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Corticosteroids in rheumatoid arthritis

Effective anti-inflammatory agents but doubts about safety remain

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The millennium brings with it the 50th anniversary of Hench's discovery that corticosteroids might be used to treat rheumatoid arthritis.[1] Attitudes towards such use have waxed and waned since then. Initial hope that steroids might dramatically alter the long term course of the disorder gave way to a recognition of the serious adverse effects that accompany high dose treatment. As a result the use of low dose corticosteroids in arthritis remains highly controversial.

Corticosteroids are used widely in medicine today. A recent survey in general practice found that 1.4% of patients aged over 54 were using corticosteroids at a mean dose of 8 mg daily[2]: rheumatoid arthritis was the indication in 23% of cases. Although rheumatologists claim to use steroids relatively infrequently, audits of patients attending outpatient departments suggest a high prevalence of use (as great as 80%).[3 4] What, then, is the quality of the evidence to support the use of corticosteroids in rheumatoid arthritis?

This question is best answered by considering the balance between the risks and benefits of steroid use for short periods (two to three months), with the objective of suppressing generalised flares of synovitis, and for longer periods (two years or more) in an attempt to modify the progression of structural disease. The best controlled data on efficacy and safety originate from long term studies that examine endpoints such as the progression of erosive disease. Yet many rheumatologists use short term courses of steroids, either as a "bridge" to suppress inflammation while other disease modifying drugs take effect or to combat acute flares of the disease.[5]

Direct comparison between the studies addressing both issues is hampered by differences in disease duration, severity, and concurrent treatment among patients recruited. One of the earliest clinical trials compared cortisone with aspirin over three years[6]: both regimens improved patient function and reduced the erythrocyte sedimentation rate, with no clear benefit attributable to cortisone. More recently, a Dutch trial comparing prednisolone 10 mg daily with placebo as an adjunct to intramuscular gold reported clinical improvement in both groups over 12 weeks; this was greatest among those treated with prednisolone.[7] However, there appeared to be a rebound deterioration when the dose of prednisolone was tapered. Finally, the Arthritis and Rheumatism Council trial randomised 128 patients to prednisolone 7.5 mg daily or placebo in addition to non-steroidal and disease modifying agents.[8] Symptomatic benefit was maintained for only 6-9 months of the two year follow up.

A meta-analysis of the effectiveness of low dose corticosteroids in rheumatoid arthritis based on 9 of 34 studies identified in a rigorous search strategy[9] compared the effectiveness of prednisolone to either placebo or active drug controls (aspirin, chloroquine, or deflazacort). Although corticosteroids tended to be better at reducing the number of tender or swollen joints and the erythrocyte sedimentation rate, these differences were not significant.

Whether corticosteroids attenuate the progression of erosive damage is also unresolved. In the Arthritis and Rheumatism Council study prednisolone had a pronounced and significant ($P < 0.004$) effect on the development of hand erosions in patients with rheumatoid arthritis of less than two years' duration. Although these results accord with those of an earlier Medical Research Council study evaluating higher doses of prednisolone (initially 20 mg daily), other trials have failed to show a convincing impact of corticosteroids on erosive progression.[10]

In this issue Gotzsche and Johansen report a further meta-analysis comparing prednisolone at a dose of 2.5-15 mg daily with placebo or non-steroidal anti-inflammatory drugs (p 811).[11] They show that at these doses prednisolone is much more effective than placebo and somewhat more effective than non-steroidal drugs at improving joint tenderness, pain, and grip strength. This study has been carefully performed, and, as expected, there was considerable heterogeneity in the results obtained for different outcome measures. Interestingly, many of the trials included in the previous meta-analysis[9] did not qualify for entry to this study, which focused on response in the first week of treatment. Nevertheless, the results agree with the clinical impression of most rheumatologists that prednisolone at these doses is an effective anti-inflammatory agent.

