In conclusion, in 17 patients with advanced bronchial carcinoma we have failed to confirm the optimistic results described by Price and Goldie in their preliminary report.—I am, etc.,

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¹ Price, L. A., and Goldie, J. H., *British Medical Journal*, 1971, 4, 336.

Chemotherapy of Candidiasis

SIR,—The paper on "Relevance of Antigenicity of *Candida albicans* Growth Phases to Diagnosis of Systemic Candidiasis," by Mr. E. G. V. Evans and others (13 October, p. 86) is most timely indeed, not only because of the increasing frequency of iatrogenic systemic candidiasis, as stated in the paper, but even more so since several promising antifungal agents have become available.

We have had the opportunity to use an injectable solution of miconazole, one such agent, which was made available to us for investigational use. Miconazole, 1-[2, 4-dichloro- β -(2, 4-dichlorobenzoyloxy) phenethyl] imidazole, is a synthetic chemotherapeutic agent which is active against most pathogenic fungi, yeasts, and Gram-positive bacteria.¹ Miconazole has proved its therapeutic usefulness in dermatomycosis² and vaginal candidiasis.³

We have used miconazole in 14 patients with systemic candidiasis proved by positive bronchial sputum, urine, or blood culture. Treatment was successful in all at the dose of 200-400 mg thrice daily for 5-30 days given intravenously or occasionally, as indicated by the primary site of the infection, also by such routes as direct instillation into the trachea, bladder, or renal pelvis. Treatment must be continued until the relevant cultures have become completely negative. The most striking advantage of miconazole has been its excellent local tolerance and the absence of renal, liver, or blood toxicity.

We also treated seven cancer patients with a persistent fever of unknown origin which was resistant to broad-spectrum antibiotics, on the assumption that the fever could have been due to candida infection though blood cultures were negative. Necropsy on such patients may reveal nidi of candida infection which could not be demonstrated during life.⁴ Miconazole given intravenously at a dose of 600 mg per day made five of the seven patients subfebrile within three days, but even prolonged treatment did not change the febrile state of the other two patients.

Clearly for this category of patients accurate and fast diagnosis of candidiasis would be most desirable since effective therapy could then be started immediately.—We are, etc.,

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- ¹ Van Cutsem, J. M., and Thienpont, D., *Chemotherapy*, 1972, 17, 392.
- ² Brugnans, J., Van Cutsem, J. M., Thienpont, D., *Archives of Dermatology*, 1970, 102, 428.
- ³ Godts, P., Vermeylen, P., and Van Cutsem, J. M., *Arzneimittel-Forschung*, 1971, 21, 256.
- ⁴ Taschdjian, C. L., Kozinn, P. J., and Toni, E. F., *Annals of the New York Academy of Sciences*, 1970, 174, 606.

Pyomyositis in London

SIR,—I would agree with Dr. P. E. T. Isaac's view (27 October, p. 235) that the interesting case of gluteal abscess described by Dr. D. W. Rogers (29 September, p. 679) falls into a different category from that of tropical pyomyositis. Denial by the patient is no guarantee that there has been no recent injection in this site, the lapse of memory being sometimes genuine and sometimes—for a variety of reasons—feigned. Tropical pyomyositis, first described by Scott in the West Indies in 1912,¹ has been reported with such frequency since then from areas confined to the tropical belt which encircles the world, that it must surely be associated with some common factor (such as parasites) encountered in these areas.

However, I would disagree with Dr. Isaac's assertion that the lesions of tropical pyomyositis are always multiple. Buxton, in his classic monograph on the disease,² did not make this distinction. In a personal series of 65 cases reported from Nigeria^{3,4} there were 55 single abscesses, while in only 10 cases were three multiple abscesses.

