immigrating to England does not seem to increase their risk of MS." I submit that the data presented do not speak to the question of the same versus a higher risk among such immigrants. At face value they would indicate only that there are notably fewer such patients admitted to hospital than expected for native Britons. Whether this reflects more than or the same number affected as if they had stayed at home is not definable.

But even the question as to the numbers observed in relation to those expected is not well satisfied here, in my opinion. I really doubt if crossing the Irish Sea alters appreciably one's chances of having MS, and yet only 168 such patients were ascertained while 225 were expected. Whether this represents input bias or an inappropriate expected number (or both) is undefined. If this be so for the Irish, how much more might this be true of the "new Commonwealth" immigrants? (As an aside, for the colonies at least, definition of specific countries incorporated into the New Britannia would have been helpful.)

The use of a 1971 age distribution for 1966 immigrants may well be questioned because of the drastic increase in numbers, there being over twice as many immigrants in 1971 as in 1961. There is a more important aspect to this increase, however. New Commonwealth immigrants to England from Asia numbered 270 000 in 1961 and 618 000 in 1971; from Africa 43 000 and 158 000 respectively. Thus, one would expect that the *majority* of such immigrants had been in England less than five years. This raises the practical problem of expectations (by age and sex) from 13 years of hospital admissions versus those from five years or so. This is not completely refuted by limitation to "first admissions of newly diagnosed cases." Some correction perhaps should have been employed for person-years of exposure to the chance of admission.

In terms of the disease itself the rapid increase in the population at risk poses yet other and more important problems. Is five years or so a sufficient period to express an increased risk of MS, as must have been the case for more than half the series? Further, is "exposure" from age 50 to 54 or from age 5 to 9 meaningful in terms of MS? Also, can lifetime "exposure" among the British be equated with shorter "exposure" among immigrants? The question of risk of MS in migrant populations gets very involved, being dependent not only on a sufficiency of people who change their residence from one risk area to another but also on their ages at immigration, their length of stay in the new land, *and* their ages at prevalence day. It is only to this last point that the expectations of Dr Dean and his colleagues are really addressed. Another problem further to confound the issue is the apparent racial predilection for MS, regardless of geography: MS seems the white man's burden.[1]

There is evidence from mortality data that moving from low-risk to high-risk MS regions does increase the risk of dying from MS.[2] Unpublished data from a large series of US veterans with MS versus military controls also support the concept of an increased risk of MS among southern-born who moved north before entry into service. We have also some information to the same effect from an unfortunately small cohort of Vietnamese who moved to France. However, these works too cannot be taken as definitive, and the question of the fate of migrants from low- to high-risk areas in terms of MS, I believe, perhaps still warrants the Scottish verdict of "not proven."

The study of Dr Dean and his colleagues is indeed a formidable one. Certainly the massive deficit of cases found does not *seem* readily explicable merely by input bias. There may be further gold to be mined therein. One simple approach would be to look only at the numerator data and to compare immigrants from the varying risk area, but according to age at immigration versus age of onset and age and calendar year of London diagnosis plus race. Distributions of the denominator by age and calendar year of immigration, by country, would also be informative.

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[1] Kurtzke, J F, *Acta Neurologica Scandinavica*, 1975, **51**, 137.
[2] Kurtzke, J F, *et al*, *Neurology*, 1971, **21**, 1186.

******As we understand it, the "new Commonwealth" consists of those countries of the old British Empire, too numerous to detail, that have achieved independence since 1945 and have remained within the Commonwealth. —ED, *BMJ*.

Folate-responsive neuropathy

SIR,—Two challenging propositions are put forth in the article by Drs M Manzoor and J Runcie (15 May, p 1176). They contend that folate deficiency causes a specific neurological disorder "clinically indistinguishable from subacute combined degeneration of the spinal cord" and that folic acid therapy reverses the neuropathy. If proved, then these observations would offer an important opportunity in the management of otherwise intractably disabled patients. Unfortunately, the hypotheses have not been rigorously tested and require more evidence before acceptance.

