It would be well to remind those faced with this difficult therapeutic problem that the only proved portal of entry of candida following cardiac surgery is the infected intravenous drip site, through which antibacterial antibiotics are often being administered, thus providing a further selective pressure.⁷ An essential part of the management is the removal and if necessary replacement of these infected intravenous lines, though this alone cannot be relied upon to be curative. Perhaps it is wise to reconsider the twice-weekly flushing of long-standing infusions with dilute solutions of amphotericin, as suggested by Brennan and his colleagues.⁸—I am, etc.,

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- 1 Record, C. O., et al., *British Medical Journal*, 1971, 1, 262.
- 2 Cartwright, R. Y., Shaldon, C., and Hall, G. H., *British Medical Journal*, 1972, 2, 351.
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- 5 Polak, A., and Scholer, H. J., *Proceedings of the 9th International Congress of Chemotherapy*, 1975. To be published.
- 6 Turnier, E., et al., *Chest*, 1975, 67, 262.
- 7 Darrell, J. H., and Garrod, L. P., *British Medical Journal*, 1969, 2, 481.
- 8 Brennan, M. F., et al., *Annals of Surgery*, 1972, 176, 265.

G.M.C. and Indian Qualifications

SIR.—There has recently been considerable correspondence on the low professional standards of Indian doctors and on excessive emigration from developing countries (7 June, p. 562, 5 July, p. 43, and 26 July, p. 229) and I hope that yet another individual's mode of solution warrants expression. Rather than emphasize reduced morale, I prefer to pay attention to the frustrations that produce this; and in India, where I have been as a visiting lecturer, this seems occasioned mainly by lack of teachers to produce the calibre for negotiating their need.

The massive problem of raising the health level and the college teaching level of a whole subcontinent, whose health directors are aware of this need, is probably best understood by those who have travelled beyond the major city centres there and who have thought proportionately about the number of hospitals and teaching centres of the top grade relative to the size of the country and the population. The major centres in Calcutta, Madras, Delhi, and Bombay and the two Christian colleges of Vellore and Ludhiana display enormous influence, yet compared with ourselves they still experience daunting hardships to overcome their environmental, social, and sickness problem. The rate of development of more than 130 other colleges is the initiative of the Indian government, plus one founded by the charity of the Indian Roman Catholic Church. Because of the struggle to reach higher standards, and to learn, a large number of postgraduates seek posts in the U.K. This is an expensive tide in the wrong direction and is occasioned by a migration to find teachers.

For three years I have personally taken package two-week haematology postgraduate lectures and practicals, of 20 sessions in all, to three lesser colleges in India (having made contacts at a preceding visit). In a five-week stay I have given these courses twice (two share a course), and in the remaining week

I have supplied selected specialist lectures to a variety of disciplines, institutes, and societies.

This system turns the tide of need and joins with college level in India, which is where medical standards are set and from which graduates disseminate. One specialist, and one fare, encompass the practical requirement of two centres there and the entire postgraduate complement of the locality having an interest in that specialty. A two-week course is a standard generous format for Britain. Its preparation by one person to suit their need has been a stimulus to moral and comprehensive knowledge also for myself, which is not lost in the stereotyped format of our own Health Service.

In such a scheme the only answer to the economic lag of developing countries is to stand the expenses from the affluent end. Over the three-year sequence and the preparatory year 12 weeks have been granted as leave of absence with pay by the regional hospital board (and its successor, the area health board, which has been more stringent). I paid the fare and the receiving institutions mostly supplied full board at their cost. The remaining weeks in each course were classed as holiday.

The clause available to consultants for negotiation in Scotland is No. 252(b) of Terms and Conditions of Service for Hospital Medical and Dental Staff (Scotland). It is a matter of opinion how much concern should be shown for the privilege gap and for experts how to resolve the major finance issues. For the ordinary person who is interested we have to pull in our belts individually and think of return for money nationally. This system does both of these. A need is met on its own ground and those Indians who still want to come to U.K. become of better calibre. It is still, however, a major exercise to decipher at which institutes in India supplementation is wanted and to elicit long-term development schemes which could be supported in this way over many years.—I am, etc.,

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Oral Contraceptives in Women Over 34

SIR.—The recent reports by Dr. J. I. Mann and others (3 May, p. 241) and by Drs. J. I. Mann and W. H. W. Inman (p. 245) confirming the association between the risk of myocardial infarction and taking combined oral contraceptive pills must cause prescribers to review their current practices. This work follows that of others.¹⁻³ It seems important that in women aged over 34 years with various predisposing risk factors, such as diabetes, obesity, heavy smoking, hypertension, and type II hyperlipidaemia, an alternative method of contraception should be recommended, as the effect of the combined oestrogen-progestogen pill is synergistic.