Far more controversial is the authors' recommendation that intermittent courses of prednisolone at doses up to 15 mg daily might be more widely used in the treatment of rheumatoid arthritis. The major limitation to the use of oral corticosteroids has always been concern about their safety, coupled with the difficulty of weaning patients off treatment. The complications of steroids are dose dependent and often occur at doses much lower than prednisolone 15 mg daily or equivalent. Thus, bone loss from the lumbar spine occurs at around half this dose and tends

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to be most rapid in the first year of treatment.[12] Furthermore, epidemiological studies link this bone loss directly with an increased risk of fracture.[13] Other adverse effects, including susceptibility to infection, alterations in glucose metabolism, cutaneous atrophy, cataract formation, and proximal myopathy, may occur in patients given relatively low doses of corticosteroids for several years.[10]

It is strange that the authors should subject the efficacy of steroid therapy to the full weight of the evidence based approach, while giving the issue of adverse effects only a partial review in their discussion. To the practising rheumatologist the great disincentive to using short term low dose prednisolone is not concern about lack of anti-inflammatory effect but the worry that stepping treatment down may be difficult, with the consequence that the patient is exposed to the risk of adverse effects. Clinicians who encounter these adverse effects in day to day practice might be forgiven for adopting a more cautious stance than that adopted by the authors from the Nordic Cochrane Centre.

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Proteases as prognostic markers in cancer

Proteolytic enzymes and their inhibitors influence the spread of cancer

Just how tumours become malignant remains an enigma, despite major advances in our knowledge of genetic susceptibility, cellular derailment processes, and environmental factors. The rapid multiplication of cells in the early phase of a tumour does not usually cause serious disease so long as the growth remains confined to its original tissue boundaries. When, however, cells migrate from their original tissue compartment, invade the normal surrounding tissue, and disseminate throughout the body they have become malignant.

The migration and invasion characteristics of malignant cells requires them to be able to cross extracellular barriers. In the primary organ these predominantly consist of basement membranes and connective tissue, collectively called the extracellular matrix. The extracellular matrix is made up of a dense network of different components including laminin, fibronectin and other glycoproteins, collagens, and proteoglycans. To invade and metastasise, tumours possess a lytic machinery made up of different proteolytic enzymes, the proteases. The main classes of proteases contributing to the lytic processes around tumours are cathepsins, plasminogen activators, and matrix metalloproteinases.[1] The first evidence of the active part played by these enzymes in neoplastic disease came from studies showing large amounts of these factors within malignant human tissues. Further evidence came from in vitro and in vivo experiments showing that non-invasive cells became invasive after gene-transfer of the proteolytic enzymes, and—conversely—that invasive cells could be functionally impaired by inhibition of the proteases.

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Each class of proteases has natural inhibitors which modulate their activity—for example, the cystatins, which inhibit cathepsins, the plasminogen activator inhibitors, and the tissue inhibitors of matrix metalloproteinases.[2] The expression and activity of the proteases is not, however, regulated only by their inhibitors. The proteolytic enzymes are first secreted as inactive proenzymes, and these become activated by proteolytic cleavage, which is thought to evolve as a cascade—cathepsins activate plasminogen activators, which convert plasminogen into plasmin, which in its turn is able to activate pro-matrix metalloproteinases. Other factors involved bidirectionally in the regulation of the proteolytic cascade include leucocyte derived cytokines. For example, tumour necrosis factor alpha induces the synthesis of matrix metalloproteinases, while the intracellular processing of this same tumour necrosis factor is regulated by a matrix metalloproteinase.[3 4] Basic fibroblast growth factor, released from the extracellular matrix through plasmin-mediated proteolysis, can induce synthesis of proteolytic factors in tumour and endothelial cells, forming another loop in the proteolytic cascade (see figure).[2]

