CORRESPONDENCE

Owing to the Government's restrictions on the use of power in industry, including printing, we have been obliged to defer publication of some letters and print others in shortened form. We regret this inconvenience. Correspondents are asked to help by keeping their letters as short as possible.

Oral Contraceptives and Thromboembolism

SIR,—Dr. P. G. T. Bye raises four important points in his recent letter (10 November, p. 354) concerning the relationship between oral contraceptives and thromboembolism on which we would like to comment.

Firstly, data published subsequently to the original articles by Inman and Vessey¹ and Vessey and Doll² have shown that the estimates of risk presented in those articles were of the correct order of magnitude, and it seems clear that doctors have not seriously misled their patients by quoting the estimates of risk "as though they were precise quantities."³⁻¹⁰

Secondly, it is likely that the changeover to low-oestrogen-dose oral contraceptives has lowered the risk; but there is, at present, no substantial evidence that this is so. The best that can now be done is to extrapolate the crude dose-response relationship provided by Inman *et al.*¹¹ to current levels of oral contraceptive use. Dr. Bye discusses this extrapolation in his letter, and further information on this point will be found in a recent article by Vessey and Inman.¹²

Thirdly, there is no additional information at present on the difference, if any, between the risks associated with oral contraceptives containing mestranol and those containing ethinyl oestradiol. It is to be hoped that more precise information on both these matters will be obtained from the large-scale prospective studies which are being carried out by the Royal College of General Practitioners¹³ and by ourselves.¹⁴

Finally, we agree that it is impossible to prove that a particular thrombosis in a particular woman is attributable to the use of oral contraceptives. This, however, is not an "intrinsic limitation of epidemiological research" so much as an intrinsic limitation of scientific knowledge in a situation where a particular condition can be caused by more than one agent. It applies, for example, in industry where an occupational exposure carries a hazard of developing a disease that also occurs under other circumstances. No matter how adequately the existence of the occupational hazard is proved (including the use of animal and human experiments), the determination of the cause in a particular instance is almost always a matter of assessment of probabilities.—We are, etc.,

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¹ Inman, W. H. W., and Vessey, M. P., *British Medical Journal*, 1968, 2, 193.

² Vessey, M. P., and Doll, R., *British Medical Journal*, 1968, 2, 199.

³ Vessey, M. P., and Doll, R., *British Medical Journal*, 1969, 2, 651.

⁴ Seigel, D. G., and Markush, R. E., *American Journal of Epidemiology*, 1969, 90, 11.

⁵ Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E., *American Journal of Epidemiology*, 1969, 90, 365.

⁶ Vessey, M. P., Doll, R., Fairbairn, A. S., and Gliber, G., *British Medical Journal*, 1970, 3, 123.

⁷ Bottiger, L. E., and Westerholm, B., *Acta Medica Scandinavica*, 1971, 190, 455.

⁸ Green, G. R., and Sartwell, P. E., *American Journal of Public Health*, 1972, 62, 680.

⁹ Collaborative Group for the Study of Stroke in Young Women, *New England Journal of Medicine*, 1973, 288, 871.

¹⁰ Boston Collaborative Drug Surveillance Programme, *Lancet*, 1973, 1, 1399.

¹¹ Inman, W. H. W., Vessey, M. P., Westerholm, B., and Englund, A., *British Medical Journal*, 1970, 2, 203.

¹² Vessey, M. P. and Inman, W. H. W., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1973, 80, 562.

¹³ Kay, C. R., *Journal of the Royal College of General Practitioners*, 1970, 19, 251.

¹⁴ Vessey, M. P., Doll, R., Peto, R., and Redman, C. W. G., *International Journal of Epidemiology*, 1972, 1, 119.

Somnolence in Children with Acute Leukaemia

SIR,—Cerebral involvement and its clinical manifestations in childhood leukaemia occur at unpredictable phases of the disease, often during remission, and have even been described as a presenting symptom.¹ In the past few years, in addition to pharmacological treatment, prophylactic cranial irradiation has been given to selected children in the hope of reducing the risk of neurological complications. Dr. J. E. Freeman and others (1 December, p. 523) have rightly drawn attention to a syndrome of somnolence attributed to the prophylactic cranial irradiation and occurring several weeks after radiotherapy in over one-third of their cases. These authors mention particularly electroencephalographic changes as "consistent with a diffuse cerebral disturbance affecting both hemispheres and without evidence of any focal cerebral lesion."

(1) In the interpretation of the E.E.G. findings a clear distinction should be made between a "diffuse generalized abnormality" indicating a process affecting all parts of the brain in a similar way and a "patchy abnormality" indicating that some regions of the brain are affected in a different way from others.

(2) In a study of the E.E.G. features in children with acute leukaemia at Great Ormond Street² we found children who became drowsy and lethargic while in remission, with E.E.G. alterations comparable to those of the five children reported by Dr. Freeman and his colleagues, but without having had any cranial irradiation. In a current survey of 20 children with acute lymphoblastic leukaemia diagnosed at this hospital between January and November 1973, 12 had their first E.E.G. on the day of diagnosis; a patchy E.E.G. abnormality was already present in

10, while only two had no E.E.G. abnormality at all.

(3) In the insidious course of leukaemia the type and distribution of the E.E.G. abnormalities may fluctuate considerably in the same patient, and particular alterations of the E.E.G. features may precede by weeks or months the clinical appearance of neurological symptoms. In the E.E.G. the occurrence of an excess of irregular slow activity with patchy distribution, even in the absence of clinically recognizable neurological trouble, may well indicate that multiple discrete areas of leukaemic involvement are already present in the brain.—I am, etc.,

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¹ Pole, J. G., *Archives of Disease in Childhood*, 1973, 48, 867.

² Butcher, D. M., Hardisty, R. M., Lange, L., and Pampiglione, G., *Electroencephalography and Clinical Neurophysiology*, 1970, 28, 209.

Comparative Activity of Minocycline and Tetracycline

SIR,—The tetracycline minocycline (7-dimethylamino-6-deoxy-6-demethyltetracycline) hydrochloride is now being marketed. I have compared its in vitro activity with that of tetracycline against 72 strains of Gram-negative bacteria. These comprised 14 strains of *Pseudomonas aeruginosa*, 12 of *Proteus* (10 *Pr. mirabilis*, one *Pr. vulgaris*, one *Pr. morganii*), 10 of *Escherichia coli*, 14 of *Klebsiella aerogenes*, 10 of *Salmonella*, and 12 of *Shigella*. The salmonellae comprised one each of the following species: *S. typhimurium*, *S. panama*, *S. infantis*, *S. heidelberg*, *S. enteritidis*, *S. dublin*, *S. anatum*, *S. senftenberg*, *S. newport*, and *S. indiana*. The 12 strains of *Shigella* comprised seven *Sh. flexneri* (two type 4, two type 5, three type 6), three *Sh. boydii* (one type 4, one type 5, one type 6), and two *Sh. sonnei*. The minimum inhibitory concentrations of each of the two antibiotics for these organisms were determined by a tube dilution technique. Doubling dilutions of each antibiotics were made in 1-ml volumes of Oxoid sensitivity test broth. Each tube was inoculated with a 0.02-ml drop of a diluted broth culture giving an inoculum of about 10⁴ viable organisms. After 18 hours incubation at 37°C the tubes were examined for turbidity. The minimum bactericidal concentrations were determined by subculturing those tubes in which there was no apparent bacterial growth. The results are shown in the figures.

Minocycline appears to be slightly more active than tetracycline against *Proteus* species. However, when interpreting these