ventricular outflow tract may also be narrowed, pressure gradients being found in 10 of the 64 patients studied by Braunwald and his colleagues.[8] Nevertheless, pulmonary stenosis is not generally recognised as a feature of hypertrophic cardiomyopathy, since studies on patients always concentrate on the left side of the heart.

The symptoms and signs of acquired pulmonary stenosis differ from those of the congenital form. The symptoms are governed by the underlying cause of the obstruction: thus patients with tumours often have cough, chest pain, and dyspnoea. Symptoms of right ventricular obstruction such as dizziness on exertion are less common but do occur.[1] The fact that the stenosis is a relatively recent acquisition means that the physical signs are less florid than in the congenital form. A systolic murmur is invariable, but its behaviour may be unusual—for example, in a mediastinal tumour it may become quieter during inspiration because this lifts the mass off the pulmonary artery.[3] A rise in venous pressure, right ventricular hypertrophy, and delay of the pulmonary component of the second heart sound provide further useful clues. The electrocardiogram may show right axis deviation, while the lateral chest radiograph may show an anterior mediastinal shadow. The role of echocardiography is seldom mentioned in published reports, but this technique may be invaluable in diagnosing pericardial tumours,[10] and will undoubtedly become increasingly important. The definitive investigation is catheterisation of the right heart, including right ventriculography, which should be undertaken whenever the diagnosis is in doubt so that proper treatment may be advised.

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Monitoring plasma concentrations of psychotropic drugs

At a Ciba Foundation symposium in London on 3-5 July an international group of scientists and clinical research workers met, under the chairmanship of Professor Louis Lasagna of Rochester University, USA, to discuss monitoring drug concentrations in neuropsychiatry. During the meeting a statement on the present position for the various classes of psychotropic drugs was prepared and accepted unanimously by all the members of the group:

Plasma concentrations of drugs are now determined with increasing frequency in many patients, including those who receive psychotropic medicines. Modern chemical methods permit the measurement of most drugs in biological fluids. Like other technological advances, this one has proved a mixed blessing.

Properly performed, drug assays at the very least can identify some causes of failure of patients to respond to treatment.[1] Some patients may not comply in taking medicines as prescribed or may not get adequate amounts of drug in their body for a number of other reasons; low concentrations result, and the drug may be clinically ineffective. Conversely, taking too large doses may lead to adverse effects. Drug monitoring is also valuable at the extremes of life.

The overlap of therapeutic and toxic concentrations, however, demands the application of clinical judgment in assessing a given drug concentration in a given patient. Furthermore, laboratory errors are all too common; grossly inaccurate drug levels are worse than no drug levels at all, and expensive to boot.

Even with drugs for which the usefulness of monitoring is established there are difficulties. The formidable problems involved in the drug treatment of epilepsy include the high prevalence of the disorder; the poor long-term prognosis in many; the need for prolonged treatment; polypharmacy; chronic toxicity; and uncertainty of the relative efficacy and toxicity of individual drugs owing to the poor quality of anticonvulsant evaluation.[2] Fortunately, the plasma concentrations of several major anticonvulsants appear related to their brain levels, to antiepileptic efficacy, and to some of the side effects. General plasma level ranges for effective anticonvulsant action without intolerable toxicity have been ascertained for some antiepileptic drugs, but assays are necessary only in the more severely epileptic patients. Prospective studies in chronic epileptics suggest considerable scope for simplifying and rationalising treatment by reducing the number of daily doses of anticonvulsants and by treating patients successfully with fewer drugs. In many epileptics, too, plasma concentrations are useful to detect non-compliance.

The use of tricyclic antidepressants is an increasingly common approach to the treatment of depression. Many drugs are available and recommended dosages vary. An appreciable proportion of patients fail to show a satisfactory or sustained clinical response; others suffer adverse reactions. Drug compliance is alarmingly low in many patients.

Measurement of plasma drug concentrations may increase the efficacy of antidepressant therapy.[3] In spite of many studies carried out over the past 10 years on the relationship between plasma concentrations of antidepressant drugs and clinical effects, the value of monitoring these drugs is still not clear. There is some evidence for the existence of a therapeutic range within which optimal antidepressant action appears to be obtained.[4]

Concentrations above and below this optimal range may be associated with poor therapeutic response. In some clinical states measurements may be of value—eg, patients who show a poor response, patients who experience side effects, those who have a complicating medical condition or in whom poor compliance is suspected, and for the control of long-term therapy.

Monitoring of lithium concentrations is now routine, not only to help ensure therapeutic levels in the prevention of affective swings but also to avoid adverse effects, both short term and long term. The evidence relating serious adverse effects to high plasma concentrations is now so strong as to preclude the use of lithium except when laboratory facilities are available.

The monitoring of plasma concentrations of neuroleptics and of benzodiazepines is not routine because the relevance of such monitoring to obtaining the best clinical response possible and to minimising unwanted effects remains to be

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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