Though these processes are strongly implicated in the spread of cancer, similar phenomena take place in (patho)physiological processes such as inflammation, (neo)angiogenesis, ovulation, and wound healing, in all of which cell migration and tissue remodelling occur.[5] Matrix metalloproteinases play an important part in the premature aging of skin by sunlight.[6]

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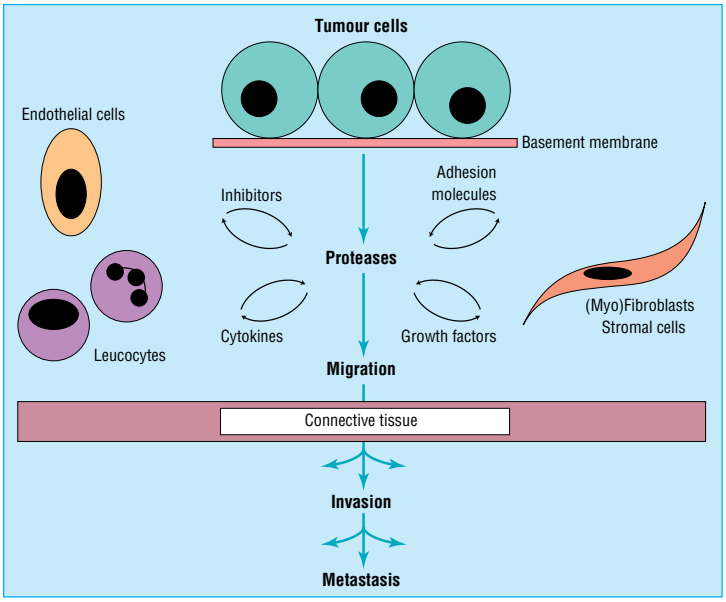

Schematic representation of the cells, regulators, and acellular contributors to protease mediated cancer invasion and metastasis

Research into the clinical impact of proteases in human malignancies was boosted in 1988 when Duffy et al reported on the links between the activity of plasminogen activators in breast cancer tissue and the clinical outcome.[7] Other groups later confirmed and expanded these observations. Compounds of the plasminogen activation system, cathepsins, and several matrix metalloproteinases were all shown to have a prognostic impact as defined by disease free interval and survival of patients with solid tumours of the breast, stomach, colorectum, cervix, kidney, and lung.[7] One of the most consistent observations was the predictive value of the concentration of plasminogen activator inhibitor-1 in extracts of tissue from cancers of the breast, stomach, and lung.[8] Recently, a high concentration of tissue inhibitor of matrix metalloproteinase-1 was also found to indicate a poor prognosis in non-small cell lung cancer.[9]

These findings were initially received with scientific restraint since the inhibitors were supposed to counteract the destructive activity of the proteolytic enzymes. It has, however, become increasingly clear that in most cancers plasminogen activator inhibitor-1 plays an important part in modulating the dynamic process of this kind of proteolysis. The mechanisms include binding to compounds such as vitronectin and adhesion molecules, and clearance of activator-inhibitor complexes via receptors, so regulating focal breakdown of the matrix and cellular adhesion and migration. The cells affected are not only the malignant cells but also myofibroblasts and leucocytes within the tumours.[2 8] The study of Nielsen et al in this issue gives an extra dimension to the clinical impact of these proteolytic factors in cancer (p 829).[10] They have shown that plasminogen activator inhibitor-1 measured in the circulation (not just in tissue extracts) is associated with the survival of patients with colorectal cancer. Multivariate analysis showed, however, that this relation with prognosis was based on the association with the Dukes stage of the tumours. Previous studies had already indicated that several components of the plasminogen activation system and matrix metalloproteinases were associated with the clinical outcome of subgroups of patients with colorectal cancer,[9-14] though the findings were less consistent than those in breast cancer.

