Section of Neurology

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Neuroimmunology

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Immunological Aspects of Gliomas

In the past fifteen years or so it has become apparent that the cells of certain forms of cancer are weakly antigenic and can evoke a host immune reaction – so-called tumour immunity – which can, on rare occasions, lead to rejection of the cancer. Most of the evidence relating to cancer immunology is derived from experimental work on animals, but increasing evidence suggests that similar immunological reactions against living tumour cells can occur in certain human malignancies such as Hodgkin's disease, breast cancer, Burkitt's lymphoma and malignant melanoma. The possibility of treating tumours by manipulating the patient's immune response to encourage tumour rejection raises the question whether this approach might be used to treat gliomas. Before considering this, it is necessary to outline some of the special problems facing glioma immunologists.

One of the major stumbling blocks which discouraged immunologists from applying their techniques to brain tumours was the conclusion drawn by Medawar (1948) that immunological rejection does not occur in the brain. It is common knowledge that a foreign skin graft transplanted from one person to another will be rejected unless the individuals are identical twins. However in his studies of skin rejection in rabbits, Medawar found that if a piece of foreign skin was implanted into the brain of a rabbit, the skin was not rejected. Medawar therefore concluded that the rejection process could not act in the brain which, to use his phrase, was 'immunologically privileged'. Clearly the immunotherapy of gliomas would not seem a very promising prospect if this were the case. It is now realized, however, that the brain is not a strictly privileged site, since rejection of foreign solid tissue and tumour grafts does occur in the brain, although rejection takes a few days longer (Ridley & Cavanagh 1969).

The rejection of foreign tissue or tumour grafts in the brain of experimental animals is associated with a lymphocytic cellular response around the graft. This histological observation suggested to Professor John Cavanagh and me that we should look at human glioma tissue for evidence of lymphocytic infiltration. Accordingly we examined autopsy slides from 100 glioma patients who had died at The London Hospital and found lymphocytic infiltration in one third of the cases (Ridley & Cavanagh 1971). Fig 1 shows the type of lymphocytic infiltration observed. A recent biopsy study of human glioma tissue by Takeuchi & Barnard (1976) also revealed lymphocytic infiltration, especially in gemistocytic astrocytomas. Similar lymphocytic infiltration has been found in other human cancers such as breast (Hamlin 1968), and it has been suggested that it may indicate a

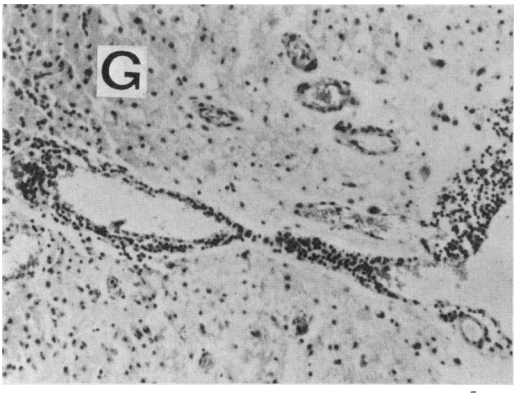

Fig 1 *Small round cell cuffing near a glioma* (G). *The brain parenchyma is lightly infiltrated with small round cells which can be seen emigrating from the vessels. H & E. × 140*

Table 1
Results of lymphocyte cytotoxicity assay in 6 glioma patients (G10–G28) and one with an acoustic neuroma (AN2)

	Residual tumour cells/well		
	Patient	*Control*	*% cytotoxicity*●
G10	375	642	42
G15	425	586	27
G16	571	735	22
G17	249	312	20
G25	33	62	45
G28	136	156	13
AN2	24	44	48

● Cytotoxicity calculated as follows:
$$\left(1-\frac{\text{Residual tumour cells per well treated with patient lymphocytes}}{\text{Residual tumour cells per well treated with control lymphocytes}}\right)\times 100$$

favourable prognosis, since it represents evidence that the patient is attempting to reject the tumour.

Another method of looking at the problem of glioma immunity is to use an *in vitro* lymphocytotoxicity technique to see whether blood lymphocytes from glioma patients can kill their own tumour cells when these cells are grown in culture. With the collaboration of neurological and neurosurgical colleagues at The London Hospital this technique has been used to study glioma patients (Rainbird & Ridley 1977), and our preliminary results suggest that the lymphocytes of some glioma patients are cytotoxic for glioma cells. Cytotoxicity of 30% or more is usually regarded as significant, and Table 1 shows that in patients G25, G10 and perhaps G15 there was evidence of *in vitro* lymphocyte killing of autologous cultivated glioma cells. Lymphocyte cytotoxicity may also be observed in benign intracranial tumours such as acoustic neuromas (patient AN2 in Table 1). It thus appears that some patients with gliomas may be able to mount an immunological attack against their tumours. If this is so, how may they be helped to mount a bigger and better attack? One method currently receiving attention involves giving repeated doses of BCG to stimulate the patient's immune defences and thereby increase his ability to resist his own tumour cells.