In this series nematode larvae in large numbers were demonstrated in the pus from intramuscular abscesses. The following aetiological hypothesis was advanced: (1) From initial nematode infestation (ancylostoma, dracunculus, etc.) shoals of larvae migrating through the systemic circulation break out through capillaries to be deposited in skeletal muscle, causing a local allergic inflammation (tropical myositis) similar to that which occurs in visceral larva migrans or in ascarid pneumonitis. (2) Subsequent autogenous infection of the lesion—for example, by staphylococci—would produce pyomyositis. These abscesses therefore differ from those caused by adult worms (such as *Dracunculus medinensis* or filaria), which inhabit subcutaneous planes or lymphatics.

Nematode infestations of differing varieties are heavy in all areas in which tropical pyomyositis is endemic. Numerous attempts have been made before and since the above hypothesis was advanced to explain the aetiology of this disease, but no other offers a factor which is common to every area in which tropical pyomyositis is endemic.—I am, etc.,

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- ¹ Scott, H. H., *Journal of Tropical Medicine and Hygiene*, 1912, 15, 97.
- ² Buxton, P. G., *Researches in Polynesia*, Memoir No. 2, London School of Hygiene and Tropical Medicine, 1928.
- ³ O'Brien, D. D., *Journal of the Royal Army Medical Corps*, 1963, 109, 43.
- ⁴ O'Brien, D. D., *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1963, 57, 313.

Nicotine Availability as a Factor in Tobacco Consumption

SIR,—Dr. M. A. H. Russell and others (1 December, p. 512) suggest that a cigarette

could be less harmful if it had "a low tar and carbon monoxide yield but a high, rather than low, nicotine yield." The high correlation between the tar and nicotine yields of cigarettes in the current "league table" precludes the likelihood of such a cigarette being obtainable.

However, there do exist cigarettes in which the nicotine availability is potentially high though the tar content remains relatively low. Nicotine is absorbed more readily in the form of a free base, as it exists in an alkaline smoke, than in the form of a stable salt, as it would be in an acid smoke.¹ English cigarettes, which are made of flue-cured tobacco of high sugar content, give rise to an acid smoke (about pH 4). It has been pointed out by Elson and Betts² that "in the smoke of 'reduced tar and nicotine' cigarettes made of high sugar tobacco not only is the nicotine low but its 'pharmacological availability' is also low because of the progressive increase in acidity during smoking. Is there not some danger therefore that the smoker of these cigarettes, in order to achieve his 'nicotine satisfaction' will smoke more, or, what is perhaps more serious, will increase his tendency to inhale?"

In contrast to this the smoke of cigarettes made mainly from air-cured low sugar content tobacco such as those popular in France and other European countries, and of cigars, becomes progressively more alkaline (to pH 8 or 9) during the course of smoking. Thus "nicotine satisfaction" should be achieved in smoking of fewer cigarettes and with less tendency to inhale. The annual cigarette consumption per head in France over the years 1930 to 1965 averaged about 900, while in the United Kingdom it was over 2,000. The death rate from cancer of the lung, bronchus, and trachea in France is less than half that in England and Wales.

The inference would seem to be that for compulsive smokers an indication toward less harmful smoking lies in the direction of decreased tar and nicotine content of the smoke together with a reduced acidity, so that a reasonable degree of "nicotine satisfaction" can be achieved with minimum lung cancer risk from inhalation of carcinogenic³ tar. Reduced acidity of the smoke can be achieved by replacing part, at any rate, of the flue-cured tobacco by air-cured tobacco of low sugar content or by the synthetic "substitute smoking materials" now being developed, which presumably contain no sugar or nicotine. With the latter however, a sufficient degree of alkalinity of the smoke may not be achieved. A further or additional possibility^{1,2} is the use of tobacco additives which give rise to an alkaline vapour at the usual temperature of combustion of cigarettes.—I am, etc.,

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- ¹ Elson, L. A., Betts, T. E., and Passey, R. D., *International Journal of Cancer*, 1972, 9, 666.
- ² Elson, L. A., and Betts, T. E., *Journal of the National Cancer Institute*, 1972, 48, 1885.

