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Rejecting scientific advice

The decision¹ by Mr Kenneth Clarke, Minister of Health, to refuse approval for the long-term use of the contraceptive medroxyprogesterone acetate (Depo-Provera) is yet another example of Government rejection of the considered judgment of its scientific advisory bodies.

Clearly the Committee on Safety of Medicines had looked at the issue very carefully. The drug has been the target of sustained attack by the Campaign Against Depo-Provera, which claims that it is given to socially deprived, black or Asian women without their being fully informed of its possible side effects and dangers.¹ Nevertheless, medroxyprogesterone acetate has been used for 20 years in many countries, and a recent television programme (BBC2, 1 March) reported that doctors in Thailand found the drug valuable and were surprised at the "unbelievable overstatements" of the pressure groups.²

Here in Britain the Family Planning Association lists medroxyprogesterone acetate as the last of its eight choices for couples wanting contraception, and the Committee on Safety of Medicines recommended that the drug should be used only when all other sorts of contraception have proved unsatisfactory. This guarded acceptance for medroxyprogesterone acetate is due to question marks over its safety and its clinical drawbacks. Firstly, tumours have been reported in monkeys given 50 times the normal dose; the Committee on Safety of Medicines comments that the "relevance of this to man has not been established." Some women given the drug have developed breast cancer—but the association is unlikely to be causal. Secondly, the drug causes unacceptable side effects in many women—menstrual bleeding becomes irregular and unpredictable and may be heavy and prolonged.

Yet with all the evidence before it the Committee on Safety of Medicines was prepared to approve the drug. Mr Clarke would not accept that advice.¹ The Government believed that the possible risks outweighed the benefits, he said, adding that "Each individual doctor cannot make a judgment about

whether a particular drug is necessarily safe. They rely on the licensing system."

As we have argued before,³ the Government should not reject the advice of its own experts without giving its specific detailed reasons for doing so. On this occasion Mr Clarke seems to have been swayed by anecdotal reports of the drug being given to mentally handicapped or mentally ill women without their informed consent. What he is saying in effect, however, is that doctors cannot be trusted to exercise competent clinical judgment in the use of a second-line drug.

Certainly there is room for improvement in the standards of prescribing in the NHS, and by no means all official warnings about drugs are heeded by prescribers. But the Committee on Safety of Medicines was set up to assess the safety of drugs on objective grounds; it has a high reputation around the world for balancing the needs of consumers against the needs of doctors and the pharmaceutical industry. Doctors have learned to pay close attention to its advice, and this is especially true of its advice on contraceptives.

In these circumstances Mr Clarke may reasonably be asked to give a much more detailed and convincing justification for his decision. Without such an explanation his actions are unacceptably authoritarian.

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Blood group antigens and bladder cancer

The discovery of A and B blood group antigens on the surface of human epithelial cells¹ and of their absence from carcinomatous tissues² led to the hope that this difference might give an early objective indication of neoplastic dedifferentiation. Using exfoliated cells from bladder tumours Kay and Wallace³ showed loss of blood antigens from patients with invasive and metastatic disease. Nevertheless, the correlation between detectability of A and B antigens and the clinical course was not close enough to be clinically useful.

Recently there has been a considerable resurgence of interest in a modification of the original test, using paraffin embedded sections and a sandwich technique with grouping sera and indicator erythrocytes of the appropriate blood group. Thus retrospective studies are possible, and indeed over a dozen papers have been published, mainly in American journals, in the last three years.⁴⁻¹⁵ For most sceptical watchers of tests for cancer the conclusions seem too good to be true.

