had an attack of clinical influenza[2]. The absence of a large outbreak last winter cannot be explained, but in fact none of these variants of the A/Hong Kong virus has caused a major epidemic in Britain. Possibly the immunity left behind from the A/Hong Kong virus epidemic gives some protection against its variants; or perhaps they are not highly virulent. Some other requirement for a major epidemic may have been lacking—a cold spell, for instance. Ignorance about the relevance of such factors makes forecasting highly speculative, but it might be tentatively suggested that there is no clear reason to expect a major epidemic this winter, but that a small one is likely to occur—influenza rarely fails to appear in the British winter.

This year doctors may prescribe not only the usual killed, injected influenza vaccines but also, for the first time in Britain, a live, attenuated vaccine given in nose drops. An injection of an up-to-date inactivated vaccine provides, with reasonable certainty, 70-80% protection against influenza for the ensuing winter. The injection causes little inconvenience to patients apart from an occasional sore arm or mild malaise. The live preparation is freeze dried and has to be suspended in diluent before use. The patient lies down with head extended, and five drops are inserted into each nostril; a second dose is given about a fortnight later. This live vaccine appears to be safe, though the possibility exists that a slight adverse effect on lung function may follow its use; and there seems to be no real risk of transmission to contacts.[3-5] Some recipients may experience slight malaise or coryza, but there are no sore arms, and nose drops are more pleasant to accept and easier to administer than an injection. But is the protection given equally good?

The live vaccine has been derived from the A/England/42/72 strain of virus, and induces protection against artificial challenge with A/Hong Kong virus,[6] but field evidence of its protective effect against natural infection due to the homologous or related viruses is still lacking. It can produce an antibody response which will cross react to some extent against the more recent variants, but the response to the A/Scotland virus is unlikely to be as good as that provided by a killed injected vaccine containing the antigens of this virus. Nor can the live vaccine protect against the influenza B virus—which is, on the other hand, included in the killed vaccines. There are expectations that live vaccines will stimulate a more solid immunity than killed, perhaps because they induce a natural (but subclinical) infection, which results in the formation of local secretory antibodies in the upper respiratory tract as well as serum antibodies. Nevertheless, until it is clearly shown that A/England/42/72 live vaccine can protect against A/Port Chalmers and A/Scotland viruses as effectively as an up-to-date injected vaccine the preferred prophylactic should probably be an inactivated vaccine.

Influenza vaccination recommendations this winter should, then, be similar to last: an injection may be offered to those at special risk from the disease, such as sufferers from chest and heart disease and the elderly and infirm. It may also be useful in residential institutions, particularly those for the elderly, where serious explosive outbreaks may occur. For ordinary, healthy adults and children vaccination does not appear to be indicated, but it may be considered for those particularly exposed to the disease—nurses, for example—and for key workers whose illness during an outbreak might cause disproportionate difficulties.

[1] *British Medical Journal*, 1975, 1, 404.
[2] *British Medical Journal*, 1975, 2, 404.
[3] Miller, L W, *et al*, *American Journal of Epidemiology*, 1975, **101**, 340.
[4] Prevost, J M, *et al*, *Scandinavian Journal of Respiratory Diseases*, 1975, **56**, 58.
[5] Rosenzweig, D Y, *et al*, *American Review of Respiratory Disease*, 1975, **111**, 399.
[6] Lauteria, S F, *et al*, *Journal of Infectious Diseases*, 1974, **130**, 380.

Prognosis in aplastic anaemia

Aplastic anaemia is characterised by cytopenia in the peripheral blood and the bone marrow. The platelet and neutrophil counts vary from case to case, and in the same patient during the course of the illness. In general, the clinical features depend largely on the degree of neutropenia and thrombocytopenia because of their association with infection and haemorrhage. Aplastic anaemia is, in fact, the result of a wide variety of pathogenic mechanisms which give rise to defects within the haematopoietic system and result in pancytopenia. It may be congenital, the Fanconi anaemia; the acquired types include those caused by an identifiable chemical or other toxic agent with a dose-dependent depressive effect on haematopoietic cell proliferation, cases of hypersusceptibility to low doses of the toxic agent, and again cases where no toxic agent has been identified but where, it seems, the aetiological factor might be a bacterial or viral infection. In each of these instances the haematopoietic suppression may affect different aspects of nucleic acid synthesis and different stages of cell maturation. Accordingly it is not surprising that aplastic anaemia may vary in its intensity and in its clinical course.