Co-trimoxazole Resistance

SIR,—The occurrence of mutants lacking in thymine (thy) has been recently described^{1,2} and led Dr. R. W. Lacey and Mrs. Evelyn L. Lewis (20 October, p. 165) to the assumption that significant quantities of thymidine are present in body tissues and that therefore

co-trimoxazole has only a bacteriostatic action—as was observed in their own experiments.

Both their experiments and their conclusions can, however, be criticized from several points of view. A bactericidal action cannot be determined in the liquid medium used by these authors (Oxoid nutrient broth no. 2), presumably because it contains thymidine, as do a variety of commercially available media.³ The bactericidal efficacy of co-trimoxazole is inseparably connected with the available thymidine (and thymine) concentrations. Though there are only a few data published on the thymidine content of human tissues and fluids we should nevertheless like to draw some conclusions from our present knowledge.

In recent experiments with *Escherichia coli* we found that the addition of 0.05 µg/ml thymidine prevents a bactericidal effect of co-trimoxazole in human blood and urine. Thymine is 10 to 100 times less effective. Microbiological determinations showed that thymine and thymidine concentrations are below 0.1 and 0.05 µg/ml respectively in the blood and urine from healthy persons—quantities insufficient to antagonize a bactericidal effect. This is in accordance with the opinion of other investigators, who have found that thymidine concentrations in mammalian tissues are extremely low,^{4,5} a fact which is further supported by the well known very short half-life of administered ³H-thymidine.⁶ The possibility remains, however, that these conditions change during infections.

Treatment of bacteria with aminopterin or trimethoprim is a widely used selective technique for the isolation of thy⁻ mutants, which are frequently obtained in the presence of thymine.⁷ This is, however, exactly what one would expect to occur under treatment with co-trimoxazole, assuming that thymidine is present. Thy⁻ mutants should develop very rapidly and lead to an appreciable number of clinical failures. This sequence, however, has not been observed and until recently the occurrence of such mutants has not been reported in spite of the widespread use of the drug for several years.

The observation that only wild type strains were isolated after withdrawal of co-trimoxazole in those few cases where co-trimoxazole resistant thy⁻ mutants appeared² underlines our assumption that thy⁻ strains do not normally survive in vivo. Though Okubadejo and Maskell² did not recover any such mutants. Such isolates, however, would than 100 patients under long-term therapy with co-trimoxazole, it may be expected that the isolation of thymine auxotrophs during co-trimoxazole treatment may occur more frequently in the future, if one looks for such mutants. Such isolates, however, would not necessarily mean co-trimoxazole-resistance or therapy failure.

The selection of thy⁻ mutants in vivo which are able to survive and are due to the use of co-trimoxazole is obviously a rare event of little importance for clinical therapy, even if one assumes that many of these mutants may have been overlooked in the past¹ owing to their atypical growth characteristics. This is in accordance with the remarkably low rate of co-trimoxazole-resistance^{8,9} and the constant high efficacy of this drug in clinical use. The incidence of drug failures due to such occurrences is

therefore not expected to increase in the future.—We are, etc.,

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- 1 Barker, J., Healing, D., and Hutchison, J. P. G., *Journal of Clinical Pathology*, 1972, 25, 1086.
- 2 Okubadejo, O. A., and Maskell, R. M., *Journal of General Microbiology*, 1973, 77, 533.
- 3 Koch, A. E., and Burchall, J. J., *Applied Microbiology*, 1971, 22, 812.
- 4 Cleaver, J. E., in *Frontiers of Biology*, ed. A. Neuberger and E. L. Tatum, vol. 6, p. 60. Amsterdam, North Holland Publishing Company, 1967.
- 5 Jaffe, J. J., McCormack, J. J., and Meymarian, E., *Biochemical Pharmacology*, 1972, 21, 719.
- 6 Rubini, J. R., Cronkite, E. P., Bond, V. P., and Fliedner, T. M., *Journal of Clinical Investigation*, 1960, 39, 909.
- 7 Bertino, J. B., and Stacey, K. A., *Biochemical Journal*, 1966, 101, 32c.
- 8 Fruensgaard, K., and Korner, B., *Chemotherapy*, in press.
- 9 Pacaud, G., Grosset, J., and Bismuth, R., in press. *Médecine et Maladies infectieuses*, 1973, 3-7, 293.

