Unusual Metastasis of a Human Colonic Tumour Xenograft in the Hamster Brain

It is commonly believed that malignant tumours do not retain their capacity to metastasize when grown in alien hosts. We have shown, however, that a number of histopathologically diverse neoplasms of human origin can become serially transplantable as highly invasive and metastatic tumours in unconditioned, adult golden hamsters¹⁻³. To explain this unusual event, I have considered the hypothesis that the malignant progression of certain neoplasms in a foreign species is related to a fusion of the genome of donor tumour cells with that of host cells; that is, the production of heterokaryons⁴. Those heterotransplantable tumours that still retain characteristics of their species of origin seem to be more limited in their malignant potential. Nevertheless, Greene and Harvey⁵ have shown that even these are capable of vascular invasion and subsequent blood passage in xenogeneic hosts, but not true metastasis. We report that a usually non-metastatic neoplasm can, in certain circumstances, exhibit metastasis in a xenogeneic host, even while retaining its original species identity.

Fig. 1. Extravascular GW-77 tumour nodules in hamster lung 20 days after intracerebral transplantation. (Haematoxylin and eosin, $\times 150$.)

A human carcinoid tumour of the transverse colon has been successfully propagated in unconditioned golden hamsters for almost 3 yr; morphologically, the carcinoid cells developed into mucin-secreting signet-ring forms characteristic of adenocarcinoma (unpublished findings of D. M. G. and E. R. Fisher). This tumour system (named GW-77) has, even after long term passage in hamsters, retained human antigen and the typically human isoenzyme mobility pattern for lactate dehydrogenase (unpublished results of D. M. G., R. D. Bhan and R. A. Pavia); the very low number of GW-77 cells in metaphase have so far precluded adequate karyotyping for additional species identification.

When transplanted in the hamster cheek pouch, subcutaneously or intramuscularly, no morphological evidence of metastasis was obtained. This is not the case, however, after intracerebral implantation of the GW-77 tumour. Contrary to the experimental findings of Greene and Harvey, who could not morphologically demonstrate metastasis to the lung after intracerebral transplantation of xenogeneic tumours, we find tumour cell emboli and authentic metastatic nodules (Fig. 1) in over 50 per cent of the thirty hamsters transplanted intracerebrally with GW-77 by methods described previously⁶. Transplanta-

tion of a 20 per cent homogenate of lungs from ten of these hamsters having 20 day old brain transplants to cheek pouches of other animals has resulted in viable GW-77 tumours in almost all cases.

This extracerebral retention and proliferation of GW-77 human colonic tumour cells transplanted to the hamster brain is, to my knowledge, the first example reported of metastasis of a xenogeneic tumour still exhibiting properties of its species of origin. Why this preferentially occurs intracerebrally is not clear, yet it does contradict the belief that the rarity of metastasis from tumours of the brain is causally related to the site of origin (blood-brain barrier, absence of lymphatic vessels, anatomical structure of cerebral vessels). The usual failure of metastasis from the brain is perhaps more dependent on factors related to the tumours themselves.

Tumour xenografts seem not only to be capable of retaining their functional differentiation and original species-specific characteristics, but also to exercise their innate biological capacity for invasion and metastasis in the alien environment, though apparently only in the special situation of intracerebral proliferation.

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Cytophilic Antibodies in Passive Antibody Induced Immune Suppression or Enhancement

It was indicated recently that simple neutralization of antigen cannot explain the suppression of immune response by passive antibodies. Moreover, the presence of the Fc fragment of the antibody molecule is required to obtain the inhibitory effect¹. Because the Fc fragment is responsible for cytophilic binding of antibodies to macrophages² or lymphoid cells³, I anticipated that cytophilic antibodies might be involved in the inhibition of the immune response and tested this by examining the immunosuppressive effect of a hyperimmune chicken antihuman serum albumin (HSA) serum deprived of cytophilic activity. The serum (50 ml.) was absorbed six times with calf spleen cells, which were previously washed four times with excess Hanks solution. At each absorption the serum was mixed with 5 ml. of packed cell sediment, incubated 60 min at 4°C and centrifuged 10 min at 1,500 r.p.m. The cell sediments were collected and resuspended in cold Hanks solution. After the last absorption, the pool of cells resuspended in 150 ml. Hanks solution without previous washing was incubated 60 min at 56°C, centrifuged and the eluate was concentrated to 50 ml. In all three preparations (original serum, absorbed serum and eluate) the titre of haemagglutinating antibodies and their cytophilic binding was determined by methods already described^{4,5}. In the absorbed serum the titre of haemagglutination (see legend to Fig. 1) had dropped to 50 per cent of that in the original serum, whereas the cyto-