It may be argued that the risk of mortality or morbidity from pregnancy for such women if they use alternative methods far outweighs even the synergistic enhancement of risk from the combined pills. The confidential inquiry for 1967-9⁴ suggests that the mortality at 40 years of age is about 800 per million total pregnancies. The inherent fecundity at this age is probably reduced by

at least one-third from that of women of 25, so a less apparently effective method of contraception such as a barrier or intrauterine device may give enough protection to reduce the mortality risk below that from taking the pill. An ideal solution would be to use a less effective method with early abortion in case of failure, provided the woman would find this policy acceptable. Alternatively sterilization might be best. Vasectomy under local anaesthesia, which carries virtually no mortality risk, seems to offer a good alternative.

The problem may be numerically small. In the King's College Hospital clinic out of 6534 registrations only 103 (1.6%) were pill acceptors over 34 at their first visit. These were only 4.2% of all pill acceptors. General practitioners may well be seeing more. In Kay's study³ 19% of pill acceptors were aged over 34. Unfortunately we have kept no routine records on smoking rates but many of the women were 70 kg or more in body weight. Other predisposing factors to acute myocardial infarction were rare. I should be very interested in the experiences of other prescribers and their views on future policy in the light of this evidence.—I am, etc.,

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- 1 Inman, W. H. W., and Vessey, M. P., *British Medical Journal*, 1968, 2, 193.
- 2 Oliver, M. F., *British Medical Journal*, 1970, 2, 210.
- 3 Kay, C. R., *Oral Contraceptives and Health*, p. 44. London, Pitman.
- 4 *Report on Confidential Enquiry into Maternal Deaths, 1967-1969*. London, H.M.S.O.

Clindamycin-associated Pseudomembranous Colitis

SIR.—We wish to report our recent experiences of two cases of clindamycin-associated pseudomembranous colitis. We feel that both cases emphasize important points in the management of this condition.

Both patients presented with sudden onset of profuse watery diarrhoea following an oral course of clindamycin. On admission, both were dehydrated, hypotensive, and prostrated. They had severe, cramp-like abdominal pain with generalized tenderness and distension of the abdomen. The bowel sounds were present but infrequent. There was associated leucocytosis in excess of $20 \times 10^9/l$ ($20\,000/mm^3$). Abdominal radiographs in both patients showed dilated colon with thickening of its walls. Sigmoidoscopic findings in both cases were typical, with creamy-yellow, raised plaques surrounded by hyperaemic inflamed mucosa.

Both patients were submitted to laparotomy because the clinical picture was that of an acute abdomen with profound shock and toxæmia. However, in both cases, straw-coloured ascites was found together with distended, boggy oedematous colon throughout its whole length. There did not appear to be lymph node enlargement. In the first case the abdomen was closed without any further surgical procedure. The patient subsequently had a protracted illness with severe diarrhoea, hypoproteinaemia, albuminuria, massive peripheral oedema, pleural effusions, and anaemia due to acute folic acid deficiency. After six weeks of supportive treatment and systemic steroids the patient started to improve and was discharged well. The second patient underwent total colectomy because of the profound toxæmia associated with dilated colon and pseudopolypoidosis on abdominal radiographs. This patient died shortly after operation from an acute myocardial infarction.

These two cases demonstrate the clinical problem of whether to operate on patients

presenting with the severe form of this illness, as described above. Surgery should be avoided,^{1,2} as the majority of cases described have improved with supportive treatment^{1,3} together with systemic and/or local steroids and more recently cholestyramine.⁴ A firm diagnosis can usually be made at sigmoidoscopy and rectal biopsy, thereby distinguishing it from acute ulcerative colitis, which the barium enema cannot do.⁵

Clindamycin-associated pseudomembranous colitis is now well described. Estimates of the incidence in patients taking this drug vary from 0.00001% to 10%.³ As this illness may be severe, protracted, and life-threatening we wish to make a plea that this antibiotic be used only for severe anaerobic infections such as bacteroides septicaemia. We feel that its activity against Gram-positive infections does not justify its use against these organisms as the drug of choice.—We are, etc.,

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¹ *British Medical Journal*, 1974, 4, 65.

² *Annals of Internal Medicine*, 1974, 81, 547.

³ Tedesco, F. J., Barton, R. W., and Alpers, D. H., *Annals of Internal Medicine*, 1974, 81, 429.

⁴ Burbidge, E. J., and Milligan, F. D., *Journal of the American Medical Association*, 1975, 231, 1157.

⁵ Shinkin, P. M., and Link, R. J., *British Journal of Radiology*, 1973, 46, 437.

Problems with Naloxone

SIR,—Naloxone is a recently available powerful narcotic antagonist. Its main advantage over similar drugs is that it has no C.N.S. depressant properties in high dosage, which enables large doses to be given to a patient when the exact dose of the narcotic previously administered is not known. When used to treat inpatients given narcotics for analgesia or during anaesthesia this drug is of great value. Problems can arise, however, when giving the drug in cases of self-administered narcotics, particularly in the casualty department.

Firstly, severe withdrawal symptoms may be precipitated by giving naloxone to narcotic addicts. Secondly, patients who arrive unconscious in casualty may become fully alert after receiving adequate dosage of naloxone. However, its duration of action is related to the quantity of narcotic taken, which is usually uncertain. Relapse into unconsciousness and the need for further treatment are always possible. Therefore all patients should be observed in hospital whatever their clinical state after primary treatment.

