With regard to other diseases, Natulan, as Mathé *et al.* (1963) suggest, may sometimes be of value in lymphosarcoma and may occasionally be worth trying in melanomatosis. The drug has not yet been used widely enough in other tumours to make an assessment.

Summary

A series of 40 patients treated with Natulan is presented, and an account given of the administration and side-effects of this drug.

Assessment of response to treatment suggests that Natulan has a place in the palliation of late Hodgkin's disease comparable with the alkylating agents and vinblastine. Further, this drug still offers a good chance of obtaining a remission in cases refractory to the alkylating agents and vinblastine. Natulan may be of value in other lymphoreticular neoplasms such as lymphosarcoma.

Dr. A. M. C. Duffus, of Roche Products Limited, Welwyn Garden City, Hertfordshire, supplied the Natulan used in this trial.

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Preliminary Communications

Hepatic Impairment During Intake of Contraceptive Pills: Observations in Post-menopausal Women

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Eisalo *et al.* (1964) recently reported that liver dysfunction developed in 10 out of 12 post-menopausal women after only 14–29 days of treatment with an oestrogen (3-methoxy-17α-ethynyl-oestradiol ; mestranol) alone or in combination with a progestin (17α-ethynyloestrenol). The patients varied in age from 52 to 80 years. The serum-transaminase levels (S.G.P.T. and S.G.O.T.) usually were elevated within 20 days of treatment. The S.G.P.T. rose as high as 1,900 units in one patient. It is worth noting that two of the patients had levels slightly above normal before starting the study. In four patients tested for bromsulphalein retention this was also found to be abnormal.

Palva and Mustala (1964) subsequently reported the cases of five patients aged 62 to 90, all of whom developed increases in S.G.O.T. within seven days of administering a closely related oestrogen (ethinyloestradiol). In addition, by the 14th day three of the five had an elevated serum-alkaline-phosphatase level and all five had an abnormal bromsulphalein retention.

By contrast, Swaab (1964) reported that in two large studies of women receiving medication for six months or more 342 S.G.O.T. determinations were well within the normal limits. However, these subjects were young (aged 21–35). A similar failure to find evidence of hepatic dysfunction was reported by Linthorst (1964) in 52 women aged 18–48 treated for 14–43 months, and by Rice-Wray (1964) in 56 menstruating women treated for 3–12 cycles. The possibility that liver impairment may be found only in menopausal women was suggested by these reports.

During the past two years a double-blind study (report in preparation) at this clinic has tested the possible value of the addition of a progestin to oestrogen in the substitution treatment of ovarian failure in the menopause. Until the above reports were published no attention had been paid to the possibility of hepatic damage, although none was suspected on clinical grounds. All available patients were then called in and tested for hepatic function.

METHODS

A total of 36 women were tested. All were menopausal; 32 had had hysterectomy. Their ages ranged from 42 to 77, with a mean of 57. S.G.P.T., alkaline phosphatase, thymol turbidity, cephalin flocculation (read at 24 and 48 hours), and cholesterol measurements, along with a complete blood count, were made in each woman and repeated in several. All these tests were performed within a six-week period. All of the patients received mestranol in a dose of 0.075 mg. daily, either alone (in three instances) or in combination with 5 mg. of norethynodrel.[1] The drugs had been administered for 1 to 24 months, with a mean of 8.76 months, at the time of testing.

RESULTS

The results are summarized in the Table.

Liver-function Tests in 36 Menopausal Women Treated with Mestranol or Enavid

	No.*	Mean	Range	No. Abnormal	Normal Limits
Age (years)	36	57 ± 1·6	42–77		
Duration of therapy (months)	36	8·76	1–24		
Cephalin flocculation:					
24 hours	39	0·89	0–2	6	0–1
48 hours	30	1·2	0–3	4	0–2
Thymol turbidity (MacLagan units) ..	41	2·14	0·6–3·7†	(1)†	0–4
S.G.P.T. (units)	41	13·6	1–59	(3)‡	5–35
Alkaline phosphatase (Bodansky units) ..	42	3·0	1–5·0	6	1·5–4
Cholesterol mg./100 ml. ..	43	253	139–285	12	150–250

* The number of some tests exceeds the number of patients because of duplicated tests.

† One value of 12·9 units omitted because it was believed to be spurious; it was 2·0 when checked.

‡ When repeated two of the three were normal.

The cephalin-flocculation test read at 24 hours was slightly abnormal in six individuals ; no 4-plus readings were observed. Similarly, six individuals (all different from those mentioned above) had an elevated alkaline phosphatase, but in no instance was it more than a marginal increase of one unit. Only one thymol-turbidity test was abnormal. Upon repetition it was found to be normal. Two of the three abnormal S.G.P.T.s were normal upon being repeated.

In addition, all the complete blood counts were normal, a bromsulphalein performed in two was normal, bilirubin and fractionation was normal in three, and protein fractionation was normal in two. The S.G.O.T. was performed in seven women and the highest value was 26 units, the upper limit of normal being 40 units.

[1] Mestranol and Enavid were generously provided by G. D. Searle and Co.