The 10 patients recorded were considered to be folate deficient on the results of the activity of *Lactobacillus casei* stimulated by their serum. In none was bone marrow aspiration recorded and only five had a macrocytic anaemia. No comment was made about the possible effect of antibacterial therapy on the microbiological assay system. No results are presented for red cell folate assay, and this more reliable test is surely essential if serious disease is to be attributed to chronic folate deficiency.

It could easily be that inadequate nutrition was secondary to the immobility described. If conclusions are to be drawn about the causative role of folate deficiency in severe neuropathy, then a minimum requirement should be estimation of serum and red cell folate activity in a matched group with comparably severe disability of known aetiology, such as Parkinson's disease.

The conclusion that therapy with folic acid lessened the observed neuropathy could be sustained only by a double-blind controlled trial against placebo. It is exceptionally difficult to single out one facet of medical care as being of overriding importance. It would be regrettable if geriatricians influenced by this article relaxed the effort to remobilise patients because of undue reliance on vitamin therapy of unproved benefit.

It hardly needs restating that folic acid therapy in undiagnosed vitamin B_{12} deficiency is potentially disastrous.

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******We sent a copy of this letter to Drs Manzoor and Runcie, whose reply is printed below. —ED, *BMJ*.

SIR,—We are grateful to Dr Bateson for his letter. The views contained therein encapsulate those clinical attitudes which we are anxious to challenge. The definition of folate deficiency states is difficult and at present imprecise. The validity of a low serum folate level is not in question, but rather the interpretation of its clinical significance. In a confused patient with red cell macrocytosis and a florid neuropathy, in our view, little clinical acumen is required to decide this. An important rider in patients with very low serum folate values is the effect of recent antibiotic therapy on this. None of our patients were so treated for at least 10 days prior to folate measurement.

The reference to immobility we find puzzling. The neuropathy we described is not a feature of severe, completely immobilising stroke, for example. Furthermore, intensive physiotherapy in our patients in the absence of concurrent folate administration is without value.

There is no place for the superficially attractive double-blind trial of folate against placebo in a neurological disorder which takes many months and possibly some years to develop and during which increasing and perhaps irreparable damage to the nervous system occurs.

We would agree wholeheartedly that the indiscriminate use of folate in obscure neurological disease is indefensible. This danger is completely avoided by measuring the serum B_{12} and folate levels together and never singly. The use of folate in such circumstances when the serum B_{12} is known to be normal is quite different and a clinical trial of such is eminently justifiable.

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Vaginal candidosis

SIR,—In your leading article on this subject (14 February, p 357) it is stated that "there is no evidence that the fungus [*Candida albicans*] develops any resistance to antifungal agents (with the one exception of amphotericin)." As manufacturers of amphotericin we are interested in this last comment since, according to our records and published evidence, we know of no substantiated clinical reports of resistance to the drug.

The early in-vitro studies of Littman *et al*[1] failed to demonstrate resistance to amphotericin in the strains of *C albicans* tested; and Athar and Winner[2] tested some 2015 clinical isolates of candida and found none naturally resistant. It was possible to produce in-vitro resistance by numerous passages, but in such cases the degree of pathogenicity was greatly reduced.[2-5] As Hamilton-Miller[3] stated as recently as 1974, "Allowing for the well-known

phenomenon of inter-laboratory variation in MICs, there is no published evidence which suggests that yeasts isolated in the late 1950s are more sensitive than those isolated in the 1970s. Thus, there seems to be no firm indication that the basic premise involved here, that polyene-resistant fungi have not emerged, is false, and indeed there seems every reason to suppose it to be true." From a clinical point of view Stieritz *et al*[6] found that no resistance occurred when amphotericin was given systemically.

With this lack of evidence that resistance occurs we made available oral and topical amphotericin in 1970. Since at that time amphotericin was the only drug available for systemic use we would clearly not have developed other forms if we had known that resistant strains could develop.

