established.[5] Technical problems with plasma estimations are not now a serious limiting factor, but to some extent it is the complexity of these drugs and their metabolites that hampers studies relating drug concentrations to clinical response. But perhaps the most important confounding factor is the heterogeneity of the disorders being treated in terms of both aetiology and manifestations.

Finally, the development of techniques for estimating drug concentrations should not lead us to neglect more direct alternative approaches. For example, monoamine oxidase levels in blood platelets provide a useful estimate of the effects of monoamine oxidase inhibitors, and parallel measurements of pharmacological actions may be of practical value in estimating the effects of other classes of psychotropic drugs.[6]

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Genetic association with bladder cancer

The search for causes of transitional cell carcinoma of the bladder has concentrated on environmental carcinogens, following the lead given by the classic studies in the dyeing and rubber industries. Among the personal habits that have been suggested more recently as enhancing the risk of this disease are smoking and coffee drinking. Assessing the relative importance of risk factors in bladder carcinogenesis has become a demanding exercise, requiring large populations in the case and control groups.[1] The latest possibility is that genetic constitution may be a factor—a suggestion advanced by Herring and his colleagues,[2] which will no doubt be the subject of considerable argument.

Herring *et al* examined the ABO antigens and leucocyte HLA types in 101 patients with transitional cell carcinoma of the bladder and 207 controls, all from the Durham hospital area. They found that blood group A was significantly more frequent in patients with bladder cancer than in controls. Two HLA genes, B5 and CW4, were twice as frequent as normal among the patients with cancer. Taking their analysis a step further, they found that patients with superficial tumours with a low incidence of recurrence appeared to be of different genetic constitution to those with more aggressive, invasive tumours. Herring *et al*[2] acknowledged, however, that a study by Terasaki *et al*[3] of HLA genes in 264 Californian patients with bladder cancer, drawn from a complex multiracial population, failed to show the association with HLA-B5, but HLA-CW4 was not in the test system used. The final conclusion of the Durham study was that a person with blood group A and the HLA genes B5 and CW4 carries a 15 times greater than average risk in developing transitional cell carcinoma of the bladder.

The association of ABO blood groups with gastrointestinal cancer and with tumours in organs that secrete blood group substances has been known for some time, but the increase in risk is only double.[4] In consequence, this work has had little practical impact. On the other hand, the study of the positive association of HLA antigens and disease has become a growth industry in applied immunology; hereditary and malignant diseases and any disorders thought to have even a remote chance of having an immunological basis are being screened and generating a plethora of results.

Relations between HLA antigens and some chronic benign diseases are now well established, but, with the exception of the acute leukaemias and Hodgkin's disease,[5] the evidence has not been clear cut from studies of common cancers.[6] The microtests of lymphocytotoxicity used for HLA testing are known to be subject to false-positive results, both from technical errors and from the nature of the lymphocytes being tested.[7] The modification of the circulating lymphocyte population that occurs in many forms of cancer might influence the interpretation of these tests.

The problems associated with the variable natural history of a cancer are apparent in transitional cell carcinoma of the bladder, which may take forms as different as a single incident of a non-invasive well-differentiated tumour and an aggressive tumour invading the bladder wall and giving rise to distant metastases. To this must be added the biological variation in the urothelium, which may vary from being near normal to total instability, when it is likely to produce a recurrent tumour at any site.

Just as there may be genetic associations for a predilection to develop a malignant tumour, possibly other mechanisms may increase resistance. The diversity of response of the urothelium to a carcinogenic insult might reflect differences in both resistance and susceptibility.

The lymphocytotoxicity against transitional cell carcinoma of the bladder cells in vitro of peripheral lymphocytes from patients with bladder cancer is known to be maximal in those with localised tumours and tends to be suppressed when metastases develop. There is also an association between cytotoxicity and lymphocytic infiltration of transitional cell carcinoma of the bladder, which may possibly be a sign of host resistance.[8]

Lymphocytes of workers exposed to industrial bladder carcinogens who have not developed transitional cell carcinoma have recently been found to show a cytotoxicity against transitional cell carcinoma of the bladder cells in vitro similar to that in patients with overt tumours.[9] The results of HLA typing of individuals with these premalignant changes would be most interesting, but, as it is the tail of the cohort of workers exposed to carcinogens some years ago, the more susceptible have already died of transitional cell carcinoma of the bladder. Here is an example of selection pressure at work in a population at risk that could influence the outcome of the study.

At present the genetic associations with transitional cell carcinoma of the bladder are still too uncertain to provide a basis for counselling workers who may be at risk from exposure to industrial bladder carcinogens. We need more information, though the combination of weak associations and fickle tests will require skill and a lot of patience to get at the truth.

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