The picture is, then, becoming clearer. Proteases and their inhibitors contribute actively to tumour invasion and metastasis. They are also good indicators of the clinical outcome for patients with many types of cancer. Future research should unravel the complex tumour-associated proteolytic cascades and will identify new participants. Prospective studies will have to establish their value in the clinical management of patients. This might be achieved by selecting patients for further adjuvant therapy on the basis of the proteolytic status of their tumours; but another exciting possibility is that the proteases and their inhibitors might themselves become targets for therapeutic intervention to prevent or inhibit tumour invasion, progression, or recurrence.[8 15] The first step along that road has been taken with clinical trials of the new generations of matrix metalloproteinase-inhibitors.[16]

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Interrupting the sympathetic outflow in causalgia and reflex sympathetic dystrophy

A futile procedure for many patients

Causalgia and reflex sympathetic dystrophy are poorly understood disorders that most commonly follow trauma to a limb, although they are also seen in other medical conditions. Patients typically develop chronic burning pain, together with various combinations of sensory disturbances, swelling, and vasomotor, sudomotor, and trophic changes.[1-3] Traditionally, the pain is treated by interrupting the sympathetic supply to the painful area. Is this an effective approach?

Periarterial sympathectomy was first used to treat causalgia, in which, by definition, major nerve injury occurs. Various forms of surgical sympathectomy have subsequently been carried out,[3 4] especially during war time, when controlled trials were not feasible, and so whether surgery was truly effective will never be known. Open surgical sympathectomy to relieve pain in causalgia and related conditions is rarely recommended now, not least because less invasive procedures—including endoscopic sympathectomy and percutaneous radiofrequency lesioning of the sympathetic trunk—have been developed, although critical evaluation of efficacy is awaited.[4]

For several decades, local anaesthetic sympathetic blockade has been undertaken with a variety of techniques.[3] Unfortunately few adequately controlled trials have been carried out, and Kozin, in a review of 500 patients treated by sympathetic block, concluded: "The majority of patients have transient or no significant pain relief."[2] Furthermore, a meta-analysis of randomised controlled trials, retrospective and prospective case series, and controlled studies comprising 1144 patients showed that the benefit of sympathetic blockade with local anaesthetic was indistinguishable from that of placebo.[5] It is therefore doubtful whether sympathetic blockade should be advocated for relief of chronic pain in causalgia and reflex sympathetic dystrophy.

There seem to be no controlled studies demonstrating efficacy of neurolytic sympathetic blocks. Possible side effects, ranging from trivial to devastating, are of even greater importance with these more permanent procedures—painful sequelae may include phenol or alcohol neuritis and postsympathectomy pain (sympathalgia), which can also occur after surgical sympathectomy.[6]

Peripheral sympathetic blockade with regional intravenous guanethidine infusion has been used for 25 years, but only recently have critical appraisals of benefit been undertaken. Jadad and colleagues found—from the few studies sufficiently robust to allow statistical assessment together with their own, subsequently abandoned, randomised controlled trial—that there was no evidence that regional intravenous guanethidine was better than placebo.[7] Similar conclusions were obtained from a double blind, randomised, multicentre study comparing guanethidine with saline placebo in local anaesthetic.[8] At present, the evidence seems insufficient to support the use of these peripheral sympatholytic procedures in the routine management of pain.

More recently the α adrenergic blocker phentolamine has been used intravenously as a test of sympathetic nerve involvement in these chronic pains in order to predict the outcome of longer lasting sympathetic blocks.[9] There have been few studies of the reliability of this procedure, and the contribution of a placebo effect is much debated.[10 11] The usefulness of the phentolamine test as a prelude to procedures that are of uncertain benefit is currently unclear.

