infection (58·8), and 86 after an episode of erysipelas (64·7). The number of pneumonia cases during follow-up was low in the latter three groups. In these groups, age but not diagnosis was significantly (p <0·05) related to the risks of pneumonia developing or of dying.

Therefore, these three groups were combined as "other infections" (OI group, n = 332) and compared with the group that was initially admitted for pneumonia (PN group, n = 241). Average follow-up was 31 months in the PN group and 35 in the OI group. Because risks of pneumonia and death were strongly age-dependent, and because mean age was higher in the PN group than in the OI group (60 vs 54 years), analysis was stratified by age. 62 cases of pneumonia were diagnosed during follow-up (50 PN group, 12 OI group). Overall incidence of pneumonia per 100 person-years was 8·1 for the PN group and 1·2 in the OI patients; the dependence of incidence rate on age is shown in the table. After stratification for age, the incidence-ratio (PN/OI) was 5·45 (95% CI 2·89–10·26, p <0·001) uniformly over age-groups (see table). No significant improvement of fit was obtained by introducing different ratio coefficients for each age-group.

94 patients died during follow-up (51 PN group, 43 OI group). 49 of the deaths in the PN group and 38 of those in the OI group were in patients over 50 years of age. The overall death rates in the PN and OI groups were 7·4 and 4·4 per 100 person-years, respectively. After stratification according to age the ratio of death rates (PN/OI) was 1·28 (95% CI 0·85–1·93; p = 0·25). However, there were 13 deaths directly associated with pneumonia in the PN group compared with only 5 in the OI group. After stratification for age, the ratio of pneumonia death rates was 2·75 (95% CI 0·97–44·6; p = 0·06).

We have shown that the risk of re-admission for pneumonia during the 3 years after discharge was more than five times higher if the initial diagnosis had been pneumonia than if it had been another infectious disease. Over one-fifth of patients discharged after a pneumonia had at least one relapse during the study (they were not assessed for multiple episodes). A previous episode of hospital-treated pneumonia seems to be an important marker for increased risk of having a new pneumonia that will require treatment in hospital. We also found that patients with pneumonia at age over 50 had substantial mortality during the 3 years after discharge. Mortality directly associated with pneumonia was significantly higher in the PN group than in the OI group, and there was a tendency for higher overall mortality in the PN group.

Since S pneumoniae is the leading cause of pneumonia among older people,[1,9] pneumococcal vaccination of patients discharged after treatment for pneumonia should be a very cost-effective measure, provided that good vaccine efficacy can be confirmed. We have therefore started a prospective, randomised, placebo-controlled study to evaluate the protective effect of the 23-valent pneumococcal vaccine in patients aged 50–85 years who are discharged after an episode of pneumonia in hospital.

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Effect of indomethacin plus ranitidine in advanced melanoma patients on high-dose interleukin-2

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Preclinical models of advanced melanoma have shown that chronic indomethacin therapy combined with interleukin 2 (IL-2) can eradicate experimental metastases. A phase II trial was done in patients with advanced melanoma. Indomethacin and ranitidine were begun at least one week before IL-2. Of the objective responses in 3 patients, 2 were achieved on ranitidine and indomethacin alone, before start of IL-2. Indomethacin and ranitidine may be responsible for some responses in melanoma patients previously attributed to IL-2.

Treatment of advanced malignant melanoma with biological response modifiers, particularly recombinant human interleukin-2 (IL-2), has attracted considerable interest. Rosenberg and colleagues,[1] using high-dose bolus IL-2 combined with ex vivo generated lymphokine-activated killer (LAK) cells, noted an objective response rate of 21%. Since then several trials of high-dose IL-2 with or without LAK cell reinfusion in advanced melanoma have been reported (mainly by the National Cancer Institute IL-2 Extramural Working Group[2-5]), with response rates of 3–22%, accompanied by considerable toxicity and cost.

