CORRESPONDENCE

Treating influenza with zanamivir

Sir—Robert Read’s Dec 12 commentary,1 on treating influenza with zanamivir is misleading. He states that zanamivir needs to be given within 30 h of onset of symptoms. This figure of 30 h is taken from a phase II study2 that showed zanamivir was effective in patients recruited within 48 h of symptom onset and that this benefit was further increased in those who presented within 30 h. The MIST Study Group3 showed efficacy in patients recruited within 36 h of the onset of symptoms. Results from a clinical trial in Europe in which 365 patients were recruited, included patients recruited up to 48 h after symptom onset showed a 2·5 day benefit from inhaled zanamivir, compared with placebo.4

Comparison with amantadine is suggested by Read, even though this drug is effective only against influenza A, has been associated with the rapid development of resistance, and has important neurological side-effects. An additional clinical trial to directly compare the two products cannot be justified.

The limitations of diagnosis to which Read refers are well recognised. However, with surveillance information and attention to clinical detail, general practitioners who co-operated in clinical trials of inhaled zanamivir correctly diagnosed about 70% of suspected cases on clinical grounds alone. The need for rapid diagnosis and a specific surveillance programme is recognised. It does not follow that a rapid diagnosis test is needed in every case.

Read’s reference to poor bioavailability after oral administration is misleading. The action of inhaled zanamivir is not dependent on absorption; furthermore, neuraminidase inhibition takes place extracellularly on the surface of respiratory epithelial cells.

The statement by Read that “resistance has rarely been observed in clinical trials” is incorrect. It is encouraging that no resistant strains have been detected in any of the clinical trials of inhaled zanamivir, now involving over 4000 patients. One instance of a resistant virus was observed in an immunocompromised patient treated with a course of nebulised zanamivir on compassionate grounds. However, the replication of the mutant virus in MDCK cells was found to be more sensitive to zanamivir than that of a virus isolate obtained on the day when treatment with zanamivir began.5 The clinical relevance of these findings is not clear.

Read suggests that widespread use will depend on the economic as much as the clinical benefits. Effects on the quality of life and productivity were also improved by treatment with inhaled zanamivir. He points out “influenza reaps a grim harvest ... a safe and effective treatment would have a tremendous impact”. By these judgments, inhaled zanamivir may already have proved itself, though further studies in high-risk patients are in progress.

Finally, it is important to clarify the meaning of oral administration, which should of course be taken to include (orally) inhaled administration.

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Authors’ reply

Sir—My commentary was not misleading. I welcomed the encouraging performance of zanamivir in treating influenza, but balanced this against considerations that have the potential to limit its utility. Published data support the assertion that the drug needs to be given early in symptomatic disease. In the first important published phase II clinical trial of zanamivir (which was reported in a publication of which D M Fleming was a co-author),1 the drug did not shorten duration of illness, or hasten resumption of normal activities in patients who had symptoms of influenza for more than 30 h before administration of drug. In patients who were treated within 30 h, zanamivir did have significant benefit. Trials with human volunteers challenged with influenza virus have also suggested that early treatment is necessary for clinical efficacy of this drug.2 No other published studies have stratified patients according to timeliness of therapy. I also pointed out that zanamivir must be administered topically because of poor bioavailability after oral administration. Patients at the extremes of age may not be able to use inhaler or nebuliser devices. The development of neuraminidase inhibitors that can be administered orally (not by inhalation) will be a useful development for this population.

There is no doubt that deployment of these drugs will be eased by the parallel development of rapid diagnostic techniques. It is reassuring that general practitioners can diagnose viral infection with reasonable accuracy, but we should heed the lesson of the current season of respiratory tract infections, in which a proportion of disease has been due to Mycoplasma spp and respiratory syncytial virus rather than influenza virus.3 In this context, the economic consequences of giving empiric therapy to a large number of patients should be obvious.

Zanamivir does need to be subjected to clinical trial and compared with amantadine or rimantadine, because prophylaxis with amantadine or rimantadine is currently recommended by the US Advisory Committee on Immunisation Practices in the context of nursing home outbreaks of influenza, and is therefore a standard of care. In fact, Glaxo-Wellcome has already sponsored a study of the efficacy of zanamivir for prophylaxis of nursing home influenza outbreaks4 and shown
that it may be at least as effective as rimantadine in prevention of disease. The fact that neuraminidase inhibitors have activity against both subtypes of influenza will make them an attractive choice of drug for this indication.

As stated in my commentary, emergence of zanamivir-resistant influenza virus is rare. Fleming describes a case report of an immunosuppressed child who persistently shed influenza virus during treatment with zanamivir. In addition to the clinical resistance to zanamivir, the neuraminidase activity of the isolated virus was 1000-fold more resistant to inhibition by zanamivir. The resistant virus carried a mutation in the neuraminidase gene. Despite this evidence, the virus seemed sensitive in a standard plaque reduction assay with Madin-Darby canine kidney (MDCK) cells. The haemagglutinin gene mutation was subsequently shown to increase binding of resistant virus to receptors particular to the surface of MDCK cells, thus reducing the requirement of the virus for neuraminidase. Thus, the MDCK plaque reduction assay was not appropriate for this virus.

