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.,

MARTIN VESSEY
RICHARD DOLL

Department of the Regius Professor of Medicine,
Radcliffe Infirmary,
Oxford

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.,

G. PAMPIGLIONE

Hospital for Sick Children,
Great Ormond Street,
London W.C.1

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

results it should be remembered that, according to the independent investigators quoted by the manufacturers, minocycline in standard dosage (an initial oral dose of 200 mg followed by 100 mg twice daily) produces serum concentrations of only 1-3 µg/ml,⁴ that ordinary doses of tetracycline (for example, 250 mg 6-hourly) will produce peak serum levels in the order of 2-4 µg/ml,⁵ and that with *Proteus* species neither antibiotic was bactericidal or likely to be therapeutically effective. With the other Gram-negative bacteria the activity of the two antibiotics appeared to be similar.—I am, etc.,

N. A. SIMMONS

Department of Clinical Bacteriology and Virology,
Guy's Hospital,
London S.E.1

- Heine, P., Thesis, 1969, University of Zurich.
- Kanazawa, Y., and Kuramata, T., *Japanese Journal of Antibiotics*, 1969, 22, 417.
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- Garrod, L. P., Lambert, H. P., and O'Grady, F., in *Antibiotic and Chemotherapy*, ed. L. P. Garrod and F. O'Grady, 4th edn., p. 154. Edinburgh and London, Churchill Livingstone, 1973.

Prevention of Accidental Hypothermia

SIR,—In the timely and excellent review of accidental hypothermia by Professor A. N. Exton-Smith (22 December, p. 727) he recommends among preventive measures the recognition of old people at risk and advice on suitable clothing and bedding. The health department of the London Borough of Wandsworth have issued home nurses and health visitors with low-reading clinical thermometers and room thermometers for the assessment of old people

at risk and of the current trial of duvets for the prevention of hypothermia. The duvets (continental quilts) being used are the type filled with Terylene P3 and are regarded as an alternative measure to blankets or low-wattage electric blankets.

The duvet is cheap, has a good insulation: weight ratio, saves much effort in bed-making, and as well as being a bed cover can be used to wrap up old people during the day. In these days of uncertain fuel supplies it is pertinent that the duvet needs no power source. As a practical community project some members of an old people's club have made duvets from "home-sew" kits and have thus saved on the cost as well as having the satisfaction of doing something active. A loan from the local Age Concern Committee made it possible for the kits to be bought wholesale, reducing the cost still further, and as the loan is repaid it will be available for other clubs. Many old people strongly resist charity, but this type of aid is acceptable since they have to participate actively and what they receive is a genuine bargain.—I am, etc.,

M. A. CHURCH

London S.W.15

Acute Pancreatitis and Diabetic Ketoacidosis in Hypothermia

SIR,—We wonder whether Dr. D. Maclean and his colleagues (29 December, p. 757) are justified in including diabetic ketoacidosis in the title of their paper since at no point is there any reference to the presence of ketones in breath, blood, or urine. The diagnosis presumably rested on evidence of acidosis, and the possibility of lactic acidosis should at least be considered in a metabolic disturbance of this degree of severity.

It has been shown repeatedly that elevation of the blood amylase level may occur in subjects with uncontrolled diabetes without any evidence of pancreatic disease.¹⁻³—We are, etc.,

JOHN MALINS
C. H. WALSH

Diabetic Clinic,
General Hospital,
Birmingham

- Belfiore, F., and Napoli, E., *Clinical Chemistry*, 1971, 19, 387.
- Knight, A. H., Williams, D. N., Ellis, G., and Goldberg, D. M., *British Medical Journal*, 1973, 3, 128.
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Rupture of Abdominal Wound after Laparoscopy

SIR,—Complete rupture of the abdominal wound after laparoscopy occurs very infrequently.^{1,2} I wish to report such a case.

A woman aged 32 years who had five children was admitted for sterilization. She was an unhealthy, thin, weary woman who smoked heavily. Under endotracheal anaesthesia a 2-cm infra-umbilical incision was made and 5 l. of carbon dioxide gas instilled through a Verres needle. The trocar (11 mm diameter) passed very easily direct into the abdominal cavity. Laparoscopy was performed, followed by tubal coagulation with a Palmer coagulation forceps inserted through a small cannula in the right iliac fossa. The gas was totally evacuated and the wounds closed with fine monofilament nylon sutures. The patient, who was discharged 24 hours later, was readmitted on the fourth day with omentum protruding from the umbilical wound. Under general anaesthesia the wound was enlarged, part of the omentum excised,

and the remainder returned to the abdomen. The wound was closed with no. 1 nylon sutures inserted through all layers of the abdominal wall and had healed soundly by the 10th day, when the sutures were removed. The patient defaulted from the follow-up clinic.

Poor abdominal muscles, a thin linea alba, and postoperative coughing may have contributed to the wound dehiscence, but the failure to use a "Z tract" when inserting the trocar was all-important. Normally the trocar should be inserted through the umbilical wound and then pushed inferiorly and subcutaneously for at least 3 cm before being thrust into the abdominal cavity. This "Z tract" acts as a valve and reduces the leakage of gas. What is equally important is that this technique minimizes the chance of rupture of the wound, which should now be numbered among the serious postoperative complications of laparoscopy.—I am, etc.,

ALAN M. SMITH

Women's Hospital,
Wolverhampton

- Bishop, H. L., and Halpin, T. F., *American Journal of Obstetrics and Gynecology*, 1973, 116, 585.
- Duignan, N. M., Jordan, J. A., Coughlan, B. M., and Logan-Edwards, R., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1972, 79, 1016.

W.M.A. and Racial Discrimination

SIR,—Ghana's original motion at the W.M.A. Assembly (*Supplement*, 3 November, p. 26) referred to discrimination on the grounds of "colour" only. The motion finally carried refers to "religion, race, colour, or politics in any form." Neither in your report (3 November) nor in subsequent correspondence (8 December, pp. 614 and 615) is it made absolutely clear that South Africa voted *for* and Ghana *against* the final motion, which "vehemently condemns" discrimination on all these grounds. In voting for the motion South Africa was merely reaffirming what the Medical Association of South Africa affirmed before a Government Commission two years before the W.M.A. was founded.¹ Even then it was ahead of the W.M.A. at Munich, as it included sex among the excluded grounds. Strangely—why?—the W.M.A. motion went on to instruct and empower the W.M.A. Council "to investigate as carefully and as fully as possible" only "the issue of colour discrimination."

May I express the hope that the Council will be much more careful in their investigations and conclusions than many of those who have written about medicine in South Africa in the medical as well as in the lay press, and that, in particular, they will be careful to discriminate between the actions and attitudes of doctors in South Africa and those of laymen and the Government?—I am, etc.,

G. W. GALE

Surbiton, Surrey

- South Africa, *Report of National Health Service Commission*, Blue Book No. 30, p. 156. Cape Town Government Printer, 1944.

Pregnancy after Hysterotomy

SIR,—Drs. W. M. Clow and A. C. Crompton (10 February, p. 321) reported a substantial risk of uterine rupture in pregnancies in women who had previously had a preg-