context of the total protein present. The Lange gold curve has declined in popularity in recent years but it may give a helpful result—and one which can be obtained within six hours.

The possibility of a virus aetiology of multiple sclerosis is still much in the news. Measles virus comes under special consideration, and the evidence for its possible implication in the disease is fully discussed, with emphasis on a specific measles virus immunity (especially to measles virus haemolysin) found in patients with MS. Perhaps visualisation of different stages of specific virus development in the brain affected by MS may still be helpful in assessing the part played by viruses—an approach to the problem which may have been given too little emphasis. The consensus of opinion on demyelination is that it is produced immunologically, but whether it is tissue-specific or virus-induced remains to be seen. The latter seems to be the more likely. Cellular and humoral immunity appears to be concerned, but a lot of work still needs to be done to define the part they play in both the demyelinating process and the inflammatory lesions.

The histocompatibility antigens and their possible relevance to the incidence of MS get the interest they deserve. Two possibilities are considered: firstly, that susceptibility to MS is governed by a gene in the HLA region, and, secondly, that MS lesions occur relatively frequently and that whether the pathological process resolves without clinical manifestations is determined by an HLA region gene. The treatments used in the disease are documented. Sadly, it is of no surprise that so far not one of them can be said to be really helpful. Perhaps a little more detail could have been given of the work of the occupational therapists and the aids they have available to make life for the disabled at home safer, more comfortable, and useful. Many physicians forget the help this department can give.

This issue of the *BMB* on multiple sclerosis maintains the high standards of the series, bringing readers abreast of the relevant features of the different approaches to the problem of multiple sclerosis in a most readable way.

[1] *British Medical Bulletin*, 1977, vol 33. Published by the Medical Department of the British Council, 65 Davies St, London W1, price £4·50 (£5·00 overseas).

Prenatal diagnosis of the haemoglobinopathies

The common genetic disorders sickle-cell anaemia and β-thalassaemia cause a major public health problem in many parts of the world and are being seen increasingly in Britain. Since these conditions may be easily identified in their heterozygous carrier states they are potentially preventable—either by population screening and genetic counselling or by prenatal diagnosis and therapeutic abortion of affected fetuses, or a combination of both.

At first sight the prenatal diagnosis of sickle-cell anaemia or β-thalassaemia seemed impossible: for they result from defects in the structure or synthesis of adult haemoglobin (Hb A), and the major haemoglobin of fetal life is haemoglobin F (Hb F), which is replaced by Hb A only in the first year of life. Hence only after birth do the clinical manifestations of these disorders become apparent. There was, however, a possible way round this impasse if (as had been suspected for a long time) some Hb A was present in early fetal life.[1 2] In the early 1970s this was confirmed by detailed chemical analysis of the haemoglobin of young fetuses, and subsequently it was shown that they produce 5-10% Hb A from about the eighth week of gestation.[3 4] By then isotopic methods were available[5 6] for measuring the relative rates of synthesis of Hbs A and F in vitro. If a small fetal blood sample could be obtained it seemed likely that it would be possible to see whether Hb A was being produced in normal quantities or not and hence to diagnose β-thalassaemia. Similarly it should also be possible to determine whether the fetus was making Hb A or sickle-cell haemoglobin (Hb S).[7 8]

This approach has proved feasible in practice. Using fetal blood samples, obtained either by placental needling or aspiration with a fetoscope, groups in Boston and San Francisco have recently been able to diagnose prenatally both homozygous β-thalassaemia and sickle-cell anaemia.[9–12]

