ELSEVIER

European Journal of Cancer 41 (2005) 12–14

European Journal of Cancer

www.ejconline.com

Editorial Comment

Infection, vaccination and protection against melanoma – a ray of hope for novel preventive and therapeutic strategies?

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Received 17 September 2004; accepted 22 September 2004
Available online 6 November 2004

In an address to the Pathological Society in London in 1874, a distinguished surgeon, Campbell De Morgan, presented his observations that cancers occasionally underwent spontaneous regression [1]. He added that such regression was sometimes associated with infections including tuberculosis. Other workers in the late 19th century confirmed the link between infection and cancer regression and one, the American surgeon William Coley, administered extracts of bacteria causing erysipelas ('Coley toxins') to patients with sarcoma, with apparent success in some cases [2]. Unfortunately, the advent of radiotherapy and chemotherapy led to Coley's therapy being sidelined and marginalised and, until relatively recently, this and other attempts to prevent and treat tumours by vaccination or immunotherapy generally met with cynicism and even hostility [3].

However, in recent years advances in cancer biology and an unravelling of the intricacies of the immune system, especially its role in immunosurveillance, has generated a much more optimistic climate. One of the reasons for a resurgence in interest in the possibility of developing effective immunological tools for the prevention and treatment of cancer is the increasing acceptance of the so-called 'hygiene hypothesis'. This hypothesis states that the immune system requires successive exposure to various micro-organisms in the environment for its normal maturation and development of regulatory pathways. Millions of years of evolution have led the immune system to 'expect' a range of microbial challenges which, in the industrially developed nations, are now denied to it by an increasingly sanitised environment. Such environmental changes commenced at least a century ago and have been particularly evident since the end of the Second World War when the antibiotic era began and lead to a further deprivation of the natural consequences of bacterial infections among those born after 1945 [4]. Accordingly, it has been postulated that the ensuing immune dysregulation is responsible for the increasing incidence of cancer as well as allergic disorders and autoimmune disease in the industrialised world [4–6].

In this context, factors enhancing the exposure of young children to a range of common infections and other microbial challenges, such as having older siblings, attending day-care facilities and living on farms, significantly protect such children against asthma and other allergic disorders [7]. Acute leukaemia, the commonest malignancy seen in children, occurs particularly in affluent societies and it has been postulated that this disease is likewise associated with an 'immune proliferative stress' resulting from environmental factors resulting in reduced exposure to 'natural' childhood infections [6].

This postulate was confirmed by two epidemiological studies which clearly demonstrated that the same hygiene-related factors, such as attending day-care facilities, that protect against allergic disorders, protect against childhood leukaemia [8,9]. These observations call for a serious consideration of possible strategies to prevent the immune dysregulation induced by today's environment in the industrialised nations. Clearly, advances in hygiene and infection control have contributed enormously to human health and there is no question of turning the clock back to the era of widespread infection

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.09.024

and its attendant mortality. However, it may be possible to use certain vaccination strategies to compensate for or replace the natural stimuli that cause the normal maturation of the immune system. This possibility is suggested by observations that Bacille Calmette-Guerin (BCG) vaccination affords protection against leukaemia, particularly when given neonatally and in regions where it also protects against tuberculosis [10].

In view of the growing evidence for a protective effect of certain natural infections and vaccinations against leukaemia, a series of multi-centre studies under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC) were undertaken to determine whether these factors also protected against melanoma, the course of which is known to be affected by host immune reactivity. One of these studies demonstrated that persons who had received BCG or smallpox vaccinations, or both, had approximately half the risk of subsequently developing melanoma than unvaccinated control subjects matched for gender, age and ethnic origin [11].

A further study by the same group showed that certain uncommon and severe infections with high fever, including pulmonary tuberculosis and sepsis due to *Staphylococcus aureus*, significantly reduced the risk of melanoma [12]. A subsequent evaluation of the impact of both infections and BCG and/or smallpox vaccination suggested that they operated through the same, or a very similar, mechanism [13]. It would therefore seem possible to use vaccination strategies to confer optimum protection rather than relying on chance and unwanted severe natural infections.

Having demonstrated a preventive effect of vaccinations on melanoma, the next question was what implication, if any, would such prior vaccinations have for those who developed melanoma? The results of a study to answer this question are published in this issue of *EJC* [14] and strongly suggest that the prognosis of melanoma patients who have previously received BCG and/or smallpox vaccination is significantly better than unvaccinated patients.