Battered Children

SIR,—It is disturbing that in the eight issues following your leading article on battering (13 October, p. 61), only one correspondent (24 November, p. 493) has queried your statement that the family doctor's first duty is to refer a child to hospital in case of suspicion.

There may be a moment in time when the disturbed people who act out their personal difficulties in this violent fashion recognize that they need help. It is just possible that by contacting a sympathetic and non-judgemental counsellor at this critical moment they can be reached and helped more meaningfully in terms of the total problem than by referral to another institution or one of the authoritarian agencies. One never knows when tragedy has been avoided.

One will always wonder which alternative could have provided the greater good to the greatest number. Hard and fast rules have no place in the management of this difficult problem.—I am, etc.,

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The Dog in Our Midst

SIR,—At long last Dr. O. A. Borg and Professor A. W. Woodruff have provided us with alarming evidence that the dog may not be man's best friend but a reservoir of infection causing blindness and at times death to his master (24 November, p. 470). Their paper, reporting that about one-quarter of soil samples from public places in Britain contained the ova of toxocara and that all incubated samples produced viable embryos, gives rise to deep concern about our prevalent attitude towards dogs. Perhaps the most horrifying aspect is that the vast amount of contamination is not on soil, where it can be presumed that some of the faecal organisms are destroyed by soil bacteria, but on the large impervious surfaces of our roads and pavements, remaining for considerable periods in dry weather.

Every year we spend millions on sanitation, hygiene, and drinking water, pass laws to deal with pollution in rivers, air, and food, and demand that noise should be controlled and streets kept free of litter. The sacred dog is allowed to foul at his leisure so that we are exposed to all types of infestation, hydatidosis, tuberculosis, leptospirosis, and salmonellosis to say nothing of the possibilities of viral infection. Surely the time has now arrived when we should demand better legislation to protect us from man's best friend.—I am, etc.,

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Points from Letters

Medical Immigration

Dr. M. M. HASAN (Member, Executive Committee, Redbridge Stratford Division, B.M.A.) writes: The letter from Dr. J. N. Docherty (22 December, p. 735) on the above subject cannot be allowed to go unchallenged, especially when he has used his position as Press Secretary of a B.M.A. Division. These uninformed comments with a racial flavour have become almost a fashion recently. He says in essence that a loss of 2,000 British doctors during the last five years is solely due to poor pay and this is because the "politicians" can obtain "cheap" and "ill-trained" foreign graduates to cover up the vacuum. How dare the G.M.C. accord registration to these inferiors?

Let us be clear about the identity of the unfortunate men and women to whom he refers, who are not Irish or Continentals but are mainly drawn from the countries of the Indian subcontinent. It is a slur to the good name of these countries. May I ask what personal experience Dr. Docherty has of the training methods that obtain in these foreign universities? . . .

Dr. K. RAGHAVAN (Edinburgh) writes: I

read with deep regret the letter from Dr. J. N. Docherty (22 December, p. 735) . . . If British doctors need more pay, let them fight it out in a rational and honourable way, without slandering foreign medical graduates. I hate to imagine what would happen to the National Health Service if it were not for the services of these same doctors, whom he calls "cheap" and "ill-trained". While I admit that all foreign doctors may not be highly educated, so also all British doctors are not brilliant. For every good British doctor, there is one equally good foreign doctor. I hope Dr. Docherty can back up his statement with facts and figures, since it is going to lose the goodwill of many foreign doctors in Britain.

As for the E.C.F.M.G. examination, I know of many doctors, including myself, who took this entrance examination to the United States and yet decided to come to Britain for academic reasons. The passing of this examination is no criterion whereby to judge the professional ability of a doctor. I also know of many doctors who went to the States after serving in the National Health Service, and not without some regret. . . .