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Sir—Influenza is a major public-health problem, and we found that treatment with zanamivir in the general population and in a subgroup of high-risk patients, significantly reduced the duration of symptoms of influenza by 1-5 to 2-5 days. Robert Read’s Dec 12 commentary in response to our report raises various issues. Hayden and co-workers previously reported that zanamivir was effective in reducing the duration of symptoms by 1 day in patients who presented within 48 h of onset of symptoms. Read draws on the increased benefit (3 days) reported by Hayden in patients who presented within 30 h of symptom onset or with a fever. However, the benefit seen in the overall population was replicated in our study, in which patients entered the trial within 36 h of symptom onset, and also in a study by Fleming and colleagues in patients who presented within 48 h of symptom onset.

Amantadine and rimantadine are not widely available so their use is limited, the rapid development of resistance is well documented as is their poor adverse event profile and lack of activity against influenza B. We therefore find the suggestion that zanamivir should be compared with amantadine surprising, especially since no more adverse events were seen with zanamivir than placebo.

Although a media campaign aided recruitment to our study, the evidence from local surveillance programmes was the key to the start and cessation of recruitment. Thus, when local health authorities indicate that influenza exists in the community, an acute febrile respiratory illness can be attributed to influenza with a reasonable degree of certainty, particularly if typical features are present.

Inhaled zanamivir is delivered directly to the respiratory tract, the lining of which is the target cell for influenza replication. This route of administration offers many advantages as systemic exposure is kept to a minimum and with it, the potential for unwanted side-effects.

Read comments that so far development of resistance to zanamivir has been rarely observed. To date, no phenotypic or genotypic evidence of resistance to zanamivir has been detected in influenza isolates from clinical efficacy trials. Up to the winter of 1998, the zanamivir clinical programme has included over 4000 patients, with over 1500 in phase III studies alone.

We agree with Read that there is a clinical need for an agent that is suitable for chemoprophylaxis. Monto and colleagues showed that orally inhaled zanamivir prevented influenza in 67% of patients and influenza with fever in 84% of patients in a community setting. Finally, our study showed significant clinical benefit in treating influenza with zanamivir in the general community. Although we also found a significant benefit in the high-risk subgroup in reducing the duration and severity of illness, and in reducing complications and associated antibiotic use, we agree that further studies are needed to confirm these benefits in high-risk patients.

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Circumcision of newborn boys

Sir—Teressa To and colleagues (Dec 5, p 1813) provide useful information on which to base decisions about offering circumcision for infant boys. Although they found a substantial reduction in the risk of urinary-tract infection (UTI) in circumcised boys (relative risk 3–7), the study shows the epidemiological principle that a large relative risk reduction may translate into a small absolute risk reduction when the baseline prevalence of risk is low.

Their results are also relevant to a group who are at increased risk of UTI: boys with vesico-ureteric reflux (VUR). Estimates of the risk of UTI in children with VUR vary; I used published data from the International Reflux study to calculate a rate of 242 episodes of UTI per 1000 patient-years of follow-up in children with severe VUR for all participants in that study. This figure should be compared with 7 per 1000 patient-years in the general (uncircumcised) population in To’s report. Calculations based on other large studies of children with VUR give estimates of the annual risk of UTI of 9% and 14%, whereas in To’s study uncircumcised boys had an annual risk of only 0–7%.

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A range of estimates suggest that the risk of UTI in boys with VUR is of the order of ten to 30 times greater than in healthy boys. In this situation, a relative risk of 3–7 has a different interpretation, and would translate into an absolute risk reduction of 50–150 episodes of UTI per 1000 boys per year, and imply that from seven to 20 circumcisions would be needed to prevent one UTI per year.

Can the effects of circumcision in healthy boys be extrapolated to those with VUR? Boys with VUR obviously have an additional factor increasing their risk of UTI, but it is unlikely that they are exempt from whatever biological mechanism causes increased risk in uncircumcised boys. The implications of UTI for boys with VUR are serious; recurrent UTI is thought to be an important determinant of renal scarring and deterioration in renal function. Circumcision in the neonatal period is increasingly an option for boys with VUR.

Trials of circumcision in VUR were suggested almost 10 years ago, but at present this procedure is not part of the routine care of VUR. The evidence provided by To and colleagues helps to make a plausible case that merits proper testing; a randomised controlled trial of circumcision in boys with VUR is urgently needed.

