accident surveillance scheme.[2] Last year we reviewed the data for 1991; we estimate that there were roughly 285 000 new attendances at accident and emergency departments for accidental injuries sustained during leisure activities and 82 000 for sporting injuries in Scotland. These represented 24% and 7%, respectively, of all new attendances at accident and emergency departments. The annual direct patient costs associated with sporting injuries were therefore roughly £85 000-155 000 per 100 000 population.[3] The specific pattern of sporting injuries in Britain is different from that in Finland, with rugby and cricket associated with the highest injury rates[4] and basketball, volleyball, and ice hockey less important causes of injury.[3]

Other data on sport and leisure accidents and injuries are incomplete and found in disparate sources. Most importantly, they are not readily accessible to sporting organisations, sports safety bodies, and accident prevention agencies that could use them to review sports safety regulations and develop strategies to prevent injury. Nor are they readily accessible to health professionals, who have to deal with a changing pattern of sports injury as sports change and new activities such as roller blading are introduced.

We suggest that three particular areas merit attention. Firstly, a strategy should be formulated to collate all existing data on leisure accidents and injuries. Individual sports safety organisations and both statutory and voluntary agencies involved in preventing or responding to accidents currently invest substantial resources in gathering such data. These data, however, are currently not brought together to produce a detailed picture. Secondly, much better linkages (healthy alliances) need to exist between national sports organisations and health agencies and health professional bodies to facilitate a better understanding of the causation of leisure accidents and injuries and to promote joint action. Thirdly, although the Finnish insurance registries' data[1] and the data from the British leisure accident surveillance scheme give a broad picture of sports accidents and injuries, epidemiological research exploring these issues in greater depth[5] is necessary to give the detailed information required for the formulation of strategies to promote safety and prevent leisure accidents and injuries.

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Adverse life events and breast cancer

Other studies have found no association

EDITOR,—The latest interview study about adverse life events and breast cancer, by C C Chen and colleagues, reports a positive link,[1] but wider review of the literature shows a contradictory picture.[2] Retrospective interview studies on this topic are hampered by unavoidable problems. A diagnosis of cancer has often been correctly predicted by the patient or interviewer before the results of biopsy are known, which increases the likelihood of overreporting of stress in an effort to explain the illness. The temporal relation of previous life events to the onset of cancer is impossible to assess because the onset of cancer cannot be dated. Furthermore, patients with benign breast disease may not be a suitable comparison group.

These limitations can be overcome by large population record studies in which the focus of interest is restricted to two major adverse life events—widowhood and divorce—which can be objectively verified and dated. Such studies yield little or no evidence that widowhood or divorce is related to the onset or outcome of breast cancer.[3-5]

Interactions among external stress, psychoneuroimmunological responses, and the breast cancer process are complex and fascinating, but their clinical importance remains in doubt. Chen and colleagues have carried out a careful study, but their claim to have shown "a significant aetiological association between life events and development of breast cancer" goes beyond their data and could be misleading and unhelpful for the patients concerned.

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Association may be due to imbalance in ratio of adrenal androgens to glucocorticoid

EDITOR,—C C Chen and colleagues report convincing evidence for an association between life stress and breast cancer but suggest that it would be a formidable task to account for this association with a biologically plausible mechanism.[1] Recent studies carried out by my group into the regulation of the synthesis of oestrogen in breast tumours from postmenopausal women have indicated a possible mechanism by which adverse life events could enhance this synthesis.

Oestrogens are the most potent mitogens available to support tumour growth, and it has recently been established that the activities of several of the enzymes that are involved in tumour oestrogen synthesis—for example, aromatase, oestrone sulphatase, and oestradiol dehydrogenase—are regulated by cytokines such as interleukin 6 and tumour necrosis factor α.[2] Most of the cytokines that are available to stimulate tumour oestrogen synthesis result from the infiltration of lymphocytes into tumours. Some of these cells, the T helper cells, are now known to exist as two main subsets, Th1 and Th2 cells; each subset secretes a different profile of cytokines. Interleukin 6 is secreted by Th2 cells, and there is now good evidence that the progression of T helper cells to either the Th1 or the Th2 phenotype is governed by the ratio of adrenal androgens and their metabolites (for example, dehydroepiandrosterone and androstenediol) to glucocorticoids.[3] Whereas plasma concentrations of adrenal androgens decrease with advancing age, production of glucocorticoid remains relatively constant.

