normal, immunocompetent animals, those suffering from an immune deficiency should display a higher incidence of cancer in early life, but a lower incidence in later life (Fig. 1b). In fact, this prediction concurs with experimental results obtained in athymic nude mice [16]. One can conclude furthermore from Fig. 1b that an immune deficiency occurring early in life will only facilitate the development of early-onset tumours such as, for instance, those of lymphoreticular origin. In contrast, an immune depression appearing late in life will inhibit the development of late-onset tumours.

In summary, the juvenile immune system apparently helps to control cancers whose incidence is associated with early life. In contrast, the immune conditions described by the ageing paradox appear to facilitate a remodelling of mammalian tissues, thereby stimulating the development of late-onset cancers.

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The Darkest Ages of Tobacco

IN THE face of suggestions of information fatigue among readers and viewers of the mass media, finding something new to say about the health risks of smoking tobacco is hard. At a meeting at the Imperial Cancer Research Fund (ICRF) in London to highlight a report in *The Lancet* (23 May 1992), Professor Richard Peto, from the ICRF Cancer Studies Unit at Oxford University, said, "Most people already know that smoking is dangerous, but most people don't realise how enormous the risks are."

In their study, Peto, with Dr Alan Lopez from the WHO Tobacco or Health Unit in Geneva and colleagues from the American Cancer Society, show that tobacco smoking will cause a much worse rate of premature death in middle-age than was previously estimated. They report a new technique to forecast the mortality from tobacco in developed countries, specifically in the 1990s and with extrapolation into the next century.

They used the absolute lung cancer rate in a population as a marker to predict the proportions of the deaths from other diseases attributable to tobacco. The advantage is that smoking-attributable mortality can be estimated from other years and from other countries. Smoking may cause about three times as many deaths from other diseases (e.g. other cancers, and respiratory and vascular diseases) as from lung cancer. The method has been made conservative to avoid overestimates and the results seem free of anomalies. The analysis was restricted to developed countries, which have reliable population and mortality statistics.

The technique shows that the annual deaths from smoking in 1985 were about 1.7 million in developed countries; the 1995 forecast is 2.1 million, or about 21 million for the 1990s. Taking middle-age as 35–69, Peto and his co-workers predict that tobacco smoking will cause about 30% of all deaths in middle-age (plus about 14% of deaths at older ages). This makes tobacco the biggest single cause of premature death. Indeed, on average, the mean loss of 1985 life expectancy from smoking in middle-age is around 23 years. With present rates of smoking, about one-fifth of the current population in developed countries will be killed by tobacco, i.e. about 250 million out of nearly 1.25 billion. This attrition rate is equivalent to the entire population of the USA.

In 1995, the number of deaths due to smoking in the European Community will be 571 000. The UK (151 000), Germany (110 000) and Italy (108 000) will have the highest rates. In the USA, the numbers will be 557 000 and, in Japan, 110 000. In the former USSR, the figure will be 507 000, and, in Poland, 102 000.

One of the reasons for the misunderstanding about the link

between smoking and dying is the long delay between cause and effect. Around the world, women generally start smoking later than men. So, whereas the increases in the numbers of men dying because of tobacco are largely due to population growth, the numbers of women dying is because of an increasing death rate due to smoking. Although the EC 'leads' for the highest number of men dying due to tobacco (466 000 predicted for 1995), the USA has the largest number of female deaths, with forecasts of 318 000 men and 240 000 women dying in 1995 because of smoking.

Peto and colleagues also forecast to the year 2025. For all developed countries at current smoking patterns, the tobacco-related deaths in 2025 could be 2.6 million for men and 0.8 million for women. However, if the female death rate rises at present trends, the figure for females could be over 1 million. For less developed countries, the investigators estimate the numbers at 5–10 million.

The tragedy for smokers is not only that they misunderstand (or perhaps have been misled) about the risks, but they also do not realise the benefits of stopping. "Those who stop before they have cancer or serious heart or lung disease avoid most of their risk of death from tobacco," stated Peto.

Premature death due to tobacco is an avoidable disaster. We must act aggressively now against tobacco use. Otherwise, as Dr Antonio Novello, US surgeon General, says, "We will fail the generations of tomorrow." In November, the EC has the opportunity to take another sort of lead, when member states meet to vote to ban tobacco advertising.

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Papers

4-Hydroxyandrostenedione: A New Treatment for Postmenopausal Patients with Breast Cancer

R. Charles Coombes, Stuart W.M. Hughes and M. Dowsett

We have evaluated 4-hydroxyandrostenedione, a specific inhibitor of aromatase, as treatment for breast cancer in a phase I dose-ranging study and a phase II study of the best-tolerated dose. 168 postmenopausal patients with locally advanced and metastatic breast cancer were treated intramuscularly. 19% of patients attained a complete or partial response but 26% of those who completed at least 4 weeks treatment responded. Side-effects were least in the group receiving 250 mg every 2 weeks. 13% of patients experienced local discomfort due to the injection and 5% had other side-effects. Serum oestradiol fell to 42.4 and 26.5% of baseline at 7 days after the start of treatment with the 250 mg and 500 mg dose, respectively. We conclude that 4-hydroxyandrostenedione at 250 mg every 2 weeks is a safe and effective form of treatment for postmenopausal patients with metastatic breast cancer.
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INTRODUCTION

IT IS GENERALLY ACCEPTED that tamoxifen is the first-line treatment for postmenopausal patients with advanced breast cancer. However, there is need for an effective second-line endocrine therapy for two reasons. Firstly, all patients eventually become resistant to tamoxifen and often relapse with metastatic breast cancer that is still hormone sensitive, and secondly more patients now have their first relapse with tamoxifen-resistant metastatic disease since often they have received tamoxifen immediately postoperatively and have relapsed despite this therapy.

Conventional treatment for these patients includes progesterone preparations (e.g. medroxyprogesterone acetate) or steroid synthesis inhibitors such as aminoglutethimide. However, these therapies often cause side-effects. The most troublesome are fluid retention and psychological side-effects for progesterone preparations [1] and inhibition of cortisol synthesis, drowsiness and skin rashes for aminoglutethimide [2].

Our strategy has been to develop a 'pure' inhibitor of the aromatase enzyme system which possesses neither the sedative effects nor the other non-specific enzyme inhibitory effects of aminoglutethimide.

Oestrogens in postmenopausal women are derived mainly

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