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Sir—In their study, Teresa To and colleagues tell us that 195 circumcisions would be needed to prevent one hospital admission for UTI in the first year of life. They cite the review by Williams and Kapila in support of the claim that one in six boys and men worldwide has been circumcised, but have overlooked the main conclusion from that review—at least 2% of circumcisions have important complications. This finding implies that sufficient circumcisions to prevent one hospital admission for UTI in the first year of life will cause at least four serious complications. To and colleagues miss the obvious conclusion that the risks of infant circumcision cannot possibly be justified by the potential benefits.

Their study does raise a more fundamental concern. We are not told how many of the 30 105 boys circumcised in their study had sufficient disease to justify removal of the foreskin, but it is likely that in most cases there was no therapeutic indication. At least 600 boys will have had serious complications. All 30 105 will have to go through a foreskin whether they like it or not.

It is not clear to what use the information generated by this study will be put. A reasonable question is whether it can be acceptable to remove normal, specialised tissue from 195 normal healthy boys to prevent one from suffering a treatable disease.

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Sir—Teresa To and co-workers (Dec 5, p 1813) 1 undermine the myth that neonatal circumcision significantly decreases the incidence of urinary-tract infection (UTI) in young boys. Previous studies that used a US Army Hospital database, did not control for several important confounding factors. By controlling for socioeconomic status, prematurity, hospitalisation bias, and neonatal complications, To and colleagues have lowered the odds ratio for a boy with a foreskin developing a UTI from 10 to 1:77 (95% CI 1:60–1:94). What will happen when the other confounding factors, such as ethnic origin, breastfeeding, maternal urinary infection, urine collection method, diagnostic criteria for UTI, and family history of UTI, are controlled for?

An expansion of our prospectively gathered data has generated similar results. Among 615 circumcised boys, six had a UTI, whereas one of 54 intact boys had a UTI (1·90 [0·22–16·06]). Our findings show no significant difference. The small difference documented by To and colleagues with a large database may represent a difference that is statistically but not clinically significant.

Although To and co-workers state, “Therefore, there is no evidence to suggest that the incidence of outpatient UTIs could have been significantly differentially under-estimated in the circumcised population”, their numbers suggest that among boys with a UTI, circumcised boys were more likely to be treated as an outpatient than non-circumcised boys (2·9 [1·75–3·27]). This significant finding undermines any study that relies exclusively on hospitalised cases of UTI, which includes nearly all published studies.

The investigators further state “the two cohorts did not suffer significantly in . . . proportions of readmissions”, but the circumcised cohort had a higher rate of readmission that was significant (1:13 [1:09–1:17]). When the UTI admissions are deducted, the difference is greater still (1:17 [1:2–1:21]). Noting circumcision’s interference with maternal interaction and feeding, is this increase in readmissions due to hyperbilirubinaemia of the neonate?

Finally, while 195 boys must be cut to prevent one UTI, all 195 boys will have their penis permanently altered in the process. All will lose the normal covering of the glans, the erogenous ridged band, and most of the penile mucosa and the penile dartos muscle. 2 The surgically altered penis has different sexual practices and decreases the sexual pleasure of the female partner. 3 The rate of immediate surgical complication is between 2% and 9%; 4 while about 8% of circumcised boys can develop mental stenosis. 5 Clearly, more boys would be injured by circumcision than protected from a treatable UTI. We could not agree more: circumcision is not a rational way to prevent UTI in boys.

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Corpses and the spread of cholera

Sir—R Bradley Sack and A Kasem Siddique’s Nov 14 commentary discusses cholera control measures and our paper on funerals and disinfection of corpses of people dying of cholera. They rightly call attention to the importance of handwashing, decontamination of water, prevention of contamination of food and, in certain instances, disinfection of corpses and restriction of “funeral feasts.”

However, we disagree that there is “little supporting evidence for this uncontrolled observation” that the spread of cholera can be limited by a policy of disinfection of cholera victims. On the contrary, our conclusion on the positive effect of disinfection of corpses is based on an analysis of well controlled regional surveillance data from rural west Africa and a case-control study on transmission routes of cholera during funerals. Disinfection of corpses of people who died from cholera has been demanded by the health authorities in Guinea-Bissau during epidemics, as recommended in some guidelines on cholera control.1 To our knowledge, no study before ours has attempted to assess the effect of such a policy.

We also disagree that in Africa “funeral feasts are not the custom”; in Africa funeral feasts are common and may contribute to the spread of cholera. West-African funeral feasts are not only attended by family and friends but also by uninvited people who come solely for the sake of food and drink.2 Furthermore, cross-cultural variations in funeral practices is incredible and funerals are often described as a rather chaotic affair.3

In a resource-poor country such as Guinea-Bissau, the implementation of cholera prevention measures is difficult. However, during the large 1994 cholera epidemic, the policy of disinfection of corpses of people who died from cholera and restrictions on funeral feasts were practical and effective measures to prevent transmission of cholera.4

Sir—Carlo Salvarani and colleagues and R J Francois (Dec 12, p 1938)5,6 raise important questions about the classification and pathology of inflammatory arthritis proposed in our hypothesis article (Oct 3, p 1137).7

First Salvarani et al suggest that it was not clear from the hypothesis whether synovitis associated with polymyalgia rheumatica (PMR) and remitting seronegative arthritides with pitting oedema (RS3PE) were classified as either primary synovial or entheseal/capsular. In fact we suggested that sudden-onset, good-prognosis polyarthritis, which is typical of both these entities (and has clinical features reminiscent of spondyloarthropathy) should be classified as entheseal-related diseases. We agree that PMR and RS3PE are part of the same spectrum of disease but we do not believe that these conditions should be classified as primary extra-articular synovial.