A phase II trial was done in patients with advanced melanoma; it was based on murine studies that showed a reduction of metastatic nodules with the chronic use of indomethacin or IL-2, with almost complete eradication when both agents were combined. Intermittent indomethacin given only during IL-2 therapy (as in most high-dose IL-2 trials, to alleviate fever, chills, and myalgias) gave poorer results than did chronic indomethacin, indistinguishable from those obtained with IL-2 alone.[6]
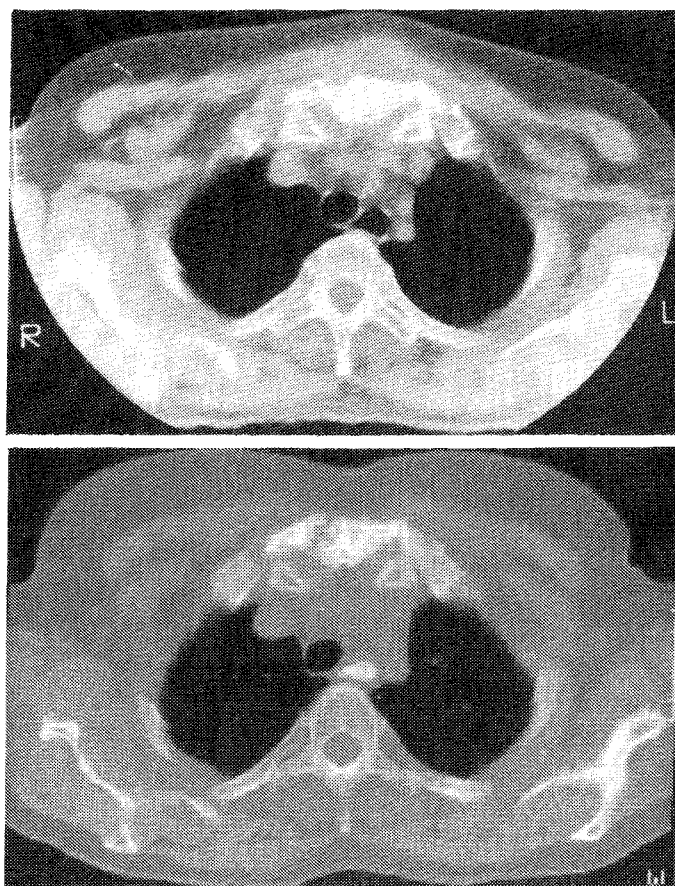
Patient 1—CT of thorax showing soft tissue mass and lytic lesion of sternum (upper) and resolution of mass after a month on indomethacin and ranitidine (lower).

Eligible patients started indomethacin 50 mg orally every 8 hours and ranitidine (to reduce dyspepsia) 150 mg orally every 12 hours. Both drugs were given for at least 7 days before IL-2, and were continued at maximum tolerated doses throughout IL-2 infusions, during rest periods, and for at least one month after completion of IL-2. Human recombinant IL-2 (Cetus, Emeryville, California) was given by continuous intravenous infusion for 5 days, followed by 6 days of rest; IL-2 doses were 18×10^6 IU/m^2 daily for the first course, with escalation to 36×10^6 IU/m^2 daily for the third course, toxicity permitting. Three objective responses were seen in 21 eligible patients; two of these were achieved before IL-2 treatment.

Patient 1—A 50-year-old woman noted pain in her upper sternum and manubrium in 1987; 1 year later a mass was found protruding in the region. It grew slowly, measuring 10×5 cm at the beginning of 1989. Biopsy revealed an anaplastic tumour with premelanosomes consistent with a diagnosis of melanoma. No primary lesion was found. Computed tomography (CT) of the thorax (figure) revealed a destructive lesion of the sternum and manubrium with a soft tissue mass. In May, 1989, the mass measured 13×10 cm; the only abnormal biochemical result was serum lactate dehydrogenase (LD) (315 U/l, normal 177 U/l). Indomethacin and ranitidine were started. Four weeks later the mass measured 9×6.5 cm; eight weeks after starting treatment it measured 6×4 cm and consisted of distorted bone. CT (figure) showed complete resolution of the soft tissue mass but a persistent lytic lesion in the sternum; LD had returned to normal. IL-2 was started, with no further change. The patient remained in partial response for fifteen months, when CT showed enlargement of the lytic lesion without recurrence of the soft-tissue mass.

Patient 2—A 60-year-old man with an ulcerated melanoma that had been previously excised was noted on routine CT to have multiple hepatic metastases measuring 1–2 cm, as well as pulmonary metastases. Two months later, repeat CT scan revealed enlargement of the hepatic metastases, and LD was raised (410 U/l). Indomethacin and ranitidine were started. One week later chest

radiography as well as CT of thorax demonstrated complete resolution of the pulmonary nodules, and CT of abdomen revealed a reduction in the size and number of hepatic metastases. Three months later, chest radiography, liver ultrasound, and CT of thorax and abdomen showed no evidence of disease, and serum LD was normal. At the patient's request, IL-2 was not started. He remained in complete response for ten months, when multiple cerebral metastases developed.

The finding that 2 patients responded objectively to the combination of indomethacin and ranitidine alone, before IL-2 was given, raises a methodological drawback of previous IL-2 trials. Most trials use indomethacin and ranitidine starting on the first day of therapy with IL-2 to relieve treatment-related symptoms. Any responses due to indomethacin and/or ranitidine would be attributed to IL-2 as the experimental, and presumed effective, intervention; these would not be detected as a result of clinical trial design. The time to response and duration of response in our 2 patients are consistent with those described in other reports of IL-2-based therapies[3] and might well have been attributed to IL-2 if the cytokine had been given concurrently. For this reason, investigators using potentially toxic cytokines should assess the contribution of co-administered drugs to the therapeutic response.

Several clinical trials have been of cimetidine alone or in combination with other agents, with mixed results.[7,8] Only one case of tumour regression (melanoma metastatic to lung) has been associated with ranitidine therapy in man,[9] and there have been no reported trials of this agent, or of indomethacin. However, the non-toxic combination of indomethacin and ranitidine may be useful in inducing responses in patients with advanced melanoma. A clinical trial of these agents alone, in the same doses used here, is now underway.

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