Thus, in contrast to the pain relief commonly achieved by sympathetic blockade in disorders such as pancreatic cancer and attributable to blocking visceral afferent nerves,[6] there is little if any evidence that interrupting the sympathetic supply is more effective than placebo in alleviating the pain of causalgia and reflex sympathetic dystrophy. Some individual patients, however, may benefit from sympathetic blockade, and there may also be groups of patients with specific clinical features, in particular allodynia,[12] whose pain is more likely to respond and who perhaps account for those reports of successful relief of pain. Pain relief is, however, invariably unpredictable, of uncertain duration, and inconsistent between the different forms of treatment and when the same treatment is repeated. Even the dogma that early treatment is more successful has been disputed.[13] The optimal number and frequency of anaesthetic or chemical blocks have not been established; one patient may receive 12 sympathetic blocks while another receives 39 regional guanethidine infusions.[13] Perhaps offering treatments of even dubious efficacy, or obtaining pain relief by exploiting the placebo effect, is better than doing nothing. All these medical interventions, however, carry risks for the patient and financial implications for all. Efficacy and safety must first be assured, particularly when licensed drugs, such as guanethidine, are administered for unlicensed uses.

The involvement of the sympathetic nervous system in causalgia and reflex sympathetic dystrophy, which forms the rationale for treatment by sympathetic interruption, has been questioned,[14] and the issues discussed here raise further questions. Contrary to predictions from experimental data, interrupting the sympathetic nervous system in practice seems futile for obtaining long term relief of pain in many if not most of these patients. How to identify the minority of patients whose pain might respond to these procedures is the next task, but fresh approaches to management are also required.

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Refugee children

May need a lot of psychiatric help

War and persecution have resulted in large migrations, and current estimates suggest there are 23 million refugees in the world.[1] About 120 000 of them are in Britain, mostly living in inner London, where they constitute significant minorities. At least 40% (50 000) are aged under 18 years, and they include increasing numbers of unaccompanied refugee children--nearly 500 in 1995. Despite their growing numbers, these children's mental health needs and service provision have received little attention.

Studies from the United States, mostly in refugee children from South East Asia but more recently those from former Yugoslavia, indicate that serious psychiatric disorder is present in 40-50%.[2-4] Since refugee children will have been exposed to similar stressors wherever they find refuge, it is reasonable to take that figure as an estimate of prevalence in Britain. This is far higher than the estimates of psychiatric disorder among non-refugee children in London (about 25% in 10 year olds[5] and 7% in infants[6]).

Refugee children have the full range of psychopathology: they may bring with them disorders they would have had at home as well as those worsened or caused by recent adversities. Disorders include psychological developmental difficulties, post-traumatic stress disorder, depression,[2-4] emotional disorders, anxiety symptoms including fears of separation, and somatic symptoms.[7] These disorders may be persistent[8] and may occur even in children born after their parents fled persecution.[9 10] Disorders associated with greater social impairment, including eating disorders[11] and psychoses,[12] also occur.

Not surprisingly, adversities that seem to put children at the highest risk of psychopathology include direct experience of or witnessing violence, loss or death of parents and family, and being looked after by parents who themselves have psychopathology and cannot cope with the children's demands.[13] The children also have to cope with learning a new culture and language and adapting to school. Growing up in a culture different from that of their parents may cause family tensions.

Reducing children's psychological distress should be seen in the context of the needs of the community and family. Providing a safe haven, including access to housing and welfare support, is important. The persecution and murder of parents and other adult relatives may mean that the care of the young is inadequate and special help is needed, perhaps involving social service departments.[14] Refugee children have the same rights as British children under the Children Act 1989. If unaccompanied they may be cared for by the local authority and defined by the Children Act as children in need. They should then be considered in the social service departments' plans and should have routine health assessments.

Many refugees can access primary care services and some are referred to mental health services, though these are underused by this group for various reasons. Parents and guardians may be unaware of or unable to consider the children's psychological distress. Culturally they may have a radically different understanding of psychological functioning. The various services established for children's needs may be bewildering, and practicalities of getting to services and fears about confidentiality, especially if the parents have not been granted formal asylum, may further reduce access.