Some patients die within a few weeks or at the most after two to three months. Others survive for longer periods, sometimes for years, in a continuing state of severe anaemia or else in partial remission before they recover fully or succumb. Clearly it would be helpful to be able to predict the prognosis when a patient is first seen and to assess which patients are more likely to benefit from specific therapies. Though aplastic anaemia is an uncommon disease, there have been several major surveys in recent years[1-6] from which it has been possible to study the disease process in a relatively large number of patients. In one such study of 60 patients, Lewis[1] found a dimorphic pattern in the survival curve. He showed that the worst prognosis, with a median survival of 12 months, occurred in patients over 40 and that this was associated with a more severe degree of neutropenia and thrombocytopenia; indeed, when the neutrophil count was less than 100×10^6/l and the platelet count less than 20×10^9 1, the patient usually succumbed within a few weeks or months. He found no difference in survival between cases with an identifiable toxin and idiopathic cases. Williams *et al*[2] made similar observations in 101 patients with drug-induced aplastic anaemia. These latter workers have recently[7] carried out a further retrospective statistical analysis on their same patients, discriminating between the patients who survived four months or less (group A) and longer survivors (group B) in order to determine whether the presenting clinical features and initial haematological data could provide prognostic information. They found that 44% of the patients were in group A and 56% in group B. Patients in the former group were more likely by two to one to present with haemorrhagic manifestations, and the mean interval from onset to first visit was 3·6 months by contrast with 14·7 months in the longer surviving group. The mean reticulocyte count was 0·6% in group A and 1·3% in group B

and the initial blood count in Group A showed a mean neutrophil count of 550×10^6/l and a platelet count of 17×10^9/l; in contrast, in group B the mean counts were two to three times higher. Another feature of interest was the fact that the proportion of non-myeloid cells in the bone marrow was significantly greater in group A; this is consistent with the observation[8 9] that a high proportion of lymphocytes in the marrow denotes a serious prognosis.

Using these findings, Lynch *et al*[7] have devised a prognostic index by means of which it is possible to identify patients as belonging to group A or to group B with a fair degree of precision and accuracy when they are first seen.

Androgens have become established as a recommended method of treatment of aplastic anaemia; but the response to this treatment is variable, and there has been great diversity of opinion on its effectiveness.[4 6 9-11] Because the natural course of the disease is so variable it is difficult to assess the extent to which therapy might have influenced the course in any individual case. The main difficulty in analysing the results of uncontrolled trials of androgen therapy in aplastic anaemia is to find an untreated group which is similar enough to the treated group to permit valid comparison. During the course of their study Lynch *et al*[7] compared results in patients who had received androgens with those who had not been so treated, using the prognostic index in order to match their patients group by group. They concluded that the survival curve did not show any beneficial influence of therapy either with oxymethylone or with other androgens. This does not, in itself, negate the use of androgens; there is a mass of anecdotal evidence that in some cases at least androgens do produce benefit and that withdrawal of treatment results in a relapse.

Response to androgen therapy takes at least three months, so that patients destined to die rapidly are unlikely to survive long enough to be able to benefit. Such patients seem, instead, to be reasonable candidates for attempted marrow transplantation. If, then, the choice of treatment depends on the prognosis, there is need for a reliable method for assessing the prognosis as early as possible. Lynch's formula is a step towards this goal, though its value is limited by the overlap between the groups, and by the fact that each patient is unique and does not necessarily conform to a pattern devised by a statistician.