Indeed since our hypothesis was published, magnetic-resonance imaging (MRI) data for a capsular/entheseal pathology in patients with self-limiting polyarthritides have been recorded.3

Second, Francois states that the histological changes of the sacroiliac joint in spondyloarthritides show prominent bone-marrow changes without entheseal abnormalities and hence the hypothesis is invalid.8

Unfortunately, the histological nature of the enthesitis lesion has not yet been defined in early human arthritis. However, a striking feature of early untreated enthesitis imaged by MRI is inflammation extending well beyond the actual tendon/ligament insertion to bone with extensive inflammation of the underlying bone marrow.5 Hence the changes described by Francois could be part of the spectrum of enthesial pathology. Although the notion of enthesitis is clinical, based on focal tenderness or swelling, the pathological lesion seems much more extensive.

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A specific treatment for hypochondriasis?

Sir—In a recent controlled trial of treatments for hypochondriasis, we found that cognitive therapy was better than an equally credible alternative, psychosocial intervention (behavioural stress management), and concluded that this finding indicates cognitive therapy is a specific treatment for hypochondriasis.1 In a provocatively titled Dec 5 commentary, David Ben-Tovim and Adrian Esterman claim our conclusion is incorrect because we used an active treatment, rather than a sham treatment as the control condition.

If a sham treatment was acceptable to patients, it would have simply controlled for the effects of therapist attention. Our control treatment involved the same amount of therapist time as cognitive therapy and, in addition, also matched cognitive therapy in terms of patients’ ratings of treatment credibility, expectation of improvement, and use of structured homework assignments. The fact that cognitive therapy was better than such a stringent control condition in eight of ten measures of hypochondriasis at the end of treatment is particularly impressive evidence for a specific effect.

By contrast with most pharmacotherapy treatment trials, which Ben-Tovim and Esterman see to view as the gold standard, we included data on patients’ symptoms at several postintervention follow-up points (3, 6, and 12 months). Throughout the follow-up year, patients who had received either treatment remained better than at before treatment. In addition, the
Sir—No matter how strong the theoretical basis of a treatment, evidence of its specific effect is best accomplished by a comparison between the treatment and a placebo. David Clark and Paul Salkovskis continue to claim that their study showed that cognitive therapy is a specific treatment for hypochondriasis. We do not underestimate the difficulty of research into hypochondriasis, but the design of Clark's study limits its capacity to show an effect that was specific to either of the two treatments studied.

The study in question was a comparison of the effectiveness of two active treatments. That kind of procedure is usually reserved for comparing a new or experimental treatment with a standard treatment of known and proven efficacy. The importance of this restriction is well illustrated by the study by Clark and colleagues.1 The absence of a placebo group rendered it unclear whether either treatment was more effective than a placebo. Given the intensive nature of the treatments involved and the training needed to deliver them, such uncertainty is not inconsequential.

One of the most welcome features of the study was its duration. We agree with Clark and Salkovskis that too many studies of psychotherapeutic and psychopharmacological interventions report scores at the end of treatment without any kind of follow-up. In a condition as persistent as hypochondriasis, the evaluation of the effect of a treatment over time is crucial for generalisation from research into clinical practice. In a study with a structured follow-up, we make no apologies for reviewing the results on an intention-to-treat basis. We agree with the comments of Clark and Salkovskis that the follow-up result does not favour either of the two treatments. The absence of a placebo still means that the specific nature of either treatment cannot be assumed.

We note with interest the impressions of Peter Tyrer and colleagues that patients attending a genitourinary clinic readily accept treatment for hypochondriacal fears. We look forward to the publication of their study results. Finally, we advocated that clinicians exercise discretion in the use of their time with...
Cranberry juice and prevention of recurrent urinary tract infection

Sir—In her Jan 2 commentary on the prevention of recurrent urinary tract infections (UTI) in women, Ann Stapleton did not discuss cranberry juice. Although the use of cranberry juice for this purpose has long been recommended, evidence to support its efficacy has, until recently, been largely anecdotal.

A possible mechanism for the activity of cranberry juice in this setting was suggested by Zafriri and colleagues who reported that cranberries contain fructose that could interfere with adhesion of type 1 fimbriated (mannose-sensitive) Escherichia coli to uroepithelium. They also identified a component which could also inhibit adherence of P-fimbriated (mannose-resistant) E coli. Howell and co-workers suggested that proanthocyanidins were responsible for the later observation. Whether these moieties are more important by acting on uroepithelium or whether they may have an effect in the colon by the elimination of a gut reservoir of uropathogenic E coli is unclear.

