ORAL CONTRACEPTIVES IN PORPHYRIA VARIEGATA

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It has been reported previously that oral contraceptives of progesterone-oestrogen type can cause disturbed liver function in postmenopausal women.[1] Recently Wetterberg from Uppsala University, Sweden, reported an attack of acute porphyria following the use of Lyndiol (5 mg. of lynestrenol and 0·15 mg. of mestranol) as an oral contraceptive in a patient with intermittent acute porphyria.[2] A number of earlier reports discussed the effects of pregnancy, oestrogen and progesterone in the porphyrias.[3-9]

At the International Conference on the Porphyrias in Cape Town (1963) the adverse effects produced by the administration of oestrogens to patients with intermittent acute porphyria were described by Redeker. In 14 trials, 2 patients had typical attacks of acute porphyria and in 7 there was a marked increase in urinary pyrrole excretion.[10]

Porphyria variegata is the autosomal-dominant type of porphyria that is common among the White and Coloured population of South Africa. It has been estimated that there are over 8,000 White South Africans alive today who have inherited porphyria variegata from 1 ancestor who brought the disorder to South Africa nearly 300 years ago.[11] This is a prevalence rate of 3/1,000 of the White population, so that there are a large number of women with porphyria variegata in South Africa.

CASE REPORT

First Attack

Mrs. L.S., aged 20, had an attack of acute porphyria 2 months after the birth of her first child in May 1963. This acute attack was precipitated by Sulfathox tablets. At that time she developed severe abdominal pain and was very emotional. Her urine was port-wine in colour and the Watson-Schwartz test for porphobilinogen was strongly positive. She had a very high excretion of porphyrin in her stools.

She was admitted to hospital and required intravenous feeding because of vomiting. Even after the vomiting had stopped, her blood sodium and chloride remained very low for 2 weeks. Fortunately she made a good recovery. At that time she was warned very strongly against taking barbiturates or sulphonamides. After the acute attack the stool porphyrin excretion remained high but the porphobilinogen test (Watson-Schwartz) became negative. Other members of her family had porphyria variegata.

Second Attack

In August 1964 she took Lyndiol tablets (1 daily) as a contraceptive measure. After taking the tablets for 2 weeks she noticed that her urine was becoming very dark and the following day that her stool was clay-coloured. She then found that her skin was very itchy particularly on the hands, arms and face (Fig. 1), and she developed a large number of blisters and sores on the exposed skin.

When I saw her on 9 September 1964 her hands and face were covered in blisters and sores, although she had stopped taking Lyndiol for the previous 10 days. Her urine was dark and contained bile but the Watson-Schwartz test for porphobilinogen was negative. Her urine fluoresced a brilliant pink in Wood's light, showing the presence of a large amount of porphyrin. Her stool was clay-coloured and a solution made from the stool did not fluoresce in Wood's light, although on the previous occasions when it had been tested it had always fluoresced

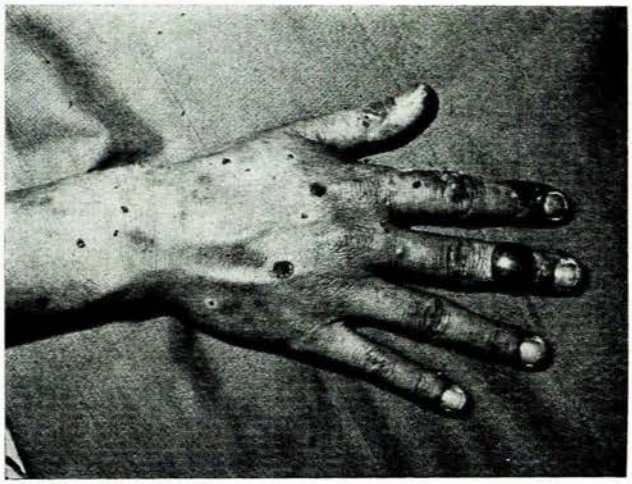

Fig. 1. The bullous eruption and other skin changes on the patient's hand at the onset of the illness.

a brilliant pink. She had no abdominal pain and she was mentally well balanced, but she could not stop scratching because of the itching of the exposed skin. She looked slightly jaundiced and her blood bilirubin was raised at 1·6 mg./100 ml.

