news and views

Immune surveillance revisited

from R. W. Baldwin

THE immune surveillance theory as developed by Burnet (*Immunological Surveillance*, Pergamon Press, Oxford, 1970) proposes that a central role of the immune response is to provide a natural defence against cancer and this was later developed to emphasise the importance of thymus-dependent lymphocytes. It was, therefore, more than a little disconcerting to find that congenitally athymic (nude) mice do not have an increased incidence of spontaneous cancers and they are no more susceptible than conventional mice to chemical carcinogens (reviewed by Stutman, *Adv. Cancer Res.* **22,** 261; 1975).

It is axiomatic, however, that nothing in tumour immunology is simple and it has recently been proposed that whereas T lymphocytes may be an important component of the responses induced by immunological manipulations, such as immunotherapy, they may not have a central role in more natural conditions such as those involved in recognising clones of transformed cells. Instead, attention is being focused on so-called 'natural killer cells' since these fit almost exactly the immunologists' design for a surveillance cell in being able to recognise and kill malignant cells without previous sensitisation. The basic observation which drew attention to natural cell-mediated immunity arose out of quite extensive studies comparing the *in vitro* cytotoxicity of peripheral blood lymphocytes from cancer patients and normal donors for cultured cancer cells. Initially these investigations were interpreted to show clear-cut specific cytotoxicity by 'sensitised' lymphocytes from patients, but in later studies by Takasugi *et al.* (*Cancer Res.* **33,** 2898; 1973) and Oldham *et al.* (*J. natn. Cancer Inst.* **55,** 1305; 1975) it became apparent that lymphocytes from normal individuals, who would not be expected to have been exposed to the relevant cancer-associated antigens, were also cytotoxic. Moreover in many instances the natural cytotoxicity of lymphocytes from normal individuals was even greater than that seen with similar preparations from cancer patients. Natural cell-mediated immunity has since been examined using more closely controlled animal systems and, as in humans, lymphocytes from normal mice and rats have proved to be cytotoxic *in vitro* for tumour cells, especially those of lymphoid origin.

In the mouse and rat, normal killer (NK) cells have been detected in most lymphoid organs, with particularly high activity in the spleen, lymph node and peripheral blood whereas in humans, studies have mostly been restricted to peripheral blood lymphocytes. In mice NK cells develop in the absence of the thymus and appear and disappear in a highly typical manner, reaching peak levels at between 5 and 8 weeks of age. NK cell activity is also under genetic control, allowing the classification of low and high NK cell strains. The position in other species, especially humans, is still unclear, but it has been proposed that NK cell activity may be related to HLA phenotype. The characterisation of NK cells is more controversial and it is this aspect of the problem which leads to most confusion. In the mouse, the NK cell is thought not to be a mature T cell because of its presence in athymic mice, although Herberman and Holden (*Adv. Cancer Res.* **27,** in the press) have suggested that it might be a primitive T cell. The characteristics of NK cells in humans are even less well understood and at present the only point of general agreement is that these cells are not macrophages.

Although it has been implied that natural killer cells may provide the host with a natural barrier against malignant cells, evidence on this point is sparse. The resistance to growth of transplanted tumours, including those of human origin, in athymic nude mice has been correlated with their high levels of natural cell mediated cytotoxicity. This evidence is not sufficiently compelling, however, since these animals have been reported by Pimm and Baldwin (*Nature* **254,** 77; 1975) to be able to reject tumours through macrophage-mediated reactions. More convincing are studies by Kiessling and his associates (*Int. J. Cancer* **15,** 933; 1975) correlating the growth potential of transplanted tumour cells in different strains of mice with their levels of NK cell activity. Also within one strain Sendo *et al.* (*J. natn. Cancer Inst.* **55,** 603; 1975) found that resistance to a transplanted tumour changed with age in a pattern similar to the known age-dependent variation of NK cell activity. These approaches have been further extended in a study now published by Haller *et al.* (this issue of *Nature*, page 609) which provides more direct evidence for a role of NK cells in suppressing tumour growth. Mice were thymectomised, irradiated and reconstituted with anti-T-cell treated bone marrow cells or foetal liver cells. When lymphoid cell donors of a compatible substrain of high NK cell activity were used, the transplanted tumours were rejected, whereas no resistance was observed in mice receiving cells from donors with low NK cell activity. These findings point to the potential of NK cells in tumour resistance, although whether they have a 'decisive role' remains to be established. In this context, it is pertinent that cells with similar characteristics to NK cells can be isolated from tumour biopsies, and that bacterial vaccines such as bacillus Calmette Guerin (BCG) and *C. parvum* which are being widely used in cancer immunotherapy trials markedly influence NK cell activity. One should guard against a too unitarian view, however, since many of the approaches for enhancing nonspecific immunity against cancer by the use of bacterial vaccines are known to require macrophages. Nevertheless the concept of a nonspecific lymphocyte which recognises abberrant cells is attractive for the immunosurveillance concept and augmentation of these cells could have therapeutic potential. □

Robert W. Baldwin is Professor of Tumour Biology in the University of Nottingham.