So far, there has been only one well designed clinical trial on the use of cranberry juice in UTI: a placebo-controlled study that showed a reduction in bacteriuria and pyuria in elderly women, but there have been no studies in younger age groups.

With the potential for side-effects and the likelihood of the emergence of resistant bacteria in patients receiving conventional antimicrobial chemoprophylaxis, the possibility of giving an apparently safe, naturally occurring substance, with no selective pressure in respect of antimicrobial resistance, such as cranberry juice deserves further consideration.

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Childhood mortality in sub-Saharan Africa

Sir—Allan Hill and colleagues (Dec 12, p 1907) report a substantial decline in rates of mortality during the past 40 years in children aged younger than 5 years in The Gambia. Besides high immunisation coverage in this country, the investigators mainly attribute their encouraging findings to the community’s commitment to village-based primary health care, which is supported by observed differences in mortality rates between the villages with primary health care and the villages without this care. However, the evidence for such a statement is weak.

The Gambia started its village-based primary health care programme in the early 1980s, and all villages with a population of at least 400 were invited to take part. Primary health care villages received 6 weeks of training of volunteer village health workers and traditional birth attendants who were equipped with some basic drugs. Subsequent evaluations of the programme did not show an overall effect on childhood mortality, with shortages of drugs, frequent absence of village health workers at the time when they were most needed, and competition with traditional healers as the likely explanations.

During the 30 years after independence (1960), infant and childhood mortality has been declining steadily in most countries in sub-Saharan Africa, with a few exceptions at times of political and economic crises. Since 1990, rising mortality trends are common, though not universal, because of paediatric AIDS. The widespread decline in mortality obviously started long before primary health care was initiated (1978), and the speed of the decline hardly changed before and after primary health care was set up. Only during the late 1980s did mortality decline seem to accelerate as a result of the effects of the Expanded Programme on Immunization.

Reasons for mortality decline are not clearly known. However, many factors seem to have a role—particularly improvements in nutrition, vertical disease control programmes, widespread availability of antibiotics and antimalarial drugs, and vaccinations. Awareness of health issues has also dramatically improved in sub-Saharan Africa. Economic development and new means of communication have had a role in reducing the isolation of African villages and have facilitated access to modern health services. Primary health care has probably also helped, but differences between villages with and without primary health care and in trends before and after primary health care are fairly small. These differences cannot explain per se the major decline in mortality from values around 400–500 per 1000 people which were common in West Africa before 1960 to values below 150 per 1000 people now. The Gambia makes no exception to the general West African pattern.

Furthermore, what was intriguing in the paper of Hill and colleagues was the rising trend in mortality after 1990 in the Farafenni area. With HIV-1 prevalence still being low in this part of West Africa, this finding could probably be attributed to the increasing occurrence of chloroquine-resistant malaria, which has been documented in the neighbouring country of Senegal.

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Appendicectomy in ulcerative colitis

Sir—In his Dec 5 commentary, R S Sandler describes epidemiological and experimental data suggesting that the appendiceal pathology, and the appendiceal gland, are involved in the pathogenesis of ulcerative colitis. He raises the question whether ulcerative colitis is a clinicopathological entity confined to patients taking oral contraceptives, and suggests that the vermiform appendix is an immunologically active lymphoid organ with a rich blood supply and numerous lymph vessels. Its capacity to respond to local stimuli by intense production of cytokines, such as tumour necrosis factor alpha and interleukin-2, derived from Th1 cells, has been shown by Sartor.\(^1\) The postulated role of cytokine imbalance in the pathogenesis of ulcerative colitis has justly received much attention and led to initial clinical trials based on anticytokine interventions.\(^2\) This role is also supported by studies of T cell receptor-\(\alpha\)-mutant mice that spontaneously develop an inflammatory bowel disease similar to ulcerative colitis and have hyperplastic mesenteric lymph nodes which actively produce cytokines.\(^3\) Perhaps some intermittent infections by enteric bacteria that involve the appendix, trigger the production of proinflammatory cytokines, which in genetically susceptible patients culminates in aberrant HLA-DR expression on colonic epithelium, antigen presentation, and an immunological cascade which leads to the development of ulcerative colitis—an organ-specific autoimmune disease.\(^4\)

Thus, no discussion of appendicectomy and ulcerative colitis should disregard the probable role of cytokines of appendicular origin, even if the discordance between ulcerative colitis and Crohn’s disease (odds ratio about 1-5) cannot at present be easily explained, except perhaps by anatomical considerations. Furthermore, laparoscopic appendicectomy should be contemplated in patients with severe or refractory ulcerative colitis, perhaps even as a primary prevention measure in first-degree relatives whose risk for the disease is increased by about ten-fold.\(^5\)

