does not form calcium complexes in bone-forming tissue. Brucellosis, also mentioned by Brock and Roach, is fortunately uncommon within the British Isles[3]; but co-trimoxazole,[4] either alone or in combination with streptomycin, offers highly effective chemotherapy.

In this vulnerable group of patients, if a tetracycline is thought to be obligatory, doxycycline would be the least toxic of the group, as its affinity for calcium has been shown to be less than that of the other tetracyclines.[5] However, even this agent is potentially dangerous in childhood and during pregnancy, and must be avoided if at all possible.

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Perspectives in spina bifida

SIR,—It is nice to know that my nephew (20 January, p 198) reads my letters in your columns but he should really read them more carefully. My letter (16 December, p 1717) was concerned only with your dubious arithmetic and I specifically disclaimed any knowledge of its application to falls in older spina bifida patients.

Dr Andrew Wright's arithmetic is no doubt sound but his physiology, I am afraid, is rather shaky. Falls from a stationary posture are seldom, if ever, due to muscular weakness because the muscles are only required to exert very small forces over very short distances (so-called "isometric" contractions) and thus exert very little power. Such falls are nearly always due to neuromuscular incoordination.

Adolescents, in any case, are more likely to fall during active movement and the cause is most probably having "outgrown their strength"—that is, grown taller and relatively thinner. This change of shape, of course, invalidates simple arithmetical calculations so perhaps we had better forget them.

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Polyunsaturated fatty acids and colchicine in multiple sclerosis

SIR,—The report by Dr D Bates and others (18 November, p 1390) on the inefficacy of polyunsaturated fatty acid (PUFA) treatment of acute remitting multiple sclerosis (MS) appears to be based on two premises, one admitted and the other covert. It is assumed (*a*) that PUFAs exert an immunosuppressive action, and for this they lean heavily on the short-term work in animals of Mertin and his colleagues; and (*b*) that immunosuppressive action will be exerted on an EAE (experimental allergic encephalitis)-like mechanism fundamental to the production of MS episodes—something for which hard evidence in this essentially human disease is, to say the least, in doubt.

Dr Bates and his colleagues are wrong in supposing that the immunosuppressive activity of PUFA in humans is anything but an acute transient effect. This we know from direct observation. Thus, Meyer-Rienecker *et al*[1] found that after six months' treatment with Naudicelle the lymphocytes of patients with MS reacted normally in the macrophage-electrophoretic-mobility linoleic-acid-depression (MEM-LAD) test. The same has been found in respect of the behaviour of red blood cells in the erythrocyte unsaturated fatty acid (E-UFA) test.[2] Collateral evidence of the limited short-term activity of Naudicelle comes from the work of McHugh *et al*,[3] who found the material of value in aiding suppression of kidney rejection only for the first six months after transplantation, the effect thereafter becoming non-significant. Clearly any result to be hoped for from PUFA cannot be based on immunosuppression over a two-year period. Bates *et al* may have been misled by the observation that γ-linolenate is about 8-10 times more active as an immunosuppressant in an acute in-vitro experiment than is linoleic acid (LA),[4] and the suggestion[2] that if in vivo activity parallels in vitro then γ-linolenate should be more effective than LA as a treatment for episodic MS. Unfortunately it is not so.

The abandoned hypothesis of long-term immunosuppression by LA or γ-linolenate in humans has been replaced by one of surface membrane changes derived from direct experimental findings in man. Treatment of patients with Naudicelle over five to six months leads to an alteration of the surface of lymphocytes[5] and of erythrocytes,[2] so that previously positive MS tests become negative. It has been postulated,[6] following Thompson's highly fruitful suggestion,[7 8] that the inborn error of UFA metabolism which underlies the anomaly of cell surface brought out in the MEM-LAD, prostaglandin E_2 (PGE_2), E-UFA, and TEEM (tanned erythrocyte electrophoretic mobility) tests may be corrected by exhibition of Naudicelle (2·664 g LA plus 413·4 mg γ-linolenate daily), not only for red blood cells and lymphocytes but also for oligodendrocytes, from whose surface membrane myelin is largely laid down. Such myelin will be abnormal.[7 8] Myelination is intensely active from mid-fetal life until the age of 5 years and continues until 16.[9] Thereafter indirect evidence (largely from animal studies) indicates that it may be produced (or at least some of its constituents turned over) for further decades.[10]

Familial studies[11] suggests that MS develops, whatever its cause or causes may ultimately turn out to be, in abnormal myelin. There may be no "cause" other than disintegration of poorly constituted myelin—that is, an "abiotrophy" in Gowers's sense. Detailed evidence and argument has been set out at length elsewhere.[12 13] If these hypotheses are correct, then the time when LA or γ-linolenate will be most effective is *before* myelin is laid down—that is, in early childhood. The young adult (15-20 years of age) is still laying down myelin with some measure of activity, so that treatment at this period might lead to at least outer myelin lamellae being stable; but at later ages (such as the mean age of 35±9 years in Bates's trial) not a great deal can be expected. Clearly the very early diagnosis of "candidates" for MS and institution of prophylactic treatment is an attractive way forward in dealing with MS. Prevention of a disease before any real knowledge of its nature is to hand is commonplace in history.

Dr D F Horrobin and his co-workers (20 January, p 199) are surely correct when they involve prostaglandins in the mode of action of γ-linolenate. Not only has PGE_2 a remarkably specific action on untreated MS erythrocyte membranes,[14] but prolonged treatment with γ-linolenate induces a striking sensitivity to PGE_2[2 5] akin to that found in normal children.[2]

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SIR,—We were interested in the results of the attempt by Dr D Bates and others (18 November, p 1390) to re-evaluate the possible role of essential fatty acids (EFAs) in multiple sclerosis (MS) at Newcastle. However, the design of the trial could lead to misinterpretation of the potential role of EFAs in the management of MS. It is generally agreed that the Belfast-London trials[1] suggested that linoleic acid may be beneficial and it is interesting that the Newcastle trial was suggestive in the same direction. But it was a pity that Naudicelle was incorporated into the Newcastle trial design at such a low level, and without dietary control.

Naudicelle contains γ-linolenic acid, which compared with linoleic acid is a more efficient precursor of the longer-chain fatty acid derivatives[2 3] that are incorporated into cell structural lipids, used in prostaglandin synthesis,[4] and involved in immune functions.[5] Naudicelle contains 8% of the total fatty acids as γ-linolenic acid. The MS group given this supplement were therefore receiving only 0·34 g of γ-linolenic acid (and 2·9 g of linoleic acid) compared with 23 g of linoleic acid in the group receiving the special margarine spread. For this dose of γ-linolenic acid to be comparable to the amount of linoleic acid used in the Belfast-London trial and the Newcastle trial, γ-linolenic acid would require to be about 70 times as potent as linoleic acid and there is no evidence that such a high activity relationship exists. At the most, γ-linolenic acid has been shown to be three times as active as linoleic acid in correcting signs of EFA-deficiency[6] and it is incorporated 10 times faster into cell structural lipids.[7 8]

Also, it was particularly unfortunate that the capsules used in the trial to provide the γ-linolenic acid contained the colouring agent tartrozine, which has been shown to inhibit prostaglandin synthesis.[9] It would be expected that prostaglandin inhibitors might abolish at least one of the potentially beneficial effects of EFA supplementation.

If there were to be another trial to examine the role of EFAs in the management of MS,