Experimental work on BCG has been carried out by cancer immunologists all over the world, but tumours of the nervous system have so far attracted little attention. In view of our interest in gliomas we decided to use an experimental system consisting of malignant schwannomas induced in pure-line rats by the chemical carcinogen ethylnitrosourea (Ridley & Rainbird 1976). We found, as have other workers using different experimental systems (Baldwin & Pimm 1973), that BCG immunotherapy can effectively slow down the rate of growth of transplanted tumours. Unfortunately, BCG has a marked effect on tumour growth only if it is brought into intimate contact with the tumour cells by direct injection into the tumour; in addition, its effect is limited to tumours of small size; once a tumour has gained a foothold, the effect of BCG is much less impressive. In the case of gliomas the tumour is usually large by the time it is diagnosed, and direct injection of live avirulent tubercle bacilli into a brain glioma poses considerable problems. Further work may lead to ways of countering these difficulties, or open up other immunological approaches.

The present position in regard to gliomas, as with other solid cancers, is that immunotherapy on its own is not yet feasible. This is not surprising when one considers how little is known about tumour-associated surface antigens in human astrocytomas (Coakham & Lakshmi 1975) or host immunity to gliomas. Nevertheless, two groups of workers, in France (Trouillas *et al.* 1969) and in England (Bloom *et al.* 1973) have attempted immunotherapy in glioma patients. Trouillas claimed that survival may have been lengthened, but Bloom's study failed to demonstrate any beneficial effect. Indeed, there was evidence from Bloom's study that immunotherapy shortened rather than lengthened survival, suggesting that immunotherapy can lead to enhancement of tumour growth instead of rejection.

Such studies seem to me to be at present inappropriate. Much more research, both in patients and in experimental animal models, is needed before we can hope to plan meaningful therapeutic studies. Meanwhile effort would be better spent in building up our knowledge of glioma immunology, leaving immunotherapy until more is known about what we can hope to attain.

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HLA Antigens in Multiple Sclerosis

Central to all mammals investigated is a group of closely-linked genes which relates to a number of different immunological processes. In man this genetic region has been designated the HLA complex, which consists of a variety of different genes; it is known to be located on a segment of Chromosome 6 (Lamm *et al.* 1974). Several different *in vitro* techniques have been used to identify some of the gene products present on the cell surfaces.

The HLA-A and -B as well as the HLA-C antigens are detected by the microlymphocytotoxic test. These specificities, considered loosely to be the HLA antigens, are expressed on cells of most tissues, although only weakly – if at all – on red cells (Fig 1).

The mixed lymphocyte reaction (MLR) is based on the ability of specific antigens on the lymphocyte surface controlled by the HLA-D locus to elicit a proliferative response in allogeneic lymphocytes (Yunis & Amos 1971). Until recently it was only possible to test for D-locus identity between two individuals. More recently, by the use of homozygous typing cells (Bradley *et al.* 1973, Jorgenson *et al.* 1973, DuPont *et al.* 1973) and sperms (Halim & Festenstein 1976), it has proved possible to type for individual D-locus specificities. The tissue distribution of the D-locus antigens is more restricted than that of the HLA-A, -B and -C antigens.

Additional antigens have been detected, almost exclusively on B cells and not T cells, by B-cell serological techniques. These antigens are considered analogous to the original Ia genes found in the I-A region of the murine H-2 system which controls antigens detected predominantly on B cells (Sachs & Cone 1973). At least two genes controlling B-cell antigens in humans have been established in the HLA complex but not yet mapped.

Several features mark the gene products of the closely linked HLA-A, -B, -C, -D and B-cell genes. They are highly polymorphic; more than twenty each of HLA-A and HLA-B, five HLA-C and eight HLA-D antigens have been identified (Kissmeyer-Nielson 1976). Also, some specificities, but not others, of the different systems occur together more frequently than can be explained by chance, e.g. HLA-A1 and HLA-B8 occur together in about 10% of individuals. Since their respective frequencies are approximately 20% and 15%, they should occur together, if randomly distributed, in only 3% of individuals. This phenomenon, known as linkage disequilibrium, also explains why, for instance, HLA-DW2 is more closely associated with HLA-B7 and HLA-DW3 with HLA-B8. In addition, the HLA complex controls genes whose products are involved overtly in *in vivo* phenomena. A number of different components of complement are controlled by genes within the HLA complex – both the C^2 and C^4 polymorphisms and their serum levels have been shown to be determined by genes located in the HLA complex (Möller 1976).

Antigens of major importance in kidney graft rejection have also been shown to be products of

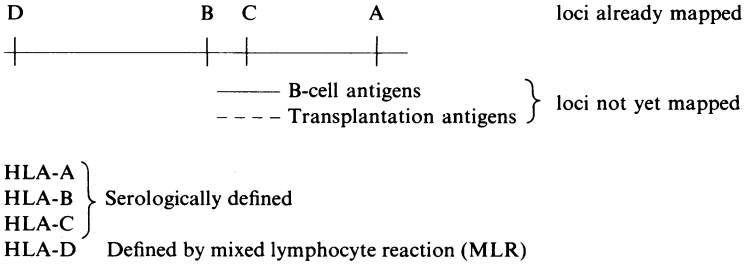

Fig 1 *HLA region of Chromosome 6*