A series of adverse life events would result in an increase in the production of glucocorticoid, which would alter the balance of the progression of T helper cells in favour of a Th2 response and secretion of cytokines that stimulate tumour oestrogen synthesis. Interestingly, some years ago Bulbrook and Hayward showed that the excretion of a low ratio of androgen metabolites to glucocorticoid metabolites (the discriminant function test) indicated women at risk of breast cancer and was also associated with an unfavourable outlook in women with the disease.[4] The discriminant function test has recently been postulated to act as a marker of the production of Th1 and Th2 cytokines and oestrogen synthesis in breast tumours.[5]

If this postulated mechanism is correct then it is worth exploring the possibility of using adrenal androgen replacement therapy to prevent breast cancer.

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Reservations about conservative surgery for early breast cancer

EDITOR,—Several points need to be made before there is a wholesale switch to conservative surgery for breast cancer.[1]

I find the proposal that tumours up to 4 cm in diameter are suitable for conservation surgery extremely worrying. Whenever new and apparently less radical treatment becomes available it is important that patients should be carefully selected. Experience in Nottingham suggested that tumour size of over 2 cm was a risk factor for local recurrence after conservation surgery,[2] and I would therefore be reluctant to treat tumours much larger than 2 cm by such surgery. It goes without saying that the tumour must be unifocal, and surgical excision margins must be clear of tumour if local recurrence rates equivalent to those associated with mastectomy are to be achieved.

Removing all invasive carcinoma is not usually particularly difficult technically, but I find it much more difficult to ensure that all resection margins are clear of associated ductal carcinoma in situ. I have the feeling that pathologists are increasingly reporting associated in situ change, and radiotherapy cannot be expected to salvage inadequate surgery.

It is a moot point whether patients with high tumour grade and lymphatic and vascular invasion should be treated by conservation surgery.[3] While the grade of the tumour may be known preoperatively from fine needle aspiration cytology or biopsy, this is by no means always the case. Furthermore, the grade is not always accurately identified on cytology or biopsy, and lymphatic

and vascular invasion is adequately assessed only in resected specimens. For that reason any woman having conservation surgery should be warned that if histological examination of the resected specimen shows adverse factors she will need a mastectomy later.

While I accept that there may be no definite evidence at present associating better local control with improved survival, I think that most of us feel uneasy when we see local recurrence in a conserved breast and wonder whether we have jeopardised that patient's chances of long term survival.

Finally, and until we have a cast iron method of detecting occult axillary lymph node metastasis before surgery, a level II or III axillary dissection must be performed in all patients having conservation surgery for invasive carcinoma.

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Use of aspirin in secondary prevention of coronary heart disease is rising

EDITOR,—We can confirm Ray King and Jonathan Denne's findings of an increased use of low dose aspirin in secondary prevention of cardiovascular disease[1] and have a suggestion for why there may be a difference in the prevalence of such treatment between the sexes and how this might be overcome.

Throughout 1994 and 1995 the Burn Brae Medical Group, a practice of six partners with 8200 patients in a market town, carried out three audits of the subject. A computer search followed by analysis of both computer and written notes identified 531 patients with cardiovascular disease (myocardial infarction 111, angina 304, transient ischaemic attack or cerebrovascular accident 92, and peripheral vascular disease 91; many patients had more than one vascular disease). Initially 255 patients were taking aspirin (men 148/280 (53%), women 107/251 (43%)). At the end of the second audit, after telephone contact or postal questionnaire and invitation to a specific consultation with their general practitioner, the number receiving low dose aspirin had increased to 342, with a significant difference between the sexes (197 (70%) men, 145 (58%) women; $P<0.01$). In July 1995 we therefore carried out a third audit of 100 patients from the original cohort. All were aged under 75 (50 men; 50 patients taking aspirin). The response to a telephone or postal questionnaire (85% response rate) showed no difference between the sexes in the advice offered by general practitioners, and heeded by patients, about stopping smoking, taking exercise, reducing dietary fat, and taking low dose aspirin. As would be expected, those not taking aspirin were less likely to have been given this advice (26/41 (66%) *v* 42/44 (95%) for both sexes). Women were more likely to complain that aspirin upset their stomach (7/43 (16%) *v* 3/42 (7%)).

One of the most interesting findings was that, while the vast majority of patients (75) confirmed that television, radio, newspapers, and magazines were other sources of information about the benefits of stopping smoking, taking exercise, and reducing cholesterol, a considerable number (24) specifically commented that they had not seen similar information about low dose aspirin.