I would be grateful therefore if you could let us have the substantiated evidence that resistance occurs to amphotericin. While it is known that resistance may occur to 5 fluorocytosine (another systemic antifungal agent in use), to our knowledge this has not been the case with amphotericin.

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[1] Littman, M L, *et al*, *Antibiotics Annual*, 1957-1958, p 981.
[2] Athar, M A, and Winner, H I, *Journal of Medical Microbiology*, 1971, **4**, 505.
[3] Hamilton-Miller, J M T, *Microbios*, 1974, **10A**, 91.
[4] Hebeka, E K, and Solotorovsky, M, *Journal of Bacteriology*, 1965, **89**, 1533.
[5] Hamilton-Miller, J M T, *Bacteriological Reviews*, 1973, **37**, 166.
[6] Stieritz, D D, *et al*, *Journal of Clinical Pathology*, 1973, **26**, 405.

SIR,—Your leading article (14 February, p 357) summarises clearly the present position on vaginal candidosis.

However, it is incorrect to say that candidosis is quite frequently associated with trichomoniasis and I cannot understand why this myth is perpetuated. Four recent studies of patients with candidosis and trichomoniasis[1-4] have shown that patients with trichomoniasis also had candidosis in only 5·6—15% of cases (mean 12%) and patients with candidosis also had trichomoniasis in only 2·2—10% of cases (mean 4·3%). Such low incidences cannot be described as frequent and there is no justification for the common practice of routinely prescribing proprietary drug combinations effective against both conditions simultaneously.

Your article also states that candida develop resistance to amphotericin. Can this be substantiated by some references please? I have prescribed amphotericin for several years with excellent results and none of my colleagues have experienced resistance developing. The only other mentions of this possibility that I have found are in two recent book reviews which also unfortunately fail to give any sources.[5-6] In fact, the infrequency of resistant strains of fungi susceptible to amphotericin B has recently been mentioned in a review of chemotherapy in the systemic mycoses.[7]

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[1] Oriel, J D, *et al*, *British Medical Journal*, 1972, **4**, 761.
[2] Cassie, R, and Stevenson, A, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1973, **80**, 48.
[3] Hurley, R, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1973, **80**, 252.
[4] Sparks, R A, *et al*, *British Journal of Venereal Diseases*, 1975, **51**, 110.
[5] Dunlop, E M C, *British Journal of Hospital Medicine*, 1975, **14**, 326.
[6] Dunlop, E M C, *British Journal of Venereal Diseases*, 1976, **52**, 66.
[7] Utz, J P, *British Journal of Hospital Medicine*, 1976, **15**, 112.

****The occurrence together of candidosis and trichomoniasis varies greatly in different series in different countries. The frequency of both infections is probably related to sexual habits, social class, promiscuity, and the overall incidence of infection in the community concerned.[1-3] The importance of these associations of disease is that when a patient is investigated for genitourinary symptoms tests for candida, trichomonas, gonococci, and other genital pathogens should always be carried out as otherwise infections will be missed.

Candida albicans and a variety of other fungi show a decline in sensitivity to amphotericin B when exposed to the drug and, of a wide variety of mycoses, *C albicans* is among the species with lower sensitivities to the drug.[4] As amphotericin B is one of the few effective systemic antifungal agents, the majority of those experienced in the treatment of the systemic mycoses think that it should be reserved for systemic use, particularly as there are many alternatives equally effective for topical use. Naturally, resistance to amphotericin B is comparatively rare, but resistance may be induced by means of amphotericin whereas such resistance cannot be induced with nystatin. Drouhet[5] has reported a case of endocarditis in which resistance developed to amphotericin B.

There is general agreement that amphotericin B should not be used as the first treatment of genital candidosis as this might lead to the selective breeding of rare strains naturally resistant to amphotericin quite apart from the question of acquired resistance. Such a development would lessen the efficacy of amphotericin B in the treatment of systemic candidosis, which is often threatening to life.
—ED, *BMJ*

[1] Pace, H R, and Schartz, S I, *Journal of the American Medical Association*, 1956, **162**, 268.
[2] Hurley, R, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1963, **80**, 252.
[3] Beveridge, M M, *British Journal of Venereal Diseases*, 1962, **38**, 220.
[4] Csonka, G W, *British Journal of Venereal Diseases*, 1967, **43**, 210.
[5] Drouhet, E, *Modern Treatment*, 1970, **7**, 539.