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Sir—We are intrigued by Robert Sandler’s commentary that history of appendicectomy confers significant protection against the subsequent development of ulcerative colitis. An odds ratio of 0.2 to 0.3 for colitis in several European and American studies is too strong to be coincidental. Can this be used to generate a valid hypothesis of the pathogenesis of the disease? The veriform appendix is an immunologically active lymphoid organ with a rich blood supply and numerous lymph vessels. Its capacity to respond to local stimuli by intense production of cytokines, such as tumour necrosis factor alpha interferon-\(\gamma\), and interleukin-2, derived from Th1 cells, has been shown by Sartor.\(^1\) The postulated role of cytokine imbalance in the pathogenesis of ulcerative colitis has justly received much attention and led to initial clinical trials based on anticytokine interventions.\(^2\) This role is also supported by studies of T cell receptor-\(\alpha\)-mutant mice that spontaneously develop an inflammatory bowel disease similar to ulcerative colitis and have hyperplastic mesenteric lymph nodes which actively produce cytokines.\(^3\) Perhaps some intermittent infections by enteric bacteria involved the appendix, trigger the production of proinflammatory cytokines, which in genetically susceptible patients culminates in aberrant HLA-DR expression on colonic epithelium, antigen presentation, and an immunological cascade which leads to the development of ulcerative colitis—an organ-specific autoimmune disease.\(^4\)

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Diagnosis of molybdenum cofactor deficiency

Sir—Hartmut Koch (Dec 5, p 1824)1 rightly draws attention to two points about correct diagnosis of molybdenum cofactor deficiency: first, the unreliability of a single sulphite dipstick test in alerting medical or laboratory staff to the need for further investigations of purine metabolism; and second, the importance of uric acid measurement for neonatal seizures. However, there are several additional difficulties for the attending physician in investigating laboratories which might obscure diagnosis.

Not all cases present neonatally with a virtual absence of uric acid in plasma and urine, the classic hallmark of this disorder.2 Although this observation applies to most early presenters, phenotypic variation in expression of the defect is now evident. Late presenters can have plasma uric acid at the bottom end of the normal range for children. Since children have a low plasma uric acid compared with adults because of a high renal clearance, diagnosis may well be missed, or delayed.3 For example, an 8-year-old otherwise healthy sibling attending Moorfields Eye Hospital for dislocated lenses was identified only during family screening when a younger sister with neurological problems developing at 12 months was diagnosed at age 2 years from a persistently low plasma urate, all other tests having proved negative.4

Confirmation of the cofactor deficiency should be made in either instance, or in any patient with a positive dipstick test (which could also indicate isolated sulphite oxidase deficiency with indistinguishable clinical manifestations, but undisturbed purine metabolism5), by measurement of the principal uric acid precursor xanthine. Xanthine accumulates only in molybdenum cofactor deficiency, hereditary xanthinuria, or patients given allopurinol.6,7 However, infection is frequent in urine collected in the adhesive bag mentioned by Koch, and bacteria rapidly degrade the original xanthine to uric acid. Urinary uric acid can thus seem normal.8 Confirmation of the sulphite oxidase deficiency (isolated or combined with xanthine dehydrogenase deficiency) can be made by enzyme assay and by analysis of urinary S-sulphocysteine or thiosulphate, which are both raised. In plasma, cystine is usually very low.

The third difficulty is lack of awareness. Koch states that only ten to 15 cases of molybdenum cofactor deficiency have been reported worldwide. The objective of our European Commission grant involving 19 countries, is to improve research and diagnosis of these genetic metabolic purine and pyrimidine disorders throughout Europe (nine of which present with neurological deficits). Our first task—a survey to gather information—has revealed that the centre in Lyon, France, to which almost all European cases are referred for confirmation of the sulphite oxidase enzyme deficiency, has diagnosed a total of 72 cases. Some of these are drawn from the 16 diagnosed in the UK. The Netherlands report 28, Italy 4, and Germany 19. Clearly molybdenum cofactor deficiency is not so rare and much more needs to be done to improve recognition of genetic metabolic purine and pyrimidine disorders—not only as a cause of neurological disease, but also those affecting the immune, haematological, and renal systems.9

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**Aspirin, myocardial infarction, and gastrointestinal bleeding**

Sir—We believe that some aspects of Christopher Isles and colleagues’ letter (Jan 9, p 148)1 and of the original report of the HOT study2 were misleading. That study reported 184 myocardial infarctions on placebo and 157 on aspirin (non-significant difference), which consisted of 127 and 82 clinically overt myocardial infarctions (significant decrease), misquoted by Isles et al as “all MI”, and 57 and 75 silent myocardial infarctions (non-significant increase) on placebo and aspirin, respectively. Thus, as might be expected with an agent that is an analgesic, even at low doses, and causes dyspepsia, aspirin seems to disguise but not reduce the risk of myocardial infarction.1 Furthermore, because the ascertainment of silent myocardial infarction will be lower than for overt infarction the HOT study may have underestimated its frequency, which could easily account for the non-significant trend in favour of a reduction in total myocardial infarction with aspirin.