Several initiatives have been developed to tackle these problems. Firstly, counselling services have been developed by refugees themselves, with refugee doctors becoming counsellors to their own communities.[15]. Secondly, a specialist service, the Medical Foundation, was established in London to provide care and treatment for the victims of torture. Much of its work is psychiatric assessment and treatment, and users include families and young children. Thirdly, refugee children and adolescents have recently been targeted through special school based mental health projects. Psychological help in schools may include therapy for the children and families and consultation with teachers, educational psychologists, and social workers. Liaison with the school health service to which children may present with physical symptoms will be facilitated.

Despite the difficulties, child and adolescent mental health services may provide help to many distressed young refugees. Collaboration between mental health, social, and education services is often required. Further research is needed to investigate the levels of psychiatric morbidity and service use, including the benefits of outreach services such as those based in school. The

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mobility of refugees and the unpredictability of future disasters, however, will always make detailed planning impossible.

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Electronic preprints: what should the *BMJ* do?

Clear labelling might be the answer

What should journals do about the circulation of "preprints"—drafts of scientific papers that have not yet been formally published? Within the research community they serve several purposes. Some researchers routinely send such drafts to colleagues for their comments. Others use them as an early warning system, to keep colleagues abreast of research that may take months to get into print. Until recently distributing preprints entailed making multiple photocopies of a manuscript and posting them. The advent of faxes quickened the pace but did little to reduce the workload, which effectively limited their circulation. All this has changed with the internet. Draft manuscripts can now be posted on institutional or individual websites. Hundreds of colleagues, instead of a handful, may now see a preprint before its formal publication. Thousands more internet users may be led to a preprint by search engines, which scour the web's pages for key words.

Some journals, such as the *New England Journal of Medicine,* have come down unequivocally against electronic preprints: "Posting a manuscript, including its figures and tables, on a host computer to which anyone on the internet can gain access will constitute prior publication"[1]—and the journal rejects manuscripts if their substance has been published already. It argues that publishing electronic preprints "sidesteps peer review and increases the risk that data and interpretations of a study will be biased or even wrong."

The *BMJ*'s stance is similar. Our advice states: "We do not want material that is published in the *BMJ* appearing beforehand in other media because doctors and patients are then presented with incomplete material that has not been peer reviewed; they cannot make up their own minds on the validity of the message."[2]

Before extending this policy to material on the internet, we wanted to hear the views of our authors and readers. We posted a discussion paper on the *BMJ*'s website and received about 50 emailed responses.[3] At one extreme were enthusiasts for electronic preprints, who regard them not as scientific papers in evolution but as near enough finished articles. To these respondents, the current long process of peer review and paper publication is detrimental to science and the public health: any way of getting scientific advances into the public domain fast is worth supporting. Some welcomed the opportunity to obtain comments from a much wider pool than traditional peer review allowed for and to have authors address these comments before formal publication. (However, the *Medical Journal of Australia*'s experiment of posting accepted papers on its website and inviting comments from visitors does not suggest that there exists a large pool of qualified referees prepared to provide detailed, high quality reviews of papers on line (C Bingham, personal communication).)

At the other extreme were respondents who thought "too much junk" was already being published. Lacking the skills to distinguish between "valuable material and garbage" journalists and the public could be misled. Where the conclusions of research might change public health policy, medical practice, or patients' lifestyles then full peer review before publication should be the rule. The circulation of preprints should be restricted to those who can properly judge them.

Might there be a middle way? Analogous to the preprint is the conference presentation or abstract, which airs research before it has been formally "written up" and peer reviewed. The International Committee of Medical Journal Editors (Vancouver group) has decided that policies designed to limit prepublication publicity should not apply to these forms of early communication.[4] Perhaps this exception should be extended to electronic preprints, providing they were clearly labelled as such. A warning along the lines of, "Electronic preprint. This research has not yet been accepted for publication by a peer reviewed journal: please do not quote" might sound the right tone. In the words of John Ziman, physicist and philosopher of science, "It must always be clear,

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in the mind of the listener or reader, whether or not, so to speak, the witness is on oath."[5] Readers of electronic articles need to be able to distinguish easily between formal publication—what is recorded in the minutes of science—and informal comunication, which has a provisional status, prone to amendment and even withdrawal.