Recent reports from Boston and London,[13] and from San Francisco,[14] summarise the latest experience of the prenatal diagnosis of the β-chain haemoglobinopathies. In the combined Boston-London study, which describes 15 attempts, one pregnancy ended in premature labour with loss of the fetus after placental aspiration. Homozygous β-thalassaemia was diagnosed in two pregnancies; both were terminated, but the diagnosis was confirmed in only one fetus and the other turned out to have β-thalassaemia trait. Seven predictions that infants would not have homozygous disease were confirmed, but in one case prediction of the sickle-cell trait proved on subsequent testing to be sickle-cell disease. The San Francisco study summarises experience with 24 cases. In two cases fetal blood samples were not obtained, and there were three fetal deaths. Of the remainder, four cases of homozygous β-thalassaemia and two of sickle-cell anaemia were terminated and the remainder allowed to go to term. There appeared to be no misdiagnosis in this series. These results underline some of the practical difficulties encountered. Fetal blood samples obtained by either method are often contaminated with maternal cells. These cells cannot easily be separated, but the method of analysis measures isotopically the relative rates of fetal and adult haemoglobin synthesis; so that a complicated correction has to be applied for contamination with maternal reticulocytes. Furthermore, the risk to the fetus using either sampling technique is still considerable. If the placenta is lying anteriorly it is impossible to use a fetoscope, and the sample has to be obtained by placental aspiration. Though the uterus is usually only entered once, it may require up to a dozen placental aspirations before a sample containing adequate numbers of fetal cells is obtained. The technique for analysing the haemoglobin requires elaborate laboratory facilities and great technical expertise.

Clearly, prenatal diagnosis of the haemoglobinopathies is still a research procedure, and it would be premature to say that the technique is ready for general use and so raise the hopes of parents who carry genes for these distressing conditions. Yet the studies carried out so far do show quite unequivocally that given an adequate fetal blood sample it is possible to diagnose at least some forms of β-thalassaemia and sickle-cell anaemia in utero. Better methods for fetal blood sampling are needed, together with simpler laboratory techniques for analysing the relative amount or type of adult haemoglobin in the sample. The long-term objective of this work should be to develop an approach simple enough for use in parts of the world where these diseases are common.

Along the way we should not lose sight of the wider problems raised by this research. While we know fairly well what is likely to happen to an infant homozygous for β-thalassaemia, there

is a surprising lack of knowledge about the natural history of sickle-cell anaemia, particularly in the developed countries. Do we really know enough about the sickling disorders to be able to predict the quality of life for any particular individual? Perhaps before we think about the wide-scale termination of pregnancies we ought to learn more about the genetic heterogeneity of these disorders and about the environmental factors that may modify them. Have we considered what effect the wholesale application of prenatal diagnosis of these conditions might have on the incidence of the carrier states? Do we know enough about the effects on a population of the genetic screening procedures necessary to implement a prenatal diagnosis programme?[15] Are we quite sure that couples at risk are being interviewed by experienced genetic counsellors who are not themselves directly concerned in the development of these new techniques of prenatal diagnosis? It is essential that our enthusiasm for new technology should not put pressure on families of this type. It may well take longer to answer these questions than it will take to perfect the techniques required.

[1] Walker, J, and Turnbull, E P N, *Archives of Disease in Childhood*, 1955, **30**, 111.
[2] Huehns, E R, *et al*, *Nature*, 1964, **201**, 1095.
[3] Kazazian, H H Jr, and Woodhead, A P, *Annals of the New York Academy of Sciences*, 1974, **241**, 691.
[4] Wood, W G, and Weatherall, D J, *Nature*, 1973, **244**, 162.
[5] Weatherall, D J, Clegg, J B, and Naughton, M A, *Nature*, 1965, **208**, 1061.
[6] Clegg, J B, Naughton, M A, and Weatherall, D J, *Journal of Molecular Biology*, 1966, **19**, 91.
[7] Alter, B P, *et al*, *Clinics in Haematology*, 1974, **3**, 509.
[8] Cividalli, G, *et al*, *Pediatric Research*, 1974, **8**, 553.
[9] Kan, Y W, *et al*, *New England Journal of Medicine*, 1975, **292**, 1096.
[10] Kan, Y W, *et al*, *Lancet*, 1975, **2**, 790.
[11] Kan, Y W, Golbus, M S, and Trecartin, R, *New England Journal of Medicine*, 1976, **294**, 1039.
[12] Alter, B P, *et al*, *New England Journal of Medicine*, 1976, **294**, 1040.
[13] Alter, B P, *et al*, *New England Journal of Medicine*, 1976, **295**, 1437.
[14] Kan, Y W, *et al*, *Lancet*, 1977, **1**, 269.
[15] Stamatoyannopoulos, G, in *Proceedings, IV International Conference on Birth Defects, Vienna*, eds A G Motulsky and W Lenz, p 268. Amsterdam, Excerpta Medica, 1974.