If this were not proof enough for no real effect of aspirin on cardiovascular events, both the HOT and Thrombosis Prevention Trial3 showed no effect of aspirin on cardiovascular or all-cause mortality. Since about 50% of all patients with myocardial infarction die within 30 days of the event any real impact of aspirin on infarction should have shown as a reduction in mortality.4 It could be argued that the number of events in the above trials was insufficient to establish whether aspirin has an effect on mortality, but this is a poor argument in favour of evidence of benefit. Including the HOT study, over 50 000 patients have been randomised into studies with about a quarter million patient-years of follow-up. So far this has resulted in 480 vascular deaths on placebo and 463 on aspirin (numbers adjusted for unequal randomisation), a non-significant reduction of only 17 vascular deaths. As Isles et al rightly point out aspirin seems an important and common risk factor for major gastrointestinal haemorrhage.5 Patients without established vascular disease should not be exposed to the risks of aspirin without much better evidence of benefit.

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Sir—On the basis of data from the Thrombosis Prevention Trial (TPT), Alberto Zanchetti and Lennart Hansson (July 14) report their calculation for all gastrointestinal bleeds of 18·4 per 1000 person years in men taking 75 mg aspirin. They contrast this figure with 3·0 per 1000 person years in the Hypertension Optimal Treatment (HOT) Trial. They do not point out, however, that in TPT routinely completed three monthly questionnaires about bleeding—including rectal bleeding, which was nearly always due to haemorrhoids and accounted for 85% of the episodes included in the TPT figure they cite. Unless routine questioning in the same detail and at the same intervals was included in HOT (which is not indicated), the apparent difference between the two trials is likely to be spurious. Similarly, TPT routinely asked about minor bleeding at all other sites, which probably accounts for the apparently higher rate for all bleeding in TPT than HOT. In any case, the TPT rates for all bleeding at all sites given by Zanchetti and Hansson (143·9 and 113·5 per 1000 person years in the active and placebo groups, respectively) are erroneous, the correct figures being 66·6 and 53 ·9 per 1000 person years. All grades of bleeding in TPT were clearly defined.

With the widespread and probably growing use of low-dose aspirin, it is important that doctors and their patients are not misled by invalid and inaccurate comparisons affecting conclusions about the incidence of bleeding in different groups of patients.

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**Antioxidant effects of herbs**

Sir—Christos Lionis and colleagues describe the value of Cretan herbs (Dec 19/26, p 108).1 Several of these herbs have a long history in Greece. Sage and penny royal are identified on Linear B tablets2—Linear B was the written language of the Minoan/Mycenaean cultures. The Egyptians collected dittany from Crete3 and sage was exported to Egypt.4 It is noteworthy that Lionis lists dittany first. It was a renowned Cretan herb in classical Greek medicine. In those days it had more powerful properties than only antioxidation—it would cast weapons out of the wound, so Cretan goats would browse on it to protect themselves against hunters.5

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**Pain relief in India**

Sir—Reading the essay by R Ghooi and S Ghooi (Nov 14, p 1625)1 was like revisiting my years as a pain therapist in India. The mother in pain is a story frequently encountered. As a cancer pain therapist in rural India, the situation is completely hopeless. When 90–95% of cancer pain can be controlled with oral or injectable morphine, not being able to use it is frustrating. The account of Mrs Ghooi in the capital city of India, with her well connected children trying their best to relieve her pain, contrasts with the more common tale of rural patients with cancer who live in abject poverty and have no access to any form of palliative care. Even the available, inadequate analgesics do not come their way. The illicit use of hashish, if available, comes as a boon at such times.

I tried to develop home-care pain relief for terminally ill cancer patients. The patients’ relatives were trained to administer the analgesic at home, but without morphine these attempts fell grossly short. The available opioids work for mild to moderate pain and soon reach ceiling effect. The morphine tablets that trickle down can run out of supply suddenly, and the patient is not only denied pain relief but gets withdrawal symptoms to add to the agony.

The Ghoois ask why palliative care is allocated an unimportant place in medicine. Doctors are reluctant to practise palliative care because it is a lost battle without rewards. Pharmaceutical companies are not interested because there are no huge profits to be made. In India, pain relief is not a medical priority, nor is it likely to become one—the doctors and hospitals to care for these patients are few and far between. By contrast, in a country like the USA, palliative care is excellent. I believe this situation does not reflect any higher priority, rather other health care is so well provided for that enough money and expertise is available for palliative care.

Palliative care will inevitably have to wait its turn. Meanwhile, pain therapy will continue to be the responsibility of patients, relatives, and a handful of pain therapists. The Ghoois efforts to make morphine available for those who need it is laudable. If they succeed it should go a long way for pain relief for cancer patients in India.