Because of the involvement of the police in such cases most patients made fully conscious by the narcotic antagonist request their discharge, often becoming very abusive. The medical officer is put in a difficult medicolegal position since not only is he unsure whether the patient will relapse into coma but also the normal discharge form could be held to have been signed while the patient was under the influence of drugs, and may be of doubtful legal worth.

Such unconscious patients would previously have been admitted to hospital and given supportive therapy. Many would have required intubation and ventilation. The introduction of this new drug may radically change the mode of treatment, but not with-

out providing complex medical, legal, and social problems of its own.—I am, etc.,

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Breast Cancer in Young Women

SIR,—Though, as you stated in your leading article (21 June, p. 649), breast cancer in premenopausal patients may carry the same prognosis as the postmenopausal disease, the two groups differ in one important way. Robbins and Berg¹ found that the risk of a second primary tumour in the contralateral breast in premenopausal patients was twice that in postmenopausal patients and 10 times the risk of a first primary in the breast in the general population. Similarly, for patients under the age of 45 years at the time of the first primary Veronesi² showed that tumours in the contralateral breast occurred 12 times more often than would be expected on the basis of rates of first primaries.

Among breast cancer patients registered at the Birmingham Regional Cancer Registry³ the risk of a second primary tumour in the contralateral breast was found to decrease with age at first primary (see fig.), ranging

from an 84-fold increase for those aged 20-24 years to a four-fold increase for those aged 40-44 years. Premenopausal patients (3773 women aged 20-44 years at first primary diagnosis) showed an overall increase of 5.6 times expectation, the maximum risk occurring two to three years after the first primary, but the constant three-fold increase between 10 and 24 years after first primary diagnosis is, perhaps, more important in this context.

Furthermore, we have found that the premenopausal breast cancer patient has a three-fold increase in incidence of subsequent primary tumours of the ovary. Whether post-mastectomy pregnancy would enhance or reduce this risk has not yet been evaluated.

In advising the young breast cancer patient it should also be borne in mind that Anderson⁴ reported that premenopausal women with breast cancer and a family history of the disease have an incidence of bilateral tumours as high as 15.5%. Lynch,⁵ also, found a high incidence of breast and

ovarian cancer in three families. Thus not only are premenopausal breast cancer patients at high risk for a second tumour but their female offspring may be more susceptible to early breast cancer.

We acknowledge the support of the Cancer Research Campaign for the survey of multiple primary tumours.

—We are, etc.,

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¹ Robbins, G. F., and Berg, J. W., *Cancer*, 1964, 17, 1501.

² Veronesi, U., et al., in *Proceedings of the 5th Perugia International Conference on Cancer*, 1974, ed. L. Severi. University of Perugia, Division of Cancer Research.

³ Waterhouse, J. A. H., and Prior, M. P. In preparation.

⁴ Anderson, D. E., *Cancer*, 1971, 28, 1500.

⁵ Lynch, H. T., and Krush, A. J., *Surgery, Gynecology and Obstetrics*, 1971, 133, 644.

Frusemide-induced Pancreatitis

SIR,—We have read the interesting paper by Dr. P. E. Jones and Dr. M. H. Delbaum on Frusemide-induced Pancreatitis. Some 400 patients are admitted to our coronary care unit each year with acute myocardial infarction. We are aware of acute pancreatitis in the differential diagnosis of precordial pain, because pancreatitis may mimic myocardial infarction in the site of the pain and in E.C.G. changes, but we had not previously seen this disease in vivo or at necropsy in our patients with heart disease. In the last few months, however, we have seen the following two cases.

(1) A 53-year-old woman was admitted with a one-year history of dyspnoea and a feeling of oppression. She had congestive heart failure, low blood pressure, and renal insufficiency. A systolic murmur was heard at the apex. She was mentally slow. The patient was treated with increasing doses of frusemide up to 1000 mg/day; digoxin; phenprocoumon; and, for a short period, metaraminol, and hydrocortisone. An attack of ventricular fibrillation due to hypokalaemia was treated with D.C.-conversion. She improved but complained of abdominal distension and epigastric pain for 24 hours. This subsided gradually during the following week. After 18 days the patient suddenly died. Necropsy showed a hypertrophic heart with dispersed fibrosis but no infarction scars. There were no infarcts in the lungs or occlusions of pulmonary arteries. A small non-bleeding gastric ulcer was found, and the pancreas was acutely inflamed.

(2) A 72-year-old woman with a history of angina pectoris for three years was admitted with an acute myocardial infarction. The patient developed cardiogenic shock and died three days later. She was treated with frusemide up to 240 mg/day, digoxin, and an anticoagulant. Necropsy showed an old and a fresh infarct in the myocardium. There were gallstones but no signs of cholecystitis. The pancreas was acutely inflamed with necrosis and haemorrhages.

These two patients are the first we have seen with serious cardiac disease and acute pancreatitis. Both were treated with frusemide, but we cannot state that it was the cause of pancreatitis. It might have been coincidence, but we shall now be aware of the possibility of pancreatitis after frusemide in high doses in patients with severe heart disease.—I am, etc.,

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