Repeated anaesthesia

Many patients who need a general anaesthetic will have had at least one previously. How much should such a previous exposure influence the choice of technique for the next? Some problems are readily identifiable, such as a prolonged response to suxamethonium or a hypersensitivity to a specific intravenous induction agent; but many of the patients needing a second anaesthetic will have had halothane during the course of the first. Some reports of liver damage after anaesthesia have concluded that such damage is more likely to be seen after repeated exposure to halothane, especially if the intervals between exposures are short.[1] A study by Walton *et al*[2] of 203 patients who became jaundiced after surgery identified 76 as having "unexplained hepatitis following halothane." Of these, 72 had had multiple exposures, and in 42 the repeated exposures had been within four weeks. The series was collected as a result of an appeal to all anaesthetists in the British Isles, so that set against the number of general anaesthetics given each year the incidence of unexplained hepatitis after halothane is small. Nevertheless, if the association is real some episodes may be preventable.

Three recent studies have taken a different approach to assessing the frequency of postoperative liver function test abnormalities after repeated anaesthesia. Trowell *et al*[3] studied patients having repeated anaesthetics during treatment of carcinoma of the cervix. In 18 patients halothane was used repeatedly; four developed serum alanine aminotransferase activities of more than 100 U/l. In contrast, none of the 21 not given halothane did so. Wright and his colleagues[4] studied a similar group of patients and found that repeated administration of halothane given at short intervals was associated with an increased incidence of raised serum aspartate aminotransferase activities: but in a second group who had had at least four anaesthetics previously but with an interval of six months since the last there were no changes in liver function test results after halothane. McEwan[5] examined a group of patients undergoing genitourinary surgery. All his patients had had repeated anaesthetics; he gave halothane as part of the first anaesthetic he studied and used other agents in the second. Disturbances of liver function, as assessed by serum alanine aminotransferase, aspartate aminotransferase, and lactic dehydrogenase activities, were greater after the second anaesthetic, when halothane was not used.

What are the implications for anaesthetic practice? Firstly, the incidence of unexplained hepatitis after halothane is small, but hepatic damage may be seen after multiple exposures, especially if these occur within 28 days. If, therefore, patients are scheduled to have several general anaesthetics within a short time this factor should be taken into account in selecting the anaesthetic technique. Whether the other risks of other techniques pose greater hazards to patients still remains to be determined. Secondly, patients who develop unexplained hepatitis after halothane should not be given it again (though Walton *et al*[2] noted that three out of five such patients re-exposed to halothane did not redevelop jaundice). Thirdly, when single anaesthetic episodes are in question there is no evidence to show that halothane presents a greater risk than other agents in terms of liver damage or anything else.

The Medical Research Council has set up a working party to consider these problems.[6] It considers that further work is needed to evaluate the effects of repeated anaesthetics, the mechanisms of hepatotoxicity, and the predictability of such risks. The council will welcome—and support under its project grants scheme—acceptable studies on those issues.

[1] Inman, W H W, and Mushin, W W, *British Medical Journal*, 1974, **1**, 5.
[2] Walton, B, *et al*, *British Medical Journal*, 1976, **1**, 1171.
[3] Trowell, J, Peto, R, and Smith, A C, *Lancet*, 1975, **1**, 821.
[4] Wright, R, *et al*, *Lancet*, 1975, **1**, 817.
[5] McEwan, J, *British Journal of Anaesthesia*, 1976, **48**, 1065.
[6] Medical Research Council, *British Journal of Anaesthesia*, 1976, **48**, 1037.

Migrainous cerebral infarction

At its simplest, the classical concept of migraine postulates an initial phase of vasoconstriction of cerebral vessels, which causes the aura, succeeded by vasodilatation of scalp vessels, which causes the pulsatile headache. This explanation has been disputed,[1] but recent studies have confirmed that cerebral blood flow is reduced[2] during the aura. In some regions of the brain the reduction in flow is severe enough to reach critical levels of oxygen supply; the reflex increase in flow normally afforded by inhaled CO_2 is abolished. Lactic acidosis has been found in the cerebrospinal fluid of selected patients with focal