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**Alice C is poor evidence against age-based rationing**

Sir—Norman Levinsky’s arguments (Dec 5, p 1849) against age-based rationing fail to convince. It is unjust, unworkable, and makes no sense to have a rigid policy by which treatments cannot be given to those over a set age. Furthermore, Levinsky’s case is badly chosen: he warns against applying generalisations to individuals, but justifies his arguments by generalising from the successful individual treatment of Alice C. Would the essay have rounded off so well if Alice, instead of being alert and enjoying life 3 years later at the age of 91, had instead languished on the intensive-care unit, or been discharged back to an unsatisfactory long-care facility to endure a lingering death?

This case was also badly chosen because Alice C, although aged 88, had been well until the previous day and the admitting physician did not know her. Under these circumstances, starting intensive care does not mean continuing it until recovery or death. A period of 24 h—to gain further information and see how the patient will do—enables a more reasoned decision.

As increasingly more expensive treatments become available, physicians have to think beyond the individual patient. The easy decision is always to treat. That is no decision at all. Doctors who deal with patients likely to die have a duty to consider the ethical element of distributive justice when deciding treatment, because the reality of health care is that if one patient is treated, another patient is denied it. And in those decisions age must be a factor. What if Alice C had been aged 98, or 108 years?

Much of Levinsky’s evidence can be used against him, or begs unposed questions. 40% of expenditure in the USA is on the over-65s, but no one contends that this whole 40% is there for the saving. He presents the analysis of the 1978 Medicare data that “only 3·5–6·0%” of the budget would have been saved by denying high-technology...
care. Even if an overestimate, it is a small percentage of a very large sum of money. Anaesthetists working in the UK, and it is unlikely to be different for the specialty in the USA, are exhorted by management to use cheaper drugs that alter the cost of a hospital stay by a far smaller percentage. Levinsky contends that savings would have to come from denying common treatments, such as penicillin. Why not just think more carefully about to which elderly patients penicillin is given?

Levinsky’s weakest evidence is to use the USA’s experience of renal replacement therapy to reject the ethical argument that rationing by age is just. The social bias in obtaining dialysis was eliminated when Medicare started to pay for everyone, and Levinsky argues that limiting availability by age will reintroduce that bias: the well off and well spoken will still get treatment whatever their age. Levinsky is correct, but the well off already get better treatment. The division between the well off and worst off is even wider when the comparison is made across, rather than within, countries, and is getting wider. Any limit to treatment, whether or not age is a criterion in deciding the limit, can be overcome by some individuals. Levinsky takes issue with the ethicists for suggesting an ideal world, but himself suggests a world that cannot exist: Medicare cannot extend to test for such deficits. None of the medical students reported ever using a pager for this purpose, whereas 31 interns and residents have used it for this purpose. Only two of the staff physicians used the pager for this test and none of the nurse practitioners ever used a pager for this purpose. This difference was significant: 31 (71%) residents used pagers at least occasionally compared with only 9% of non-residents (p=0.0001). 15 (23%) respondents used a pager either frequently or always to test vibratory sense.

A review of ten British and American physical diagnosis tests found only one that mentioned this technique,1 and a Medline literature search did not reveal any citations on the accuracy or reliability of pagers for vibratory testing. Pagers are commonly used for both the cranial as well as the extracranial system. Also, a Medline literature search did not reveal any citations on the accuracy or reliability of pagers for vibratory testing. Vibration testing. Pagers are commonly used for both the cranial as well as the extracranial system. Also, pagers, and 33 respondents reported using a pager to test vibratory sense. None of the medical students reported using a pager for this purpose, whereas 31 interns and residents have used it for this purpose. Only two of the staff physicians used the pager for this test and none of the nurse practitioners ever used a pager for this purpose. This difference was significant: 31 (71%) residents used pagers at least occasionally compared with only 9% of non-residents (p=0.0001). 15 (23%) respondents used a pager either frequently or always to test vibratory sense.

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We were surprised on rounds to see a medical resident use the vibration mode of a pager to test vibratory sense and wondered how frequently pagers were used for this purpose. A self-administered, anonymous survey was distributed at inpatient and outpatient morning report to ambulatory care staff at the Denver VA Medical Center. There were 66 responses: ten from medical students, 17 from interns, 27 from residents, eight from staff physicians, and four from nurse practitioners. 64 respondents carried pagers, and 33 respondents reported using a pager to test vibratory sense. None of the medical students reported ever using a pager for this purpose, whereas 31 interns and residents have used it for this purpose. Only two of the staff physicians used the pager for this test and none of the nurse practitioners ever used a pager for this purpose. This difference was significant: 31 (71%) residents used pagers at least occasionally compared with only 9% of non-residents (p=0.0001). 15 (23%) respondents used a pager either frequently or always to test vibratory sense.

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