NEWS AND VIEWS

Cancer and Immunity

IT would be hard to find a cancer researcher who would these days deny that the state of an animal's immune defence system crucially affects its response to carcinogens and transplanted cancer cells or that the growth of cancer cells into a tumour is correlated with at least a partial failure of the immune system. Indeed it has been seriously argued that the immune system first evolved as a defence mechanism against autochthonous tumour cells and only secondarily became adapted as a defence against infecting microorganisms and other foreign antigenic materials arriving from outside the individual. But if one of the chief functions of the immune system is to provide a surveillance mechanism which can recognize and destroy cancer cells because they carry tumour antigens on their surfaces which are not present on normal cells, how do tumours ever develop? In other words, by what mechanism is the immune system undermined to such an extent that tumours can grow and metastasize?

In an attempt to shed some new light on this crucially important question, Ambrose, Anderson and Coggin at the Oak Ridge National Laboratory have analysed the role of circulating antibodies during the development of tumours in hamsters injected with Simian Virus 40. And as they report on page 321 of this issue of *Nature*, they believe that cytostatic antibodies play an important part in tumorigenesis, during the early stages of which they seem to prevent the rapid proliferation of the initially arising tumour cells. Once the tumour, in the face of these antibodies, reaches some critical mass, however, tumour antigen becomes locally in excess, swamps the available antibody and cell mediated immunity and uncontrolled growth ensues.

In spite of its limitations, Ambrose and her colleagues chose to use as their model system Simian Virus 40 as a carcinogen for baby hamsters for three chief reasons; first, the virus reproducibly induces tumours; second, all SV40 induced tumours bear the same transplantation antigens; and third, and most importantly, it is possible to block the induction of tumours by immunization with either SV40 virus or SV40 tumour cells killed by irradiation.

The first problem encountered by Ambrose *et al.* was to devise ways of distinguishing the effects on tumorigenesis of humoral or antibody immunity responses from those of cellular immunity mediated by sensitized lymphocytes. That cellular immunity plays an important part in the defence against cancer is, of course, indisputable—non-immune animals, for example, can be protected against tumour cells by injections of lymphocytes from immune animals—but the role of antibody immunity is much more obscure and is something Ambrose *et al.* were intent on elucidating. To test whether antibodies as well as lymphocytes in animals immune to SV40 tumours can kill or at least prevent the proliferation of SV40 tumour cells, they placed such cells in plastic chambers permeable to antibodies in the peritoneal cavities of immune and non-immune hamsters. Circulating antibodies in the immune animals, but not those in the controls, retarded or prevented the proliferation of the cells.

The Oak Ridge group then exploited this technique to follow the course of appearance of these cytostatic, if not cytotoxic, antibodies during the latent period between the injection of SV40 virus into newborn hamsters and the appearance of tumours months later. During the first ten weeks of life the amount of circulating cytostatic antibody increases and in those animals which do not develop tumours, even after 500 days, antibody persists, but in those animals fated to develop tumours the amount of this antibody declines precipitously after about ten weeks. These findings suggest that during the first ten weeks after injection with SV40, transformed tumour cells are present but latent and indeed such cells can be detected by histopathology. Furthermore, by incubating SV40 tumour cells with sera from normal hamsters, immune hamsters and tumour bearing animals, Ambrose and her colleagues proved that sera of immune animals but not tumour bearing animals prevent the multiplication of tumour cells *in vitro*.

There can be no doubt that circulating antibody from immune animals is cytostatic, but sera from animals with tumours lack this material. A further set of experiments established three important facts about this antibody: first, it seems to be invariably produced before tumours appear; second, it retards tumour growth; and third, it is always present in immune animals. And if the transient appearance of the antibody precedes the appearance of tumours, what happens when tumours are removed by surgery; does the antibody reappear? As might be anticipated, it reappears in at least some animals.

What is the simplest interpretation of all these data? Ambrose and her colleagues, who firmly believe as a result of their own experiments as well as those of others, that the so-called tumour specific transplantation antigens are probably normal early embryonic antigens caused to be re-expressed by transformation, draw an analogy between the tolerance of a foetus and the survival of a tumour. They believe that immediately after exposure to a carcinogen, a small tumour mass is established and may for a few hours grow without restriction. But as cytostatic antibodies are produced the rate of proliferation of surviving tumour cells is greatly reduced and during the latent period the tumour mass increases only gradually. When, however, a critical mass is reached the cytostatic antibodies are locally mopped up by an excess of tumour antigen. The tumour cells can then grow rapidly producing more antigen and as this excess builds up circulating antibody becomes undetectable and amounts of antigen always outweigh amounts of antibody, unless of course the tumours are removed by surgery. And once antigen is in excess, antigen–antibody complexes may block cellular immunity and even cause immune enhancement.

This scheme clearly contains many elements of speculation but it is nonetheless attractive and suggests that assays for antitumour antibodies, be they cytostatic or cytotoxic, might provide an early warning system for human cancers still in their latent period and an indication of when treatment of established tumours is being successful.