Journals would then have to convince the public and the press to trust only those findings published in full in peer reviewed journals—no easy task in a journalistic culture that values getting a story first over getting it right.[6] They would also have to show that peer review is a value worth adding to manuscripts[7]—especially as peer review may be one function of paper journals that the internet does not eventually replace.

The early responders to our preprint on preprints were against them, and this was from a group well versed in the internet. But more recently the realisation has been growing that researchers will use electronic preprints because of their benefits—however much journals may rail against them. Before deciding the *BMJ*'s policy, we would like to know what more of our readers and contributors think, particularly of our suggestion that the clear labelling of electronic preprints on web sites might provide the solution.

Tony Delamothe *Deputy editor, BMJ*

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Europe's health research: getting the right balance

Preoccupation with technology mustn't erode public health research

Negotiations on the European Union's fifth framework programme of research are at a critical juncture. Within the next few weeks discussions between the council of ministers and the European parliament will determine the direction of collaborative multinational research in Europe over the next five years. Funds for the life sciences programme, which includes health, are likely to amount to 2-2.5 billion ecu. The programme will be based on "key actions" proposed by the European Commission. These currently include food and health, vaccines, health and the environment, biotechnology, and aging.[1] How funds will be apportioned is yet to be decided, but it is very important that research on disease prevention is given a high priority.

Implementing a policy orientated towards prevention will require a commitment to fund transnational collaborative epidemiological, environmental, and public health research and this must be made explicit in the framework programme. Such research not only reflects the mandate of the Maastricht Treaty but also holds considerable potential for improving the health of Europe's populations. The wide dietary variations across Europe, for example, present an ideal opportunity to investigate the link between diet and the development of cancers and other chronic disorders such as ischaemic heart disease. One such study, the European prospective investigation into cancer (EPIC) study, has already been set up and includes over 400 000 adults in nine countries.[2] Subjects will be followed for 10 years to assess the relation of cancer and other diseases to nutritional intake, biochemical variables, and genetic markers. In addition, longitudinal studies of newborn infants have been established for a life course investigation of health in different European settings. Currently the international study on asthma and allergy in childhood (ISACC) is investigating patterns of disease across Europe and the extent to which they relate to exogenous allergens, other environmental agents, and susceptibility factors such as previous infections and immunisations.

Cross national research is essential to determine the health effects of meteorological and climatic change. It also has a key part to play in determining the health impact of social and economic change and of the new healthcare policies that are being introduced throughout Europe. This is now widely accepted, even by those who are critical of EU research policy.[3] There is, however, a view, currently propounded by pressure groups within the European Parliament, that the fifth framework programme should adopt technological research as its main area for support. It is argued that Europe lags behind America in such research and that funds for such research should be increased.

But the health of populations depends less on technical fixes—clinical or environmental—than on broader changes in social relations, living conditions, consumer choices, and personal behaviour. Epidemiologists and experts in public and environmental health must therefore be called in to draw up convincing, detailed research proposals which can be built into the programme, in which the population research components are clearly delineated. It would be regrettable if this opportunity to mobilise European funds and skills for such research were missed.

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1 European Commission.*COM (97) 553* Final. 5 May. Brussels: European Commission, 1997.
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3 The European Community spends a lot of money on scientific research. Is this worthwhile? *Economist* 1998:14 February;93-4.

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Putting the rest cure to rest—again

Rest has no place in treating chronic fatigue

"Go home and rest" is still the advice given to many patients who complain of chronic fatigue. The refrain is echoed in self help books and magazines and adopted by many patients. What are the origins of rest as a treatment, does it work, and what evidence is there on which to base our advice to patients?