The consensus gives grounds for great optimism, particularly in the early recognition of the one patient in five with a superficial tumour of the bladder who will ultimately develop an invasive recurrence. To summarise, patients with superficial cancer whose cells have the appropriate surface blood group antigen have a good prognosis with only a 5% chance of developing invasive recurrence. The test may be a better index of subsequent aggressive tumour behaviour than cell grading. A recent critical review¹⁶ showed that of 100 patients with high grade tumours 23 had a positive test for antigen, and only one of these went on to become invasive. The author emphasised that the test could be of most use in this group, since such patients might escape cystectomy at the hands of a surgeon who

would otherwise be most influenced by initial tumour grading. Unfortunately possible drawbacks may have been overlooked in the initial wave of enthusiasm.¹⁷ The complexity of the technique is usually underestimated and should deter inexperienced laboratory workers. Few of the published studies list patients' blood groups. These data might have an important bearing on a population showing predominance of group O, since the H antigen is more difficult to identify than A or B. Another problem is how the result should be quantified. Some workers will register a positive test only when every epithelial surface is covered with the indicator cells, while others attempt to arrange the results on an arbitrary scale, considering the test positive for the top two or three out of four grades. There may even be variation in staging tumours for correlating the extent of invasion by recurrent growth with the specific red-cell-adherence reaction. Though strict interpretation would mean that any tumour not affecting muscle should be labelled as non-invasive, surely the extension of recurrent growth through the basement membrane and lamina propria should not be placed in the same broad category as tumours restricted to the mucosa. So one of the uncertainties is how many of the initial "non-invasive" tumours with antigen deletion had in fact shown signs of early invasion.

These and other problems may explain inconsistencies in the test results which may be confused with changes in reactivity of possible biological importance. Certainly some explanation is needed of the considerable variation in the errors of prediction of subsequent behaviour of the tumour among different studies on similar groups of patients from different centres¹⁸ and of reports of patients showing variable serial reactivity.⁹ Another possible cause of confusion of any clear relation between loss of antigen and prognosis is that radiotherapy might restore reactivity to an invasive tumour.¹⁹ If it could be shown that patients in whom such a change occurred were those who responded to treatment by a reduction in the stage of their tumour the test might again have prognostic significance. Unfortunately the findings of this particular study were virtually invalidated by the fact that different groups were compared before and after treatment.

In a recent publication²⁰ the authors showed that antigen deletion was best interpreted according to known synthetic pathways of blood group antigens. Their results suggest that the action of malignant cells is to suppress to a variable extent conversion of H to A and B antigens and perhaps H from precursor substance. If that is so then data on the presence or absence of A, B, and H antigens singly are insufficient, and all must be assayed in any one tumour to define degrees of antigen deletion. This study also underlies a possible drawback from the use of paraffin sections: in the past the potential degradation of the glycolipid element of these surface antigens by the dewaxing process may have been overlooked.

The future of the test is uncertain. More reliable methods are needed for identifying antigens, possibly with the help of monospecific antibodies. Quantitation must be standardised, and the question of how tissue should be fixed and embedded quickly resolved. The most useful studies will probably be those that are prospective with serial determinations on frozen sections.

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Problems of clubfeet

Clubfoot—talipes equinovarus—has been recognised as far back as ancient Egypt, and a statue of a dystrophic dwarf with a clubfoot is in the Tutankhamun collection.¹ It remains the most difficult of orthopaedic congenital anomalies to treat successfully. The problem is to correct a deformity which is in three planes and affects several joints at the same time, in an environment which is constantly changing under the influence of growth.² Twenty years ago Gartland stated³ that "we are still grappling with a disorder the cause of which is unknown, the pathological anatomy uncertain, the behaviour unpredictable, and the treatment controversial," and his words remain true today.

Most investigators have reported an incidence of 1-2 per 1000 live births. Boys are more frequently affected than girls by about 2:1. Wynne-Davies⁴ investigated genetic factors, finding a rise in incidence among first-degree relations and siblings; the rate of 2.9 per 100 is between 20 and 30 times greater than normal. The only large twin study, from Germany in 1939,⁵ found that 13 out of 40 monozygotic co-twins were concordant but only four of 134 dizygotic twins were. This wide difference indicates a strong genetic factor, though environmental influences must also play a part.

Histochemical analysis and electron microscopy of calf muscle biopsy specimens taken from 60 children under 5 years old have suggested that there is an important neurogenic factor in the development of clubfoot.⁶ In a similar type of