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Preliminary Communications

Liver Function after Long-term Progestational Treatment with and without Oestrogen

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Several reports have appeared indicating that a number of therapeutically valuable steroids may alter the excretory function of the liver, as judged by the results of the so-called liver-function tests and the (sporadic) occurrence of jaundice. The presence of an alkylated group at C17 has been incriminated with regard to the hepatic effects observed with compounds such as methyltestosterone, norethandrolone (17 α -ethyl-19-nortestosterone), methyltestosterone (17 α -methyl-19-nortestosterone), and methandienone (Δ^1 -17 α -methyltestosterone) (Sherlock, 1962). The particular importance of checking the possible hepatotoxicity of any steroidal product intended for long-term use as an oral contraceptive has been emphasized (*Lancet*, 1962). In this connexion some data have been reported for norethynodrel (17 α -ethynyl-5(10)-oestrenolone) (Marquardt *et al.*, 1961), norethisterone (norethindrone; 17 α -ethynyl-19-nortestosterone) (Drill, 1959; Rice-Wray *et al.*, 1962), and norethisterone acetate (Perez-Mera and Shields, 1962), which suggests that these steroids, all of which have proved useful for contraception, may similarly affect hepatic function, though this, at least for norethynodrel, has recently been denied by a group of investigators with very wide experience in the matter (Garcia and Pincus, 1964).

In the past three years we have acquired much experience with the progestational and ovulation-inhibiting steroid 17 β -hydroxy-17 α -ethynyl-4-en (lynoestrenol; Orgametril) and its combination with the oestrogen mestranol (as Lyndiol). Orgametril (5 mg. tablets) and the combined products, Lyndiol (tablets with 5 mg. lynoestrenol and 150 μ g. mestranol) and Lyndiol 2.5 (tablets with 2.5 mg. lynoestrenol and 75 μ g. mestranol), have been successfully given to over 300 women either for the management of various gynaecological disorders or for contraceptive purposes (Linthorst, to be published). Although we have in no instance observed jaundice or other signs of hepatic involvement, we decided to ascertain, by means of adequate blood tests, whether any disturbance of liver function occurred in long-term treatment with these products.

MATERIAL AND METHODS

Liver-function tests have been performed once in 52 women aged 18 to 48 who had been receiving Orgametril (26 women), Lyndiol (23 women), or Lyndiol 2.5 (3 women) for periods of

14 to 43 months, and who were still taking the tablets when the tests were carried out. Orgametril was administered at a daily dose of 5 mg., without interruption, whereas Lyndiol or Lyndiol 2.5 was usually given cyclically in daily doses of one tablet for 20 days (days 5 to 24 of the cycle) in order to restore or mimic menstrual periodicity. Indications for starting the treatment with any of the three products included menorrhagia, endometriosis, and dysmenorrhoea in a total of 38 women; the remaining 14 women received either Orgametril (2 women) or Lyndiol (12 women) primarily for contraception.

The blood examinations performed were the following (upper limits of the values considered normal in the laboratories concerned are given in parentheses): total serum bilirubin (1 mg./100 ml.); serum alkaline phosphatase (2.3 Bessey-Lowry units or 6 Bodansky units); thymol turbidity test (2.5 units); serum glutamic oxalo-acetic transaminase (S.G.O.T.) (40 units); serum glutamic pyruvic transaminase (S.G.P.T.) (35 units). Serum alkaline phosphatase and thymol turbidity tests were performed in all the women, the other tests in all but 12 women (six receiving Orgametril and six Lyndiol).

RESULTS

Except in two questionable cases, specified below, the results of the liver-function tests did not reveal any value outside the normal limits. The values obtained for bilirubin ranged between 0.30 and 0.91 mg.; for alkaline phosphatase between 0.8 and 2.2 Bessey-Lowry units or between 1.4 and 4.2 Bodansky units; for thymol turbidity test between 0.2 and 2.2 units; for S.G.O.T. between 5 and 21 units; and for S.G.P.T. between 4 and 31 units. In one woman aged 42, who had been treated with Orgametril for 31 months because of endometriosis, an isolated value of 2.4 Bessey-Lowry units for alkaline phosphatase was found; in this woman bilirubin was 0.64 mg., thymol turbidity test 1.3 units, S.G.O.T. 10 units, and S.G.P.T. 7 units. In another woman, 30 years old, who had taken Lyndiol 2.5 during 18 months for menorrhagia, the thymol turbidity test was 2.6 units; in this case also the other values were normal (bilirubin 0.72 mg., alkaline phosphatase 1.4 Bessey-Lowry units, S.G.O.T. 5 units, and S.G.P.T. 10 units).