SIR,—With reference to your leading article on this subject (14 February, p 357) I disagree with your concluding sentence on two counts: firstly, on the comparison with oral metronidazole; and, secondly, on the assumption that systemic antifungal therapy will be any better than local treatment of vaginal candidosis.

Oral metronidazole is highly effective in the treatment of trichomoniasis as this is a genitourinary infection and therefore any treatment confined solely to the genital tract is likely to be associated with a high relapse rate. There is no evidence, on the contrary, that vaginal candidosis is any more than a local infection, although surveys[1-3] have suggested a correlation with rectal candidosis. Which causes which, if either, is not clear. There is no evidence that treatment designed to reduce rectal candidosis is itself associated with a reduction in the relapse rate of vaginal candidosis. Systemic antifungal therapy has been tried[4] without significant improvement over local therapy alone. Local antifungal drugs currently in use are effective in eradicating candida from the vagina. Resistance to these drugs, as you state, does not develop (amphotericin B excepted). Therefore the tendency of some patients to have recurrent episodes of vaginal candidosis is more likely to be due to a local susceptibility of the patient to candida infection than to failure of local therapy. If this is true, then one would not expect systemic antifungal therapy to have any advantage over local antifungal therapy. What is required is clarification of the patient's altered susceptibility to candida infection and treatment designed to correct the imbalance and thus permanently prevent recurrence.

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[1] Hilton, A L, and Warnock, D W, *British Journal of Obstetrics and Gynaecology*, 1975, **82**, 922.
[2] Sousa, H M, and Uden, N, *American Journal of Obstetrics and Gynecology*, 1960, **80**, 1095.
[3] Sonck, C E, and Somersalo, O, *Archives of Dermatology*, 1963, **88**, 846.
[4] Hirsch, H A, and Dedes, M, *Postgraduate Medical Journal*, 1974, **50**, suppl 1, p 83.

SIR,—Your leading article (14 February, p 357) suggests that vaginal candidosis is essentially a venereal infection.

However, in many cases of primary or recurrent vaginal candidosis there has been no previous sexual contact. Moreover, women who are treated for vaginal candidosis are cured in most cases by local measures. In recurrent cases it is often necessary to treat also the mouth and the digestive tract of the patient, and rarely the mouth and the digestive tract of the male partner.[1 2] On the other hand it is rare to find an asymptomatic male partner carrying *Candida albicans* in the urethra.[3]

In a series of patients (to be published) it was found that oral treatment with 5-fluorocytosine in resistant cases of recurrent vaginal candidosis is effective when the patient only is treated, and the disease is generally eradicated without treating the patient's partner.

For all these reasons we believe that vaginal candidosis—in contradistinction to infection with *Trichomonas vaginalis*, *Haemophilus vaginalis*, mycoplasma, or chlamydia—is in nearly all instances a non-venereal infection of a "venereal organ."

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[1] Pumpianski, R, and Ganor, S, *Israel Journal of Medical Sciences*, 1968, **4**, 1268.
[2] Pumpianski, R, and Ganor, S, *Harefuah*, 1970, **79**, 311.
[3] King, A, and Nicol, C, *Venereal Diseases*. 2nd edn, p 223. London, Baillière, Tindall, and Cassell, 1969.

Fetal activity and fetal wellbeing

SIR,—I was pleased to see that Mr James F Pearson and Miss Judith B Weaver (29 May, p 1305) have evaluated quantitatively a symptom on which I have placed considerable reliance for several years—namely, diminishing fetal movements as a danger signal and, just as important, vigorous movements as a reassurance of wellbeing when other factors such as weight loss may be causing some anxiety. I have come to the conclusion that any vigorously kicking fetus will not die