when cellular oncogenes are activated by ceptive field interpretation comes from a more recent observation on mirror-image grating discrimination — that performance is independent of the number of grating cycles exposed (I.R., M. Hübner and T. Caelli, manuscript in preparation). That is, the underlying mechanism is strictly local. Third, the position of our stimulus patterns varied randomly between presentations. Thus the neural mechanism at issue should have the very property in terms of which Hubel and Wiesel[5] characterized cortical complex cells: the loss of (*absolute*) spatial localization conveyed by simple cells.

While we agree with Livingstone and Hubel that the difficulty in discriminating mirror-image patterns is related to spatial localization, it is not apparent how a cortical cell of known receptive field properties may distinguish between mirror-image grating bars. A class of symmetry-opponent cells would need to be found to explain how the *relative* position of the darker stripes with respect to the background striation is encoded. Such units are expected to give on- or off-responses to bars with skew luminance profiles (or to edges), depending on whether the luminance peak is on the one or on the other side of the bars. When bars with symmetric luminance profiles were shown, the cells should give little or no response. We feel that the existence of such mechanisms for breaking spatial pattern symmetries would be indispensable for understanding the quality of form at the level of single unit responses. Otherwise, the idea of neural template matching would seem insufficient and relational concepts of visual pattern analysis[6] should be considered.

It is obvious that symmetry-opponent cells would be functionally analogous to colour-opponent cells. While the first would encode the relative position of peaks (or troughs) within a spatial luminance distribution, the latter recover information on how the spectral energy is distributed within the wavelength domain. Whether or not such an analogy between the visual analysis of form and colour is more than pure speculation has to be established by physiological research.

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The immunology of host–tumour relationships

SIR—In their helpful review of the impact of molecular biology on our understanding of the development of tumours, George and Eva Klein say *inter alia* that when cellular oncogenes are activated by non-viral mechanisms "the transforming oncogene products are either normal or only slightly modified cellular proteins" and "it is difficult to see how they could provide a rejection target for the immune system".

Yes, indeed, but they omit to say — and the omission may mislead readers less well informed on these matters than the Kleins — that there may be asociated phenotypic changes, and that these may include the expression of what George Klein himself has called "tumour associated antigens with a rejection inducing potential in the autochthonous host (TAARIPAH)". This, it would seem, is the explanation of the high immunogenicity of many chemically-induced animal tumours. Whether tumours which develop in animals or humans as the result of exposure to environmental carcinogens will also be immunogenic depends partly on the properties of the carcinogen and partly on the pattern of exposure; in general, it seems that a single large dose, such as is commonly used experimentally, is much more likely to induce an immunogenic tumour than chronic exposure to small doses of the same or similar agents, which is what happens in many animals or patients who develop so-called spontaneous tumour.

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KLEIN AND KLEIN REPLY—Woodruff's points are very well taken. We wish we could relate the rejection-inducing antigens of the chemically induced rodent tumours to the oncogene field. The fact is, however, that more than 25 years after their discovery, the nature of these remarkable antigens is still unknown. We find essentially nothing new on the subject since we last reviewed it in 1977 (*Proc. natn. Acad. Sci. U.S.A.* **74**, 2121–2125).

One of the important facts mentioned by Woodruff, the difference in the immunogenicity of tumours induced by strong versus weak carcinogens, probably relates to the latency period prior to tumour development. As shown by Old, Prehn, Baldwin and others, immunogenicity is inversely related to the latency period even within a group of tumours induced by the same carcinogen in the same inbred strain. This is probably due to immunoselection. Highly antigenic tumours can only develop if they outpace the immune response. With the passage of time, low or non-antigenic tumours would have a selective advantage and therefore dominate the picture. As Woodruff points out, the latter is a better model of tumour development after the exposure of humans to environmental carcinogens than are experiments conducted with strong carcinogens.

Nevertheless, the molecular basis of the highly specific, individually distinct antigenicity of chemically induced rodent tumours is of the greatest interest. In view of our present ignorance, speculations may range from specific interactions of the carcinogen with certain hot spots of the genome, coding for crucially important surface moieties, perhaps related to the major histocompatibility complex (MHC), to phenotypic changes due to activated oncogenes, as Woodruff suggests.

In the latter context, the effect of the mutation-activated products of the *ras* oncogene family are of particular interest. We have previously argued that immune surveillance against potentially neoplastic clones is most efficient in cases where the host species has been preselected to *anticipate* a large number of transformants with the same or similar antigenic changes. This is best exemplified by the virtually watertight surveillance of mice against polyoma induced tumours or of humans against Epstein–Barr virus (EBV) transformed lymphocytes. Although the nature of the target antigens has still not been clarified, it is noteworthy that products of the viral genome like polyoma virus MT or the LT-3 protein of EBV, the most likely candidate targets of the surveillance reaction, are associated with the inside, or the lipid bilayer of the plasma membrane, rather than the outside. They cause changes in the cell membrane that readily evoke a T-cell mediated, rejection geared response, with avoidance of suppression, but do not, or only with great difficulty, induce the formation of serum antibodies.

As Weinberg repeatedly emphasized, tumorigenic activation of the ras oncogenes cannot by itself lead to tumour development *in vivo*, since its consequences would be lethal for most members of the species at an early stage. This may not happen because of the multi-step evolution of tumours, as discussed in our review, that is, the need for additional genetic changes. Since the p21 *ras* protein is associated with the inner plasma membrane, it is also conceivable, however, that the host immune system may recognize a mutation-altered *ras* product, particularly if it would influence the expression, presentation, or specificity of MHC products.

In view of the frequent mutations of the ras genes, a similar "*immunological anticipation*" may exist as in the viral tumours. This possibility could be readily explored by transfecting non-immunogenic tumours with appropriate *ras*-carrying constructs.

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