referred to in the personal communication to Swedberg, but in our trial withdrawals for this reason were according to prespecified criteria and in line with usual clinical practice.

The size of our trial was indeed based on a comparison of active with placebo treatment, but, as we pointed out, an assessment of the two active agents was an important secondary objective from the outset. The advantage of the diuretic over the β blocker was clear, particularly for coronary events, and is also suggested by other recent results.[1] Swedberg is surely not suggesting that findings of such immediate clinical relevance should remain unreported.

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Life events and breast cancer prognosis

EDITOR,—As Jennifer Barraclough and colleagues[1] point out, the findings of their prospective study of life events and breast cancer prognosis differ from those of a cross-control study undertaken at Guy's Hospital.[2] Possible reasons for these apparently discrepant results should be sought before any influence of severe life experiences on relapse of breast cancer is dismissed.

At Guy's Hospital cases and controls were carefully matched for the major factors that influence outcome, including histological grade and number of involved nodes. At Southampton this information was not available. Thus important imbalances could have been present between patients with and without severe life experiences.

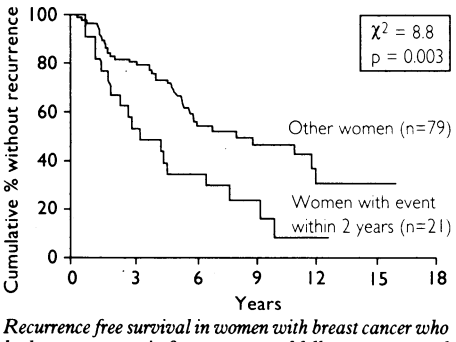
Clearly, knowledge of relapse status introduces the possibility of bias, but this is possible in any life events study as events can be ascertained only retrospectively. In the Southampton study the patients were not blind to their disease status at the time of an interview, and it must have been difficult for the interviewer to remain so. Bias in the rating of severity of events can be minimised if this is done by a panel of judges who are unaware of disease status, as was the case at Guy's Hospital.

At Guy's Hospital all interviews were conducted with the patients themselves, whereas for 11 of the 47 patients who relapsed at Southampton a final interview was conducted only with next of kin and for two other patients who relapsed no interview was performed. This could have led to under-reporting of severe life experiences in a most important group.

The apparently high incidence of severe "own health" experiences not related to breast cancer observed at Southampton, affecting 21 patients during the 42 month follow up, was surprising. No such severe health experiences were recorded at Guy's Hospital. We were therefore interested in the finding that severe own health experiences had a significant adverse effect on outcome ($p=0{\cdot}01$). The authors comment that it makes intuitive sense that patients with breast cancer in poor general health are more vulnerable to relapse. This is unproved.

The power of the Southampton study was diminished by the fact that 42 patients declined to participate and that these patients had a higher death rate (and presumably higher relapse rate) than those interviewed. We estimate that with 204 patients entered and a 23% relapse rate the study had about a 50% chance of detecting a difference between the groups if the true relative risk attributable to serious life experiences is 2·0.

Differences in the use of tamoxifen between the two studies may be important. At Southampton most postmenopausal women with positive nodes received tamoxifen. None of the patients at Guy's Hospital received tamoxifen (all patients presented initially before 1987). An intriguing possibility arises that the beneficial effect of tamoxifen could be partly mediated by counteracting any adverse effect of severe events. This benefit might be most pronounced in hormone sensitive tumours. In the Guy's Hospital study the influence of severe events on relapse was most apparent among the patients with tumours positive for oestrogen receptors.[3]



Recurrence free survival in women with breast cancer who had a severe event in first two years of follow up compared with other women in study (patients followed up to January 1991)

In our view the question of whether serious life experiences influence relapse is still unresolved. We are conducting a prospective study similar to that reported by Barraclough and colleagues, in which we are also assessing the impact of severe events on immunological and endocrinological variables. We would also encourage Barraclough and colleagues to re-examine the outcome for their patients after a longer follow up. This would not entail collection of further data on life events as we found that severe events occurring within the first two years after diagnosis were largely responsible for the positive outcome of our study (figure).

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EDITOR,—Jennifer Barraclough and colleagues report the lack of an association between psychosocial stress and relapse in breast cancer.[1] The results of their prospective study contrast with those of two studies showing a positive association between adverse life events and the onset and relapse of breast cancer.[2,3] The results of all three studies are based on data obtained with the same interview (the life events and difficulties schedule), suggesting that Barraclough and colleagues' opposite conclusions arise from differences in the design and analysis of their study.

