the intake after 20 days owing to migraine, vomiting, and pain under the right costal margin (no gallstones present; ? biliary dyskinesia). Then she received only Orgametril (ethinyloestrenol) for 60 days without any side-effects. After this she started to take Lyndiol again and after 20 days was very ill with vomiting, pruritus, migraine, and pain under the right

costal margin. Ten days later she became jaundiced (bilirubin 12.3 mg./100 ml.). It should be pointed out that the main difference between the drugs causing liver disease and the one that was well-tolerated was the content of a synthetic oestrogen in the drugs causing jaundice and high serum transaminase. The second case reported by Adlercreutz⁹ was of a patient only 19 years old who had had no pregnancies. She developed the same type of jaundice as the other two cases described. It is interesting to note that she had a history of migraine and biliary attacks (no gallstones).

There is no definite evidence to suggest that the same mechanism is responsible for the jaundice during pregnancy and that caused by the contraceptive pills. However, it seems possible that all three patients had some sub-clinical disturbance of liver function which was aggravated by the contraceptive pills or the pregnancy.—We are, etc.,

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REFERENCES

- ¹ Sherlock, S., *Diseases of the Liver and Biliary System*, 1963, 3rd ed. Blackwell, Oxford.
- ² Brown, D. F., Porta, E. A., and Reder, J., *Arch. intern. Med.*, 1963, 111, 592.
- ³ Ikonen, E., *Acta obstet. gynec. scand.*, 1964, 43, Suppl. No. 5.
- ⁴ Svanborg, A., and Ohlsson, S., *Amer. J. Med.*, 1959, 27, 40.
- ⁵ Adlercreutz, H., Svanborg, A., and Anberg, A., unpublished results.
- ⁶ — and Schauman, K.-O., *Acta med. scand.*, 1964, 175, suppl. No. 412, p. 141.
- ⁷ — *Nord. Med.*, 1959, 61, 427.
- ⁸ Bearn, A. G., Kunkel, H. G., and Slater, R. J., *Amer. J. Med.*, 1956, 21, 3.
- ⁹ Adlercreutz, H., *Nord. Med.*, 1964, 72, 1004.

Buccal Oxytocin

SIR,—The following case report illustrates the danger of buccal oxytocin and is presented in support of Dr. F. A. Best (10 October, p. 942) and others who have recently condemned its use.

A.B., aged 38, para. 7, was admitted to the Maternity Department, Galway Regional Hospital, on 11 October with secondary post-partum haemorrhage. On 28 September 1964 she had had a low forceps delivery at term, outside our service. Twenty-four hours after spontaneous rupture of the membranes labour was not established and three buccal tablets Pitocin (oxytocin) were given over a period of three hours. There was apparently no response until after the third tablet; thereafter there were very strong uterine contractions and delivery took place within one half-hour. There was slight vaginal bleeding on the third post-partum day with a recurrence of bleeding three days later. Severe bleeding with collapse occurred on 11 October, and the patient was attended by the obstetrical flying squad and taken to hospital after resuscitation. Examination under anaesthesia revealed a transverse tear about 2 in. (5 cm.) long in the lower segment above the bladder reflection, and this was confirmed at laparotomy; there was some organizing blood clot and granulation tissue adherent to the edges of the uterine rupture. Because of pyrexia and intestinal distension treatment was by total hysterectomy with conservation of both tubes and ovaries; convalescence, so far, is satisfactory.

—I am, etc.,

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