Discussion

This small study fails to give support to the suggestion that menopausal women might have a peculiar hepatic sensitivity to mestranol or Enavid. Since both of the previous reports of uniform liver impairment (see introduction) originated in a single city (Helsinki), it is possible that differences in climate, nutrition, or endemic hepatitic virus explain our failure to confirm their findings.

None of the patients reported herein gave clinical evidence of hepatic impairment, and the minority who had marginal abnormalities on test probably would not exceed the expected incidence in a control group of the same age. It was not thought necessary to discontinue treatment in any case because of these test results. About one-third of the menopausal women in this series had a subjective preference for the oestrogen-progestin combined therapy (Enavid) rather than the placebo or mestranol alone. There seems to be no reason why they should not remain on this treatment indefinitely.

Another source of information about the possible hepatotoxicity of oral oestrogen-progestin therapy in older women is its experimental use in the treatment of rheumatoid arthritis. These studies differ significantly in that the patients already had a serious illness and the dose was often much larger than that used for contraception or to replace ovarian deficiency. Waine *et al.* (1963), in nine patients treated with 15 to 50 mg. of Enavid daily for 8 to 300 days, found "no major changes in serum bilirubin, prothrombin time, alkaline phosphatase, thymol turbidity, bromsulphalein retention, cephalin flocculation, or the S.G.O.T." Similarly, in 17 patients, Gilbert *et al.* (1964), using 40 mg. of Enavid daily, report no significant changes in the S.G.O.T. Although ages were not reported, personal communication revealed that many were in the menopausal age range.

It is concluded that there is not enough evidence to implicate mestranol either alone or in combination with an oral progestin, such as Enavid, as a cause of impaired liver function either in younger women using it for contraception or in menopausal women.

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Medical Memoranda

Case of Thyrotoxicosis Presenting as Hypoproteinaemic Oedema

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The manifestations of hyperthyroidism are protean, but there are few reports of oedema, unrelated to heart failure, as a presenting feature. Ivy (1963) reports the case of a woman of 50 that is essentially the same as the one reported below, and Chapman and Maloof (1956) record the case of a woman of 50 presenting with unexplained oedema, but she had normal serum proteins; both these patients recovered completely on correction of their hyperthyroidism.

Case Report

An artificial-limb fitter aged 48 presented as an out-patient at St. George's Hospital on 23 November 1962, with a history of swollen eyes, ankles, and face for two weeks and of dyspnoea for one week. The only abnormal signs were a short aortic ejection murmur, which has remained constant throughout, and slight tenderness in the right loin. He had suffered from acute nephritis in 1944 but had had no further urinary symptoms at any time; there was no history of an antecedent streptococcal infection, and the urine on this and many subsequent occasions was completely normal. The other investigations (see Table) supported a diagnosis of "nephrotic syndrome."

He was admitted to Queen Mary's Hospital, Roehampton, on 10 December for further investigation. In the meantime he had an attack of paroxysmal atrial fibrillation treated at home with digitalis. He was found to have a slightly enlarged thyroid and a fine hand tremor, but there were no eye signs of thyrotoxicosis and the loin tenderness had disappeared. He had lost a stone (6.4 kg.) in weight in the previous four weeks. The haemoglobin, blood count, serum electrolytes, liver-function tests, creatinine clearance, E.C.G., chest *x*-ray picture, barium-meal examination, throat swab, Wassermann reaction, and antistreptolysin titre were all normal. The serum albumin was greatly lowered, the faecal fats were high (8.8 g./24 hours), and the formiminoglutamic acid (Figlu) test for folic-acid deficiency was positive. Thyrotoxicosis was confirmed by a B.M.R. of 25% above normal, and a four-hour radioiodine of 70% in the neck (normal up to 33%). While he was being investigated he had a further attack of paroxysmal atrial fibrillation, confirmed by E.C.G., which again responded to digitalis.

He was treated with carbimazole, and then a pre-operative course of Lugol's iodine preparatory to subtotal thyroidectomy on 25 February 1963. At this time his serum proteins had returned almost to normal and the Figlu test was negative. The oedema had disappeared. The histology of the thyroid was compatible with thyrotoxicosis treated with carbimazole. Post-operative progress was uneventful. He was reassessed eight months later, when he was completely free of symptoms, and had gained 2 stone (12.7 kg.) in weight. The serum proteins were normal, the faecal fats 5.5 g./24 hours, and the B.M.R. was 24% less than normal. When last seen he remained well, on no treatment, but was developing pretibial myxoedema.

Comment

There seems to be little doubt that the patient's oedema was due to reduced serum albumin, and that this was related to his hyperthyroidism.

It has been shown (Shirer, 1932) that there is often a slightly reduced albumin and raised globulin in cases of thyrotoxicosis. The reduced albumin has been confirmed (Lewis and McCullagh, 1944) and shown to be probably due to increased catabolism greater than the increased anabolism; however, the reductions found were much smaller than in the above case. In artificial thyrotoxicosis in man (Rothschild *et al.*, 1957) this finding was coupled with the demonstration of an increased plasma volume which may well have been a factor in the pathogenesis of the oedema in this case. Nikkilä and Pitkänen (1959) found a reduced amount of cellular enzymes in liver-biopsy specimens from hyperthyroid patients, but all the liver-function tests were normal in the present case.