Given the slow evolution of many breast cancers, the period of assessment before relapse may need to be several years. Geyer found an excess of adverse life events in the eight years before diagnosis in patients with breast cancer compared with controls.[2] The study of Ramirez *et al* covered life events over a median of 30·5 months before relapse.[3] A comparable figure is not given in Barraclough and colleagues' paper, but as the maximum period of assessment was 42 months the average period covered by the life events and difficulties schedule was probably shorter.

Barraclough and colleagues' patients were older (54·3 years) than those in the studies of Ramirez *et al* (49·5 years) and Geyer (45·5 years). These age differences may be clinically important as they are likely to be associated with differences in menstrual status, pathology, and the types of adverse life events experienced. Sixty per cent of Barraclough and colleagues' patients were postmenopausal compared with 31% in the study of Ramirez *et al*. As it may be hypothesised that psychosocial stress influences the onset or progress of cancer through indirect hormonal effects, these differences between study samples may be important in explaining contradictory results.

It would also be relevant to know what proportion of patients in both studies received tamoxifen, and their hormone receptor status. Allied to this, certain combinations of medical and surgical interventions may conceivably conceal the limited effects of psychosocial adversity on the disease process. Differences in treatment may also account for the lack of an association between life events and prognosis in certain studies.

These studies make the questionable assumption that all patients react similarly to adverse events. Yet, clearly, some people become more upset than others after the death of a spouse, loss of employment, or other major events. The link between adverse events and physical health may become clearer if an attempt is made to understand the way in which psychosocial stress interacts with personality and coping style to influence physiological processes.

The possibility of an association between psychological factors and the course of physical disease is a fascinating but clinically unimportant issue in the assessment of patients with cancer. Although future studies may confirm that adverse life events do not shorten the life span of such patients, psychological interventions can result in a significant improvement in quality of life for many of them.[4]

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Psychological influences on cancer and ischaemic heart disease

EDITOR,—Anthony J Pelosi and Louis Appleby summarise recent research by Eysenck and Grossarth-Maticek about psychosocial influences on cancer and ischaemic heart disease.[1] They raise several critical questions; among them they suggest that "one is left to speculate whether the authors have made the mistake, during reanalysis of their data, of reassigning individuals to personality types after causes of death were known."

In an issue of *Psychological Inquiry*[2] a target

article by Eysenck was published,[3] based mainly on the work of Grossarth-Maticek. Over 15 commentaries, nearly all of them highly critical, have addressed the statements made by Eysenck (and Grossarth-Maticek).

In my commentary I described part of a study reanalysing the data collected by Grossarth-Maticek.[4] I concluded that information about survival and mortality, as provided by Grossarth-Maticek, in some treated and control subjects from the individual treatment study is misleading and does not represent actual longevity due to a mix up of names, addresses, and actual cause of death. I also showed that Eysenck and Grossarth-Maticek published in 1991[5] mortality data that they had withdrawn in 1988.

In my commentary I also stated that the treatments, as described by Grossarth-Maticek and Eysenck,[6] were not fully documented. Inspection of a German language source shows that the individual treatment included many more detailed ingredients, such as taking part in an exercise programme, changes in the diet, and taking vitamins and medications.[7]

It is a disservice to scientists, therapists, and patients that the "revolutionary" results of Eysenck and Grossarth-Maticek could have been published without adequate description of all the methods used to obtain them. Colleagues and I have shown that psychosocial interview responses and some somatic data (blood cholesterol concentration and the number of leucocytes) were used twice in Grossarth-Maticek's Heidelberg studies.[8,9] All of this is bad news for the trustworthiness of Grossarth-Maticek's data from the Heidelberg studies of 1972.

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Altitude induced illness

EDITOR,—In writing on altitude induced illness A J Pollard makes two controversial assertions.[1] The first is that people with the highest ventilatory response to hypoxia have the least symptoms of acute mountain sickness, and the second is that high carbon dioxide concentrations (from inspired air in experimental conditions) worsen the symptoms of mountain sickness.

Though some studies have suggested a correlation between a poor ventilatory response and the development of acute mountain sickness,[2] several more recent studies fail to show such a correlation.[3,4] Indeed, neurological symptoms (including memory loss, aphasia, and impairment in visual motor tasks) are often worse in subjects who have a higher hypoxic ventilatory response, and such symptoms last longer in this group on return to lower altitudes.[5]

There may be two reasons for these findings. The first is that while subjects with high ventilatory response to hypoxia have greater oxygen saturation when they are awake and active, they may suffer longer periods of desaturation when they are asleep due to periodic breathing (Cheyne-Stokes respiration). Periodic breathing has been reported to be greater in people with a higher hypoxic ventilatory response,[6] and the effect of the resulting low oxygen saturation during sleep may predominate as a cause of acute mountain sickness. The second reason is that a high hypoxic ventilatory response results in a low arterial carbon dioxide partial pressure, which causes cerebral vasoconstriction and so reduces cerebral blood flow. While this may reduce susceptibility to cerebral oedema, it may also reduce oxygen delivery to the central nervous system, and in some subjects this latter effect may predominate in the genesis of neurological symptoms.