Chronic fatigue syndromes are not new.[1] Victorian physicians diagnosed them as neurasthenia and routinely prescribed rest. This approach was typified by Silas Weir Mitchell's "rest cure,"[2] which was so popular as to be described as "the greatest advance of which practical medicine can boast in the last quarter of the century."[3] Despite such accolades, the popularity of the rest cure was short lived. By the turn of the century the same private clinics that once provided it were changing to more active treatments and to the newer psychotherapies.[1] The years that followed saw the end of the rest cure; Karl Menninger poured scorn on the lack of psychological sophistication shown by its proponents,[4] while Richard Asher drew attention to the "the dangers of going to bed."[5]

Despite Asher's warnings, rest, as a treatment for chronic fatigue, resurfaced recently in conjunction with the rise in popularity of the diagnosis of myalgic encephalomyelitis, now called chronic fatigue syndrome.[1] Few articles or books on this subject have failed to emphasise the key role of rest in its treatment: Weir Mitchell himself would no doubt have concurred with the suggestions that "aggressive rest therapy" was what many patients needed. While a few dissenters drew attention to the hazards of excessive inactivity,[6] books, magazines, and some doctors continued to emphasise the virtues of rest and the need to avoid exercise.

The scientific evidence, however, tells us that Asher's warnings against bed rest were well founded. Studies of the effects of prolonged inactivity in healthy volunteers conducted for the American space programme have confirmed that the adverse physiological effects are both profound and prolonged. Furthermore, they include many of the symptoms considered typical of chronic fatigue syndrome, such as loss of strength, poor sleep, postural hypotension, and fatigue.[7] Not only have the known dangers of inactivity and its potential role as perpetuator of chronic fatigue been ignored, but the hazards of exercise have been overstated: the evidence indicates that patients with chronic fatigue syndrome can exercise under controlled conditions without risk of damage or relapse.[8]

If excessive rest is harmful, does exercise help? Evidence from a recent randomised trial suggests that it does. This study showed clearly the superiority of graded aerobic exercise over a low activity stretching programme in improving both functional capacity and fatigue.[8] Interestingly, the clinical improvement observed was independent of improved muscle strength and aerobic capacity, suggesting that the benefits were not simply due to overcoming physiological deconditioning. That psychological effects such as improved confidence and reduced fears of the consequences of exercise are also important is suggested by the similar improvements found in controlled trials of cognitive behaviour therapy.[9,10] Cognitive behaviour therapy does not involve aerobic exercise but instead emphasises consistency in activity management and the gradual attainment of behavioural targets. Taken together this evidence suggests that it is important to differentiate between the needs of the patient with acute fatigue and the patient with a chronic fatigue state; rest may be indicated for the former, but a gradual increase in activity should be at the heart of the treatment plans for the latter.

In making these suggestions we are certainly not advocating the opposite extreme to rest. Aggressive exercise therapy may be as unhelpful as aggressive rest therapy. Menninger also drew attention to the abuse of forced exercise, which he suggested was based more on its appeal to "hard boiled industrialists and misguided army officers whose conception of neurotic illness is that its victims are lazy liars or yellow dogs feigning disability to avoid duty" than on scientific evidence of its efficacy.[4] We find no reason to alter his verdict today. Rather we suggest a middle way of gradual, individually tailored activity, planned collaboratively with the patient, starting at an easily tolerable level and increased only at a manageable pace. Rest is not denied but included in a way that is planned and predictable and not solely as a response to symptoms. The Victorians gradually turned their backs on the rest cure. We should too. Today's patients also deserve better treatment than simply being told to "go home and rest."

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Correction

MMR vaccination and autism 1998

A typographical error occurred in this editorial by Angus Nicoll et al (7 March, p 715). In the final paragraph the fourth sentence should have read: "While *no* vaccine can be guaranteed to be without any risk, this has to be weighed against the huge advantages of protection against disease." We regret that the "no" was omitted.

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