Treatment. She was immediately admitted to hospital and sedated with 400 mg. of meprobamate *t.d.s.* In view of the evidence of hepatic damage it was decided that she should not be given chlorpromazine. A calamine and phenol lotion was used to soothe the itching of the skin which was kept covered from light as far as possible. The stools remained clay-coloured for a further week and then started to regain their normal brown colour. As the bile pigments returned to the stools porphyrins also returned and at about the same time her urine became less dark. Throughout this time her urine fluoresced a brilliant pink in ultraviolet light (Wood's light) and so did the blood serum, but not the faeces. On 14 September her stool coproporphyrin was only 12 μg. and protoporphyrin 15 μg./G dry weight. The results of the examinations of her skin, urine and faeces are annotated in Table I. It will be seen that there was a marked disturbance of liver function.

Progress. After 2 weeks in hospital she was allowed to return home although her skin was still blistering. It was necessary for her to wear gloves and 2 pairs of black stockings and to cover her face as far as possible. She also used a protective cream against ultraviolet light (Hamol Ultra). By 21 October the stool porphyrin had returned to its previous high level. Although there was a slight increase in porphobilinogen, the Watson-Schwartz test with Ehrlich's aldehyde reagent remained negative.

TABLE I. LABORATORY TESTS

Date	*14.9.64*	*24.9*	*2.10*	*21.10*	*4.11*	*5.12*
Skin						
Blisters on exposed skin	+++	+++	+++	+++	+++	+++
Jaundice	+	+	+	—	—	—
Blood						
Bilirubin (mg./100 ml.)	1·7	—	1·64	0·56	0·44	—
Direct (mg./100 ml.)	1·1	—	0·7	—	—	—
Indirect (mg./100 ml.)	0·6	—	0·9	—	—	—
Coproporphyrin (μg./100 ml.)	69	—	—	—	—	—
Protoporphyrin (μg./100 ml.)	81	—	—	—	—	—
Alkaline	—	—	—	—	—	—
Phosphatase (units)	—	14·2	11·2	—	—	—
Bromsulphthalein	—	—	++ (12% at 45 minutes)	—	—	—
Zinc sulphate (units)	—	4·7	—	—	6·6	—
Thymol turbidity (units)	—	0·3	—	—	1·2	—
SGOT (units)	—	—	39	—	14	—
SGPT (units)	—	—	72	—	18	—
Protein (G/100 ml.)	—	7·0	—	—	6·65	—
Albumin (G/100 ml.)	—	3·6	—	—	3·86	—
Globulin (G/100 ml.)	—	3·4	—	—	2·79	—
Serum fluorescence (UVL)	+++	+++	+++	+++	++	++
Urine						
Colour	Very dark	dark	lighter	normal	normal	normal
Fluorescence (UVL)	+++	+++	++	+	+	±
Watson-Schwartz	—	—	—	—	—	—
Uro+coproporphyrin (mg./1.)	7·8	++	+	+	+	±
PBG (mg./1.)	1·4	—	—	14·5	—	—
ALA (mg./1.)	5·2	—	—	—	—	—
Bilirubin	—	—	—	—	—	—
Urobilin	+	—	—	—	—	—
Urobilinogen	—	—	—	—	—	—
Stool						
Colour	clay	clay	darker	normal	normal	normal
Stercobilin	—	—	+	+	+	+
Coproporphyrin (μg./G)	12	85	286	806	+++	+++
Protoporphyrin (μg./G)	15	167	918	1,300	+++	+++

In spite of the evidence of improved liver function her serum still fluoresced brilliantly in ultraviolet light and she still had fresh crops of blisters and sores on her hands, legs and face until December. She suffered no abdominal pain. Only by the middle of December, 3 months after the onset of her illness, was there clinical evidence of diminished skin sensitivity. By then, in spite of great efforts to protect the skin, there were many remaining pigmented scars on the face, hands and feet (Fig. 2).

Different Effect

The effect of the oral contraceptive Lyndiol on this patient with porphyria variegata was not the same as the effect of barbiturates and sulphonamides. In fact this was not an attack of acute porphyria in the ordinary sense, but rather an attack of 'hepatitis' in which there was obstruction to the passage of bile pigments and porphyrin from the liver, clinical jaundice of a mild degree, a very high circulating porphyrin and high urinary content of porphyrin. In acute porphyria, on the other hand, while there is some rise in the circulating porphyrin and in the excretion of urinary porphyrin, the main change is the high level of serum porphobilinogen (PBG) and δ-aminolaevulinic acid (ALA) and the excretion of large amounts of PBG and ALA in the urine. Although there was a slight elevation of PBG and ALA in this patient's blood and urine there was never sufficient increase to give a positive Watson-Schwartz test.

Eales has reported a patient with porphyria variegata who developed similar symptoms after taking the oral contraceptive Enavid together with chlorpromazine. During the jaundiced phase her faecal porphyrin fell to very low levels and the skin lesions became very much worse. As the jaundice improved so the faecal porphyrin

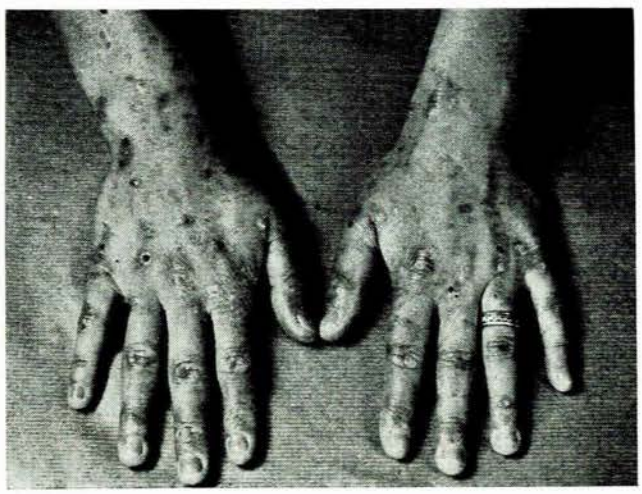

Fig. 2. Remaining scars 5 months after the onset of the illness.

rose and the urinary porphyrin fell to approach its former levels.[12]

CONCLUSION

It would appear that oral contraceptives are potentially hepato-toxic in patients with porphyria variegata and until more is known about their action it is advisable that women who have inherited porphyria variegata should not use oral contraceptives but should, if they desire, use an alternative contraceptive method.

I should like to thank Dr. Harold Miller of Port Elizabeth for consulting with me about this patient. Dr. H. Abrahamson and Organon Laboratories supplied information about Lyndiol and numerous references on the effects of oestrogens in porphyria. Professor L. Eales of Cape Town informed me about a similar case he had seen at Groote Schuur Hospital following the use of Enavid and permitted me to mention his patient. The CSIR/UCT Renal Metabolic Unit undertook some of the chemical analysis. I should also like to thank Dr. H. D. Barnes of the Department of Chemical Pathology, St. Mary's Hospital, London, and the South African Institute for Medical Research, Port Elizabeth, who carried out laboratory investigations: Dr. Philip Perl who took the photographs and Mr. Bruce Mann who photographed the pink fluorescence of the urine and blood serum in ultraviolet light (Wood's light). Finally, I should like to thank the patient for cooperating so well with the research side of this study.

REFERENCES

1. Eisalo, A., Järvinen, P. A. and Luukkainet, T. (1964): Brit. Med. J., **2**, 426.
2. Wetterberg, L. (1964): Lancet, **2**, 1178.
3. Levitt, G. J., Nodine, J. and Perloff, W. H. (1957): Amer. J. Med., **22**, 831.
4. Watson, C. J., Runge, W. and Bossenmaier, I. (1962): Metabolism, **11**, 1129.
5. Walshe, M. (for Warin, R. P.) (1963): Brit. J. Derm., **75**, 298.
6. Eales, L., Dowdle, E. B., Saunders, S. J. and Sweeney, G. D. (1963): S. Afr. J. Lab. Clin. Med., **9**, 126.
7. Welland, F. H., Hellman, E. S. *et al.* (1964): Metabolism, **13**, 251.
8. Leading article (1964): Brit. Med. J., **2**, 1278.
9. Dean, G. (1953): *Ibid.*, **2**, 1291.
10. Redeker, A. G. (1963): S. Afr. J. Lab. Clin. Med., **9**, 302.
11. Dean, G. (1963): *The Porphyrias.* London: Pitman.
12. Eales, L. (1963): S. Afr. J. Lab. Clin. Med., **9**, 261.