Contrary to Pollard's assertion, breathing gas with a high concentration of carbon dioxide (2-5%) can actually improve the symptoms of acute mountain sickness. This was first suggested by Douglas and Haldane, from this laboratory, in 1913,[7] and the observation has been repeated numerous times since then.[8-10] Carbon dioxide probably works by causing cerebral vasodilatation and so improving blood flow and oxygen delivery to the brain in those subjects in whom it is impaired. Certainly, the best treatment for altitude induced illness is to descend, but the physiology is less clear cut than Pollard's editorial suggests.

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AUTHOR'S REPLY,—Jaideep J Pandit draws attention to the controversy surrounding the pathogenesis of altitude induced illness, which I alluded to in my editorial.[1] I support Pandit's view that the relation between a poor hypoxic ventilatory response and symptoms of acute mountain sickness is still not clear, although there is some good evidence of a correlation. The most convincing data for a protective effect of a brisk hypoxic ventilatory response come from a study of 42 trekkers by Hackett *et al*, who inferred the hypoxic ventilatory response from measurements of carbon dioxide partial pressure (pCO_2) before and at the end of a trek from Kathmandu to Pheriche (4243 m).[2] Subjects with the lowest pCO_2, implying a high hypoxic ventilatory response, had the highest oxygen saturations and the least symptoms of acute mountain sickness. Many other field studies, but not all, are flawed by the few subjects and other confounding factors such as age differences and previous experience of altitude, and it is difficult to draw satisfactory conclusions about the role of hypoxic ventilatory response.

Pandit's comment that subjects with the best hypoxic ventilatory response suffer the worst long term neurological deficit is not related to the previous argument. Indeed, Pandit agrees that a brisk hypoxic ventilatory response protects against cerebral oedema by lowering pCO_2 and therefore decreasing cerebral blood flow while at the same time reducing the delivery of oxygen to the brain and increasing the risk of neurological deficit.

Pandit's suggestion that breathing carbon dioxide improves symptoms of acute mountain sickness gives cause for concern. There is considerable evidence that hypocapnia protects against mountain sickness and that normal or raised levels of carbon dioxide precipitate symptoms by increasing cerebral blood flow. Maher *et al* studied people in a hypobaric chamber and showed that eucapnic hypoxia increased the severity of acute mountain sickness.[3] Field studies by others have supported this view.[2,4,5] Possibly the degree of hypoxia determines whether carbon dioxide has a beneficial or deleterious effect, and this deserves further attention. Carbonic anhydrase inhibitors probably work in prophylaxis against mountain sickness by stimulating the respiratory centre (through a reduction in intracellular pH), increasing ventilation, and lowering pCO_2 and therefore cerebral blood flow rather than by a direct effect on pCO_2.[6]

Inhaled carbon dioxide should not be recommended in treating altitude illness while there is such strong evidence that it may cause a deterioration in the person's condition. If in doubt go down.

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1 Pollard AJ. Altitude induced illness. *BMJ* 1992;**304**:1324-5. (23 May.)
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EDITOR,—A J Pollard gives sensible, practical advice on preventing and treating altitude induced illness and mentions using acetazolamide to prevent the symptoms of acute mountain sickness.[1] Though prophylactic treatment with acetazolamide for those ascending to altitude helps protect against acute mountain sickness,[2] it does not necessarily protect against the severe life threatening complictions of high altitude pulmonary or cerebral oedema. Indeed, by masking the symptoms of acute mountain sickness treatment with acetazolamide may encourage trekkers or mountaineers to ascend more rapidly than is advised and hence put themselves at increased risk.

The advice that acetazolamide should be used above 3000 m seems appropriate for the Himalayas or Andes, but many of the climbing huts in the Alps are also above this altitude. Descent to lower altitudes is usually, however, much simpler in the Alps, and it seems inappropriate to treat walkers or climbers visiting the Alps with acetazolamide.

Acetazolamide may help prevent the symptoms of acute altitude sickness in visitors to high altitude. It should not, however, be used to shorten the time spent in acclimatisation. The best treatment for people with more severe symptoms or high altitude cerebral or pulmonary oedema is rapid descent. Whether it is appropriate to use