[1] Lewis, S M, *British Medical Journal*, 1965, **1**, 1027.
[2] Williams, D M, Lynch, R E, and Cartwright, G E, *Seminars in Hematology*, 1973, **10**, 195.
[3] Najean, Y, Bernard, J, Wainberger, M, *et al*, *Nouvelle Revue Française d'Hématologie*, 1965, **5**, 639.
[4] Vincent, P C, and DeGruchy, G C, *British Journal of Haematology*, 1967, **13**, 977.
[5] Wolff, J A, *Pediatric Clinics of North America*, 1957, **4**, 469.
[6] Sánchez-Medal, L, *Progress in Hematology*, 1971, **7**, 111.
[7] Lynch, R E, *et al*, *Blood*, 1975, **45**, 517.
[8] Frisch, B, and Lewis, S M, *Journal of Clinical Pathology*, 1974, **27**, 231.
[9] Li, F P, Alter, B P, and Nathan, D G, *Blood*, 1972, **40**, 153.
[10] Sánchez-Medal, L, *et al*, *Blood*, 1969, **34**, 283.
[11] Smith, E C G, Ahuja, S, and Lewis, S M, *British Journal of Haematology*, 1971, **20**, 670.

Heritability of diabetes

Genetic factors play a part in the aetiology of diabetes—it tends to run in families, and twins are more often both diabetic when they are identical than when they are fraternal.[1] Furthermore over 30 specific genetic syndromes are associated with diabetes.[2] Yet in spite of numerous attempts there has been a notable failure to find a simple mechanism of inheritance. There are difficulties: there is no reliable genetic marker, ascertainment is often incomplete, and published figures relate to clinical or chemical diabetes and are not always comparable; but the two main problems in studying the inheritance of diabetes are that it is genetically heterogeneous both in man[2 3] and in animals[4] and that environmental factors almost certainly influence expression of the genotype.

It is becoming clearer that diabetes is not a single entity but a number of different diseases in which a raised blood sugar is the common feature, rather as a low haemoglobin is the common feature of the anaemias. The most familiar division is into the maturity-onset and juvenile-onset types. Recently, however, a mild maturity-onset type of diabetes affecting young people (MODY) has been described,[5] or rather redescribed, as it was probably first recognised as long ago as 1907.[6] MODY may simply be an earlier expression of the disorder that affects middle-aged patients, and, indeed, evidence of dominant inheritance has been obtained in this type of diabetes in both early[3 5] and later life.[7]

The influence of heredity in classical juvenile-onset diabetes is much less clear. The difference is exemplified in two studies. In the first, one-tenth of the siblings of classical juvenile-onset diabetics were found[3] to be either clinically or chemically diabetic compared with over half of the siblings of patients with MODY. In the second, a series of monozygotic twins,[8] all pairs in which the index twin developed diabetes over the age of 45 were concordant (both co-twins diabetic) and nearly half had a diabetic parent. By contrast, in those pairs in which the index twin was diagnosed under 45 only half were concordant, the non-diabetic twin remaining unaffected in the other pairs, and very few had diabetic parents. Diabetes in the affected members of these discordant pairs must presumably have been mainly environmental in origin.

Evidence from serological[9] and epidemiological[10 11] investigations has revived interest in the possibility of a virus aetiology of juvenile-onset diabetes. It is known that viruses can induce diabetes in some animals.[12] The recently described association of juvenile-onset diabetes with the HL-A system[13 14] suggests a possible mechanism for inherited susceptibility to pancreatropic infective agents, as genes closely linked to the HL-A chromosomal loci probably influence an individual's immune responses.[15] The frequencies of the histocompatibility antigens HL-A8 and W15 are increased in juvenile-onset diabetics,[13 14] and affected siblings of diabetics tend to have at least one and in many cases both HL-A haplotypes in common with them.[16] Both these findings are consistent with the presence of a diabetogenic gene or genes at a locus closely linked to the HL-A chromosomal loci. Different alleles at the HL-A linked diabetogenic locus may interact with different environmental factors to produce clinical disease—for example, one allele might be linked more strongly to HL-A8 and another to W15. A recently published study of HL-A types in diabetic identical twins[17] tends to support this suggestion. The frequency of the W15 antigen was equally increased in the concordant and discordant juvenile-onset pairs, but HL-A8 was increased only in the concordant. If this finding can be confirmed it suggests that HL-A8 and W15 may represent different risk factors in the genetic susceptibility to diabetes.

Maturity-onset diabetes, which is not HL-A linked, appears to have a strong hereditary tendency. It has been calculated[18] that 60% of the children of two maturity-onset diabetics will themselves develop mild diabetes by the age of 60. On the other hand, contrary to previous theory,[19] classi-