Taken together, these findings add to the growing evidence that immunological events early in life can have a lasting impact on the risk of developing a cancer and they show, for the first time, that they affect the course of the disease in those in whom it is not prevented. This clearly calls for a hypothesis to explain these challenging and exciting observations and one is presented in a further paper in this issue of *EJC* [15]. In this hypothesis, the role of human endogenous retroviruses (HERVs) in the both the pathogenesis of, and the induction of immune protection against, melanoma is discussed. There is growing evidence that HERVs, which make up some 8% of the human genome and have been sequentially acquired over millions of years, have played a key role in evolution by their ability to generate multiple copies of themselves which insert into various promoter and other regulatory genes [16]. HERVs, like volcanoes, ultimately become dormant, but more recently acquired ones such as those of the HERV-K series may show some activity and have the potential to disrupt intracellular functions, particularly those promoting oxidative stress [17], leading to malignant change, but also to the coding of antigenic determinants that are presented on the cell surface and serve as targets for various immune defence mechanisms. These defence mechanisms may result in classical cytolysis of the malignant or pre-malignant cell, but may also facilitate the repair of cells that have not reached an irreversible stage of malignant change. Therapeutic correction of defects in the regulation of these immune responses could result in optimum protection.

There is increasing evidence that HERV expression is not only linked, as cause or effect, with several cancers including melanoma, sarcoma, and carcinoma of kidney, ovary and breast, but also with autoimmune disease [18]. This suggests that such expression is affected by the hygiene-related factors that have been linked to the increasing incidence of these diseases in industrialised nations. Accordingly, 'hervology' may become an important subject in 21st century medical research.

It is important that the apparent protection afforded by vaccination with BCG and/or vaccinia against melanoma demonstrated in the EORTC studies, and the previous claims that BCG vaccination protects against childhood leukaemia, is confirmed by other investigators. It will also be of great importance to determine whether protection against other solid tumours is likewise conferred. Although questions of cause and effect remain, there is evidence that several cancers are associated with immune dysregulation superficially manifesting as changes in the balance between Th1 and Th2 helper T lymphocyte populations, notably by a 'Th2 drift'. Cancers in which such changes are demonstrable include colorectal, bladder and renal cell carcinoma and papilloma virus-associated cervical cancer [19].

If firm evidence for protection against some or many cancers is demonstrated, a re-introduction of BCG vaccination, at least as a first step, for all newborns should be given serious consideration. Subsequently, the characterisation of HERV-encoded antigens expressed by tumours may well facilitate the development of a more specific anti-cancer vaccine, perhaps based on the yellow fever vaccine or the MVA variant of vaccinia as a carrier. Alternatively, the carrier could be a mycobacterial adjuvant affecting immune regulation with, in particular, a downregulation of inappropriate Th2 T cell activity [19].

Confirmation of the hypothesis will require detailed studies on the role of oxidative stress in the induction of malignant change, now greatly facilitated by the techniques of fluorescence activated cell sorting and X-ray microanalysis [17], and on the underlying mechanisms

of immunoregulation. In addition, studies of vaccination strategies in different environments, with high and low incidences of melanoma and other cancers, will shed light on underlying mechanisms. It is possible that protection against melanoma and possibly other cancers by vaccination may be high in regions with a rising incidence of disease due to increasing immune dysregulation, but relatively less so in regions with a low incidence of disease in a population with more effectively regulated immune responses. In this context, the protective efficacy of BCG vaccination against tuberculosis varies enormously from region to region as a result of environmental factors affecting immune reactivity [20].

In addition to prevention of cancer, these studies encourage further efforts to develop immunotherapeutic strategies for use in this disease. The congruency between malignancies shown in the past to respond to therapy with Coley toxins and those often expressing the HERV-K-encoded antigen on their cell surfaces is noteworthy. It has recently been suggested that the fever induced by Coley toxins has an essential therapeutic action by generating certain co-factors required for an effective immune response [21]. Indeed, in the early 1970's, attempts to treat human cancers by active 'non-specific' immunotherapy took advantage of observations that chronic infection with the living intracellular protozoa *Toxoplasma gondii* or *Besnoitia jellisoni*, conferred resistance to experimental mouse tumours and even totally suppressed the endogenous-retrovirus-associated spontaneous leukaemia in AkR mice [22,23], an effect thought to result from activation of macrophages [24]. Alternatively, a suitable adjuvant might be used to ensure that the immune response to the antigen is an appropriate and well regulated one.

Although much more work in the field and the laboratory is required, these studies add significantly to the growing conviction that the human body is not defenceless against cancer. On the contrary, it has very powerful defences, although these can be adversely affected by environmental factors. These studies provide hope that such adverse effects can be counteracted by simple vaccination strategies and that effective immunotherapeutic strategies against established cancers may not be far away.

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