Pretreatment control values were not available, but these, in view of the results obtained, would have proved unnecessary. As mentioned above, none of the women reported or showed any clinical sign of liver disease during treatment with Orgametril, Lyndiol, and Lyndiol 2.5.

DISCUSSION

The described results of the liver-function tests (a total of 224 determinations) are obviously reassuring. These data are

essentially in agreement with and complement those obtained in a double-blind contraceptive field trial carried out in the Netherlands with Lyndiol and Conovid (tablets with 5 mg. norethynodrel and 75 μ g. mestranol). The trial comprised 500 women, and each preparation was given during six months; liver-function tests were performed monthly in 30 women receiving Lyndiol and 30 receiving Conovid. The results confirmed that no impairment of hepatic function throughout these first months of treatment had occurred (Swaab, 1964a, 1964b).

In a recent paper from the Finnish investigators Eisalo *et al.* (1964) reversible elevations of serum transaminase levels and bromsulphthalein retention were reported immediately after the administration of Lyndiol or mestranol, but not that of Orgametril, in a series of 12 post-menopausal women. Other tests of liver function (total serum bilirubin and serum alkaline phosphatase) remained normal in nearly all the cases investigated. These results appear to be strikingly different from those obtained in the Netherlands and show only some partial agreement with the changes, much more benign, briefly mentioned for Orgametril and Lyndiol in some cases of endometriosis by two other Scandinavian investigators (Soiva and Castrén, 1963; Borglin, 1964). Although it seems difficult to account for such a discrepancy, one might speculate whether the high age (59 to 80 years) of the women in the study of Eisalo *et al.*, or perhaps other characteristics of the population sample chosen, may have played a part in the results obtained. Our own data in a fairly large series of women of fertile age do not indicate that long-term administration of Orgametril, Lyndiol, or Lyndiol 2.5 results in any influence upon the status of liver function.

SUMMARY

Liver-function tests were carried out on 52 women who had been receiving long-term treatment with a progestational and ovulation-inhibiting substance (Orgametril), or its combination with oestrogen in two different concentrations (Lyndiol and Lyndiol 2.5), for the management of menorrhagia, endometriosis, or dysmenorrhoea or for contraceptive purposes. No laboratory or clinical indication of hepatic dysfunction during treatment with these products could be found.

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Medical Memoranda

Haemoglobin J_{Baltimore} in a Kent Family

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Details of a variant of adult haemoglobin not previously reported in an English person are given here.

CASE REPORT

A widow of 66 was admitted to Lewisham Hospital in December 1963 with acute bronchitis. She gave a history of recurrent bronchitis and vague ill-health for the past 12 years. The only relevant finding on routine examination and investigation was a severe hypochromic anaemia, for which no obvious cause could be found. Further films suggested a haemolytic process. Investigations showed: haemoglobin 6.2 g./100 ml.; M.C.H.C. 25%; test for occult blood negative; direct Coombs test negative; haemoglobin electrophoresis showed an abnormal haemoglobin but no cause for haemolysis. There was haemosiderinuria and a Ham acid serum test (19% haemolysis) was positive. The diagnosis of paroxysmal nocturnal haemoglobinuria having been made, interest now centred on the results of electrophoresis. On occasion a "fast"-moving haemoglobin fraction, presumably haemoglobin A₃, had been seen on electrophoresis in other patients with paroxysmal nocturnal haemoglobinuria. This one, however, proved to have the mobility of haemoglobin J—that is, on paper electrophoresis at pH 8.6 and 8.9 it moved more slowly than haemoglobin N but faster than haemoglobin K (Fig. 1).

IDENTIFICATION OF HAEMOGLOBIN J VARIANT

Globin was prepared from the purified abnormal haemoglobin using acid/acetone according to Anson and Mirsky (1930). The globin was digested with trypsin in 0.5 M ammonium hydrogen carbonate buffer and the digestion products "finger-printed" according to Ingram (1958) and Baglioni (1961). The "finger-print" showed that the spot corresponding to peptide β TpII which

FIG. 1.—Paper electrophoresis at pH 8.9 of the propositus's haemoglobin, showing haemoglobin A and haemoglobin J.