Eur J Cancer, Vol. 28A, No. 12, pp. 1939–1940, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Immune Ageing and Cancer

AGEING IS commonly considered the major risk factor for the development of cancer. The age-related increase in the incidence of most types of cancer appears to be coupled to the intrinsic ageing process rather than merely to the chronological time of exposure to potential carcinogens [1, 2]. Consequently, the ageing process seems relevant to current cancer research [2]. How ageing influences the development of cancer is largely unknown as yet. However, there is general agreement that ageing and cancer share potential primary causes, which can be summarised as involving some form of genetic instability [3, 4]. Precisely how genetic instability is related to the ageing process remains to be investigated.

One possible link between ageing and cancer is provided by the immune system. The classical model of immune surveillance predicts that the age-associated rise in cancer incidence is due to the decline of normal immune function which occurs with age [5]. But a consistent role for immune surveillance in opposing the cancer process does not find general consent. On the other hand, immune stimulation of carcinogenesis has been suggested [6]. It is possible however that both aspects can be combined to give an integrative approach which appears to be useful in understanding diverse features of cancer. Genetic instability is taken here rather arbitrarily to increase linearly with age.

Immune ageing is characterised not only by a progressive deficiency in the normal response to neo-antigens but also by an increasing response to self-antigens. This phenomenon is referred to as the "ageing paradox" (Fig. 1a). The associated immune conditions may interfere selectively with the development of altered cell phenotypes which arise owing to genetic instability. Normal T-cell responses can decline substantially with age [7]. Regarding autoimmunity, mainly the humoral response which is directed preferentially to intracellular antigens [8] has thus far been studied. However, although rarely investigated, there appears to be a further age-related cellular activity directed towards autologous cell-surface antigens. For instance, during ageing of mice, T cells acquire the ability to respond to syngeneic target cells [9, 10]. As a result of such changes in the T-cell responder repertoire, one would speak of a primary autoimmunity which is possibly related to an age-dependent functional abrogation of clonal deletion in the involuting thymus [11]. A potential autoimmune response is considered here to be affected by the general decrease of immune function with age [12], thus providing a lower apparent autoreactivity (Fig. 1a).

In mammalian life, then at least three periods of differing immunological conditions should be distinguished (Fig. 1b). In the first period of life, the fully developed immune system is expected to eliminate all such aberrant cells which can be recognised by presentation of neo-antigen on their surface. Consequently the selective pressure to maintain the originally established antigen repertoire will keep cancer incidence low.

In a second period, the age-related decline of normal immune function will increasingly allow aberrant cells to survive. Simultaneously, a growing autoimmunity directed to normal cells will select for aberrant cell variants which display high genetic instability and can therefore, by an altered expression of cell surface antigens, escape autoimmune elimination. In consequence, the probability of cancer developing will be substantially enhanced, and its incidence can be expected to increase. In parallel, cancer cells will be allowed to display greater immunogenicity.

A third period arising in old age may be characterised by the gradual loss of all immune functions. At this point, cancer incidence is expected to return to the level determined solely by genetic instability.

In this way, the probability of cancer development should increase up to old age and decline again thereafter. The incidence of human cancer, combined for all sites, in fact supports this expectation [13]. The behaviour of single cancer types can be expected to differ from this general tendency, as has been shown [14].

According to the given model, the age-associated rise in cancer incidence will be related mainly to the existence of an autoimmune response directed to cell-surface antigens. In fact, cancer appears to be accompanied by an unusually high autoimmune activity [15].

In the past, immunodeficient or immunosuppressed animals have been considered suitable to investigate the role of the immune system in cancer development. As compared with normal, immunocompetent animals, those suffering from an

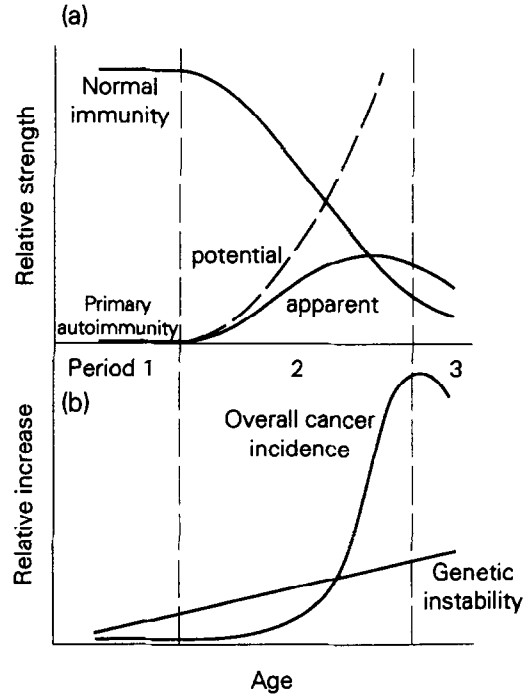

Fig. 1. Schematic presentation: (a) The immunological ageing paradox as characterised by both an age-related decrease of normal immune responses and an autoimmunity whose potential increase likewise undergoes an age-dependent depression. (b) Age-dependent overall cancer incidence as qualitatively predicted from the combined action of genetic instability and immune ageing.

Received 3 June 1992; accepted 23 June 1992.

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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Acknowledgements—I thank Prof. A. Macieira-Coelho for a critical comment. This study was supported by a grant from the Sandoz Foundation for Gerontological Ressearch.

Eur J Cancer, Vol. 28A, No. 12, pp. 1940–1941, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

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