We suggest that, although low dose aspirin is being increasingly prescribed, general practitioners should give specific advice to take aspirin to all high risk patients. Possibly women are less tolerant of low dose aspirin than men. Finally, national health educational bodies should target the media to increase society's knowledge of the benefits of low dose aspirin in the secondary prevention of cardiovascular disease.

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Misoprostol in patients taking non-steroidalanti-inflammatory drugs

Analysis excluded important events

EDITOR,—N Maiden and R Madhok's editorial[1] highlights the rough halving of the incidence of serious gastrointestinal complications associated with non-steroidal anti-inflammatory drugs that was achieved with coadministration of misoprostol in a recent trial in almost 9000 patients.[2] The authors point out the relevance of these results to clinical practice by adopting the valuable "numbers needed to treat" approach advocated by Cook and Sackett.[3] They do not, however, take into account that the study's statistical power was based on the overall rate of serious upper gastrointestinal events, incorrectly asserting that bleeding was no less common in patients taking misoprostol. They therefore focus inappropriately on, and apply the number needed to treat values solely to, one subgroup of events (perforation and gastric outlet obstruction). Consequently, the risk-benefit implications of the overall results are not explored fully. This exclusion of events regarded as serious by predefined criteria gives a misleading perspective.

The serious events comprising the primary end point (perforation, gastric outlet obstruction, and bleeding) showed a 68% higher incidence in the group unprotected by misoprostol; this was attributable to 17 additional cases, of which eight were associated with bleeding. Number needed to treat analysis, if it is to help determine the overall benefit to the community in both medical and cost terms, must at least take account of all the events on which the primary end point was based.

On an annualised basis the number who would have to be treated with misoprostol to prevent one such serious event was 132. Within this figure there was substantial variation among high risk groups (table 1). These data suggest that age groups other than just those over 75 receive significant benefit from coadministration of misoprostol, and the data are comparable to those for other prophylactic treatments, such as antihypertensive drugs, that are routinely used to prevent complications of comparable severity.[4] Furthermore, an annualised rate of 1·5% for serious iatrogenic gastrointestinal complications[2] suggests that these complications are arguably relatively common, rather than "relatively rare" as the editorial suggests. Complications induced by non-steroidal anti-inflammatory drugs are, for example, 50-100 times more common than thromboembolism in women taking oral contraceptives and carry a fivefold greater risk of death, with an annual mortality of the same order as that from carcinoma of the cervix or asthma. The 40-50% reduction in serious complications provided by misoprostol needs to be considered in this context.

Table 1—*Number of patients who would need to be treated for one serious event to be prevented*

Patients	No to be treated to prevent one serious event		
	All ages	Age ≥65	Age ≥75
All	132	110	150
With previous cardiovascular disease	102	71	72
With previous peptic ulcer disease	26	20	11
With previous gastrointestinal bleeding	20	16	7

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This reduction in risk is deemed worth while in other circumstances

EDITOR,—In their editorial N Maiden and R Madhok discuss the prophylactic use of misoprostol in patients over 65 who are taking non-steroidal anti-inflammatory drugs.[1] They conclude that 493 patients would need to be treated to prevent one gastrointestinal complication (defined as perforation or gastric outlet obstruction). Despite acknowledging the potential deaths arising from such events they do not recommend universal prescription of misoprostol, stating as a major reason the relatively large number who would have to be treated, along with the side effects and cost.

This reduction in risk could, however, be compared favourably with other, better established, aspects of prevention in medicine. For example, the Medical Research Council's trial of treatment of mild hypertension in 1985 concluded that one stroke could be prevented for every 850 patient years of treatment with antihypertensive drugs.[2] Yet few people would deny the potential side effects or cost involved in this commonplace primary care intervention. Another, more topical example concerns dilemma faced by those women deciding whether to continue to take a third generation oral contraceptive. In fact, over 330 000 women would have to change their pill from one containing gestodene or desogestrel to an older combined pill to prevent one death from venous thromboembolism a year.[3] Nevertheless, this small scale of risk does not seem to have prevented the prompt issue of specific warnings from the Committee on the Safety of Medicines to the public[4] or from the Family Planning Association to the profession.[3]

The decision to intervene therapeutically in any given situation obviously depends on a variety of medical and social factors. Being consistent with regard to the true risks and benefits is evidently still a long way down on our list of priorities.

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