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

Br Med J: first published as 10.1136/bmj.1.6060.532-a on 26 February 1977. Downloaded from http://www.bmj.com/ on 19 April 2024 by guest. Protected by copyright.

neurological symptoms in the prodromal phase—a potentially serious condition associated with cerebral vasomotor paralysis and paradoxical responses of blood flow to both constrictor and dilator drugs.[3]

Not surprisingly, therefore, migraine may lead on occasion to prolonged neuronal ischaemia and ultimately to oedema and infarction. The initiating factors that determine the migrainous vascular disorder are still not well understood, though currently suspicion[4] is directed at several possible humoral agents and deficiencies of monoamine oxidase A and B. A greater puzzle is identification of the factors that cause the localisation of the major zones of ischaemia when there is a general reduction of cerebral blood flow, and what prolongs the ischaemia to produce death of brain tissue in such cases.

Clinically, migrainous infarction has been postulated ever since Liveing's description[5] in 1873 of migrainous hemiparesis, Féré's[6] suggestion of vasospasm leading to actual vascular occlusion in 1883, and the record of permanent retinal infarction by Galezowski[7] in 1882. Subsequently many individual cases of persisting hemiplegic,[8 9] aphasic, hemianopic,[10] and retinal[11] sequelae of migraine attacks have been described.

Modern advances in measurements of cerebral blood flow, radionuclide brain scanning (scintigraphy), angiography, electroencephalography, and, most recently, computer assisted axial tomography (CAT) have been helpful in examining both physiological and anatomical aspects of this particular complication. Brain scanning usually shows an area of breakdown of brain tissue and of its blood-brain barrier; the area of uptake in the early scan is seen to shrink if repeated in the first eight weeks. Angiography is occasionally needed to exclude a tumour, angioma, or aneurysm but may be hazardous[12] in patients with migraine and should if possible be delayed until several days after the ictus, when the patient's vasomotor and neurological status should have become stable. The finding of major vascular thrombosis is uncommon except in cases complicated by the use of the contraceptive pill or by atheromatous large vessel stenosis.

Pathological verification of migrainous infarction is extremely rare.[13–15] A recent series[16] of CAT scans between attacks in 53 patients with exceptionally severe[17] or clinically complicated migraine is, therefore, of considerable interest. Results were normal in 28; unequivocal evidence of mild generalised cerebral atrophy was shown in 14, but it tended to be related more to age than to the severity of the migraine, and its significance is uncertain. Infarcts were identified in six patients: in three they corresponded to a definable migrainous event, but in the other three vascular stenosis or occlusion was present, and in these migraine was probably not the cause of the infarct. Focal atrophy, a recognised sequel of infarction, was shown in eight patients and correlated in some cases with the patients' symptoms.

At first sight these figures may provoke both scepticism and alarm; but in fact the claims and qualifications are reasonable, for they show that in a highly selected group of patients with unusually severe or complicated migraine infarction and focal atrophy may result. Even so, in many patients the sensitive CAT scan showed no abnormality despite lifelong severe migraine attacks. The finding of cortical and white matter atrophy always raises the question of dementia. Atrophy as visualised on the CAT scan (a relatively new procedure) has yet to be fully correlated with postmortem atrophy. As yet, therefore, there is no evidence to implicate migraine in the general causation of dementia.


[1] Sacks, O W, *Migraine*. London, Faber and Faber, 1970.
[2] Simard, D, Paulson, O B, *Archives of Neurology*, 1973, **29**, 207.
[3] Skinhøj, E, *Archives of Neurology*, 1973, **29**, 95.
[4] Sandler, M, Youdim, M B H, and Hanington, E, *Nature*, 1974, **250**, 335.
[5] Liveing, E, *On Megrim, Sick Headache and Some Allied Disorders*. London, Churchