Oral Contraception and Depression

Delay in the recognition of serious side-effects of new drugs is commonplace in psychiatry. The addictive potential of barbiturates and amphetamines and the hypertensive crises found with monoamine oxidase inhibitors are three examples, and it was a long time before serious depression caused by long-term medication with chlorpromazine was seen to be a much commoner and more troublesome side-effect than either jaundice or agranulocytosis.

It is no surprise, therefore, in a different context to find that the effect on mood of oestrogen-progestogen mixtures is displacing thromboembolic episodes at the focus of disquiet about oral contraceptives. Though as far back as 1961 T. B. Lebherz and C. D. Fobes\(^1\) noted that 7 out of 112 patients being treated for endometriosis showed emotional distress, and that two of them became severely depressed, the general tenor of impressionistic reports until recently has been sanguine. From 5–30% of women complain of such symptoms as irritability, tension, and depression, but many have had premenstrual symptoms before they started on the pill, and in any case those who complain are balanced by the 10–20% who experience relief of premenstrual tension and an increased sense of well-being. High rates of depression appear to be associated with pills with a high progestogen content,\(^2\)\(^3\) and depression diminishes with change to a more oestrogenic pill. When massive doses of the progestogen norethynodrel were given to 20 patients with endometriosis J. W. Scott and P. Brass\(^4\) reported mood changes in all of them. Three developed depression of moderate severity, but it responded to antidepressant drugs.

A. Lewis and M. Hoghugh\(^i\) have recently compared the depressive side-effects in 50 women taking oral contraceptives with 50 well-matched controls from the same group practice. Of the "pill" group 13 were mildly and 6 severely depressed, compared with only 2 and 1 respectively of the controls. Two of the severely depressed women had made suicidal attempts unknown to their general practitioners. The patients with a previous depressive history were significantly more depressed than those who had not—a finding that confirms earlier reports.\(^5\)\(^6\) Two other trends emerged but did not reach the level of "significance": there was more depression with the more strongly progestogenic pills; and the longer a patient had been on the pill the more likely she was to be depressed. This last observation has been made before.

It seems, then, that the pill can precipitate depression in predisposed women of child-bearing age. But need these women, and others who become depressed out of the blue on such medication, be denied the undoubted benefits of oral contraception? Recent work suggests that prevention of this iatrogenic depression may be possible. Steroids, including cortisol and oral contraceptives, appear to influence tryptophan metabolism.\(^7\)\(^8\) The net effect seems to be to create a functional deficiency of pyridoxine, a coenzyme in the conversion of tryptophan both to nicotinic acid nucleotide and to 5-hydroxytryptamine. There is evidence that premedication with pyridoxine prevents the disturbance of tryptophan metabolism by cortisone,\(^9\)\(^10\)\(^11\)\(^12\) and some evidence, too, that a very few cases of "pill"-induced depression have responded to pyridoxine.\(^13\) A contraceptive pill incorporating pyridoxine has already been marketed in Spain.\(^14\)

Last year K. J. Dennis and J. d’A. Jeffrey\(^i\) commented that "At present it is probably true to say that depression and reduced libido associated with the administration of oestrogen–progestogen mixtures cause more women to discontinue oral contraception than any other single cause," and other workers agree that depression is the most distressing, though not the commonest, side-effect.\(^15\) R. H. Moos\(^16\) believes that up to 25% of the women who start on the pill soon abandon it, and H. Ratner states that there is gross under-reporting of side-effects.\(^17\) If the pill is to remain man’s best hope of controlling the population explosion its

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\(^6\) Daly, R. J., Kane, F. J., and Ewing, J. A., Lancet, 1967, 2, 444.
\(^8\) Wearing, M., Canadian Medical Association Journal, 1963, 89, 239.
\(^12\) Rose, D. P., and McGlotype, C. Clinical Science, 1968, 35, 1.
\(^15\) Dennis, K. J., and Jeffrey, J. d'A., Lancet, 1969, 2, 454.
\(^16\) Moos, R. H., Archives of General Psychiatry, 1969, 18, 87.
side-effects should be eliminated wherever possible, and the value of pyridoxine in treating depression should be studied further. Meanwhile doctors should be careful about prescribing oral contraceptives for anyone with a clear-cut history of depression.

Urinary Symptoms in General Practice

In domiciliary practice 12 per 1,000 consultations are on account of symptoms suggesting infection of the urinary tract. This figure underestimates the morbidity from urinary-tract disease in the population, since only 40% of patients with urinary symptoms consult their doctor and also because the figure refers solely to symptoms of infection. In this issue Dr. J. Steensberg and his colleagues report the prevalence of urinary-tract disease of all kinds among 22,000 adults aged 16 and over who attended ten general practitioners in a suburban area of Copenhagen over a period of one year. They discovered 741 cases of urinary-tract disease, which amounted to 34 per 1,000 consultations in the year. Women outnumbered men by 3 to 1. As might have been expected, the commonest complaints in both sexes were frequency, dysuria, urgency, and foul-smelling urine. In 54% of the women and 56% of the men with these complaints evidence of urinary infection was obtained, but in the remainder evidence for infection was doubtful or non-existent. This observation confirms the findings of D. J. A. Gallagher and colleagues and N. C. Mond, who showed that only half of all women with symptoms suggesting urinary infection had a positive urine culture.

Dr. Steensberg and colleagues’ data allow a comparison to be made among patients with symptoms of urinary-tract infection between those with an infected urethra and those in whom the urine was not infected. Women in whom the urine was sterile were younger and their symptoms were more frequently those of “cystitis” than upper urinary-tract disease. In the uninfected women vaginal discharge and vaginitis were more frequently encountered than in the infected group, whereas genital prolapse was a common finding in the older infected women. Marital status did not affect the prevalence of symptoms in the uninfected group, whereas symptoms among the infected women were more common among judicially separated, divorced, and married women than among spinsters. Proteinuria, leucocyturia, and haematuria were all more commonly encountered in the infected group. Among the males symptoms of urinary-tract infection in the absence of significant bacteriuria were common in the younger age groups, whereas infected urines were frequently noted in old men with enlarged prostates.

These observations contribute to our understanding of the urethral syndrome—the syndrome of dysuria, frequency, and urgency in the absence of an infected urethra. It is clear that this disorder is sometimes caused by a primary disorder of the genital organs. Furthermore, this puzzling syndrome does not appear to be confined to women, since bacteriuria was not found in 44% of all the men presenting with symptoms of urinary infection. It has been claimed that in males the syndrome results from chronic bacterial prostatitis and in females from infection of the para-urethral glands. But the urethral syndrome probably has a variety of causes, since some patients can be relieved of their symptoms by avoiding such precipitating factors as cold, excessive trauma during sexual intercourse, antiseptic douches, deodorants, bubble baths, contraceptive foam, intrauterine devices, and rubber, to which they may have sensitivity reactions. But most patients find relief of symptoms difficult to achieve.

The findings of Dr. Steensberg and his colleagues also draw attention to the frequency of urolithiasis in middle-aged men and women. The rate for men was 3 per 1,000 consultations per annum as compared with 1 per 1,000 for the women. These observations underline the need for radiological investigation of patients presenting with urinary symptoms, since urolithiasis may be amenable to treatment. Diseases other than those mentioned above were much more rarely encountered during the period of the survey. Only four cases of bladder papilloma and two of bladder carcinoma were seen among the 741 persons with urinary tract disease. Dr. Steensberg and his colleagues have performed a service by once again focusing attention on the urethral syndrome as a common source of morbidity. Their observations are a stimulus to further research in this field.

Treatment with Neutrons

The neutron generator is the latest in a long series of machines devised by nuclear scientists and adapted for radiotherapy. The cyclotron at Hammersmith Hospital has been used experimentally over several years, but a specially built neutron therapy machine developed by co-operative effort from users, manufacturers, and Government departments will be installed at the Christie Hospital, Manchester, next summer and will probably be in full use early in 1971. In penetrating power the neutrons to be used for cancer therapy are comparable with 250 kV x rays of a generation ago, but their potential efficacy depends on other factors. Anoxic cells, which may exist in the centre of a tumour, are more than ordinarily resistant to damage by radiation. This observation is the basis for the use of hyperbaric oxygen in radiotherapy, a technique still undergoing clinical trial. The protective effect of cellular anoxia is distinctly less with neutrons than with x rays, and it is for this reason that neutron therapy is now being studied. The technical problems are formidable but appear to be soluble ; the equipment to be installed in Manchester will be comparable in size and cost

1 Fry, J., Dillane, J. B., Joiner, C. L., and Williams, J. D., Lancet, 1962, 1, 1, 1318.
4 Mond, N. C., Proceedings of the Royal Society of Medicine, 1964, 57, 1119.