had no hyperacidic peptic ulceration. As regards the second patient, simply overseeing perforations leads to further surgery in 20% of cases in five years. This is extremely rarely required within two months.² The occurrence and timing of recurrence of ulceration in both cases strongly suggests that cimetidine treatment or its withdrawal was implicated.

When H₂-blockade of acid-secreting cells is withdrawn, it is more likely to lead to excessive sensitivity to normal stimuli than to hyperplasia.

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¹ Wychulis, A R, *et al*, in *Surgery, Gynaecology and Obstetrics*, 1966, 122, 89.

² Illingworth, C F S, *et al*, *British Medical Journal*, 1946, 1, 787.

SIR,—The discussion about cimetidine and duodenal ulcer by Dr J H Baron and others (20 January, p 169) has important implications for general practitioners as well as hospital-based specialists.

If, as is suggested, progressively more patients are being treated medically then the disease becomes one which should be treated in the primary care situation. There seems to be agreement that rapid relapse after one or more full courses of treatment warrants referral for surgery even if many patients would prefer the unknown risk of long-term drug therapy to the known risk of operation. What is not clear, in general practice, is which patients should be started on treatment. I, and some of my colleagues, felt initially that the criteria should be relatively rigid. All patients should have had a duodenal ulcer demonstrated radiologically or endoscopically or should have suffered a catastrophe such as haemorrhage or perforation in the past. This may lead to numbers of patients with classical symptoms being referred to outpatients for expensive, time-consuming, and unpleasant diagnostic procedures. If, as Mr J Alexander-Williams states, patients are being referred to him with a diagnosis of duodenal ulcer but with symptoms uncontrolled by cimetidine, and that this almost certainly indicates that the pain is due to something else, then surely we have in our hands a diagnostic weapon which can relieve hospitals and patients of a tiresome burden.

It could be argued that at least in the younger patient with upper abdominal pain a therapeutic trial of cimetidine for one week should be carried out as a first step in investigation. The same argument would hold for differential diagnosis of retrosternal pain when reflux was a consideration. My experience so far has suggested that the answers given by such a policy are helpful.

MICHAEL DRURY

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Colostrum deficiency

SIR,—I wonder if anybody has ever seen a baby die for want of colostrum. Only this week I saw five very agitated mothers who evidently thought that their might. One had respiratory distress and another a large cleft palate, and a third persistently vomited all his "unique maternal gift." The mother of the fourth had a complicated delivery and was herself unwell, while the fifth had inverted nipples and was unable to produce any colostrum or milk.

All worked themselves up into a frenzy because their babies had not had their "cholesterol" (sic), although all five babies are making excellent progress.

I am, of course, familiar with the multifarious properties of this substance but colostrum deficiency would appear to be a new iatrogenic disease of the maternal mind, springing from the same sources which are responsible for so much unnecessary anxiety today.

HERBERT BARRIE

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Age and death in breast carcinoma

SIR,—I was interested to read your leading article (27 January, p 211) on the above subject. During the last year before my retirement some 18 months ago, I decided to review all my cases of carcinoma of the breast, to see whether anything of interest might turn up. Despite the small number—about 400—this was a fairly mammoth task, and when it was finished I found that I had really nothing to offer, so did not publish. The survey, however, provided me with two surprises.

The first surprise was that, contrary to what one had always thought, age seemed to have little or no bearing on prognosis and old people seemed to fare no better—or worse—than youngsters. The second fact that emerged—not altogether a surprise—was that small local recurrences treated with subsequent surgery did not seem to prejudice the ultimate result. I was warmly surprised at the number of younger people, either with or without local recurrences, who were alive and well at the 10-year milestone, despite having had no radiotherapy or chemotherapy.

Do we sometimes err on the side of over-treatment, or is that the rationalisation of an old surgeon who is a little out of harmony with the modern young oncologist?

ROBIN BURKITT

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Premenstrual tension syndrome

SIR,—Your leading article on premenstrual tension syndrome (27 January, p 212) clearly documented the conflicting data relating to the aetiology of this common problem with reports of both an increase and a decrease in plasma progesterone, oestradiol, prolactin, and aldosterone levels. However, you failed to mention the obvious conclusion that whatever the details of the hormone imbalance, and no doubt they vary from case to case, the ultimate cause of premenstrual tension must be a change in plasma hormone values from the time of ovulation.

The symptoms for this common condition can usually be relieved by ablating these hormone changes. This can be done simply by the combined oestrogen-progestogen birth control pill given continuously, thus avoiding ovulation and menstruation; a more successful method is the insertion of a 75 mg or 100 mg oestradiol implant into the fat of the abdominal wall. With this method endometrial hyperplasia is avoided by the administration of 5 mg norethisterone for five days each month. It is our experience that many of these implant patients who have their symp-

toms completely abolished by this technique will complain of their own characteristic premenstrual tension symptoms during one or two of the five days of the progestogen, suggesting the likely cause of the syndrome in many of these patients.

JOHN STUDD

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SIR,—One of the now well documented and accepted, yet still sadly neglected, causes of tension and depression in women is included under the blanket heading of the premenstrual syndrome. The possible aetiology is discussed in your excellent leading article (27 January, p 212).

At one time I was using intramuscular progesterone with success in the relief of these symptoms, although the method did not appear to be generally accepted.¹ It seemed that here was a logical form of treatment for a universal problem which had a more reliable physiological explanation than was generally considered at the time. If the endocrine basis of this very common problem can be shown to be the cause, then the prescription of any form of psychotropic medication is inappropriate.

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¹ Waxman, D, *British Medical Journal*, 1968, 4, 188.

SIR,—I am surprised that in your otherwise excellent leading article on premenstrual tension (27 January, p 212) you repeat the myth that progesterone therapy is "expensive." You cite a reference from that well-known journal *Current Medical Research and Opinion*¹ in support of this statement.

I hasten to say that I have no criticism of this particular paper, except that it repeats this strange claim (seen in the advertising literature of a rival product²) that progesterone is "expensive."

I have no axe to grind for either therapy, but I do think we should get our facts straight. I have recently put a number of women on progesterone suppositories—so to speak—and I took the precaution of finding out the cost first, using my trusty *MIMS*.

The truth is that one cycle's treatment with progesterone (Cyclogest suppositories) normally costs £4.20. One cycle's treatment with the rival synthetic progestational agent which you mention in your leader (dydrogesterone—Duphaston) costs £6.70. Which is more expensive?

DAVID DELVIN

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¹ Kerr, G D, *Current Medical Research and Opinion*, 1977, 4, suppl 4, p 29.

² Duphar Laboratories, *Duphaston in Premenstrual Syndrome*, p 12.

Tetracycline preparations for children

SIR,—I must take issue with Dr P G Brock and Maryanne Roach (13 January, p 126) over the use of tetracyclines in the management of infections in children and in pregnant women.

Tetracyclines are valuable drugs, but are never the sole effective agent for any given infection. Erythromycin is effective against the vast majority of strains of *Mycobacteria pneumoniae*,^{1,2} and, unlike the tetracyclines,

does not form calcium complexes in bone-forming tissue. Brucellosis, also mentioned by Brock and Roach, is fortunately uncommon within the British Isles³; 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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¹ Ogilvie, C M, *British Medical Journal*, 1978, 1, 771.

² Garrod, L P, Lampert, H P, and O'Grady, F, *Antibiotic and Chemotherapy*, p 384. Edinburgh, Churchill Livingstone, 1973.

³ *Lancet*, 1975, 1, 436.

⁴ Garrod, L P, Lampert, H P, and O'Grady, F, *Antibiotic and Chemotherapy*, p 321. Edinburgh, Churchill Livingstone, 1973.

⁵ Forti, G, and Benincori, C, *Lancet*, 1969, 1, 782.

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.

B M WRIGHT

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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 suggestion² 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 lymphocytes⁵ 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 E₂ (PGE₂), 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 studies¹¹ 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 $\pm$ 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 PGE₂ a remarkably specific action on untreated MS erythrocyte membranes,¹⁴ but prolonged treatment with γ -linolenate induces a striking sensitivity to PGE₂^{2,5} akin to that found in normal children.²

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¹ Meyer-Rienecker, H J, *et al*, *Lancet*, 1976, 2, 966.

² Field, E J, and Joyce, G, *European Neurology*, 1978, 17, 67.

³ McHugh, M I, *et al*, *Transplantation*, 1977, 24, 263.

⁴ Field, E J, and Shenton, B K, *Acta Neurologica Scandinavica*, 1975, 52, 121.

⁵ Field, E J, and Joyce, G, in *Harry Weaver Memorial MS Symposium*, p 197. Amsterdam, Bohn, Scheltena, and Holkema, 1977.

⁶ Field, E J, *Lancet*, 1978, 1, 780.

⁷ Thompson, R H S, *Proceedings of the Royal Society of Medicine*, 1966, 59, 269.

⁸ Thompson, R H S, *Biochemical Society Symposium*, 1973, suppl 35, p 103.

⁹ Yakovlev, P I, and Lecours, A R, *The Myelogenetic Cycles of Regional Maturation in the Brain*. Oxford, Blackwell, 1967.

¹⁰ Dawson, R M C, and Gould, R M, *Advances in Experimental Medicine and Biology*, 1976, 72, 95.

¹¹ Field, E J, *et al*, *Journal of Neurology*, 1977, 216, 135.

¹² Field, E J, in *Multiple Sclerosis: A Critical Conspectus*, ed E J Field, p 245. Lancaster, Medical and Technical Publishing, 1977.

¹³ Field, E J, in *Multiple Sclerosis: Recent Advances in Aetiopathogenesis*, ed J B Cavanagh. London, Churchill Livingstone, 1979.

¹⁴ Field, E J, and Joyce, G, *International Research Communications Systems, Medical Science*, 1977, 5, 158.

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 trials¹ 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-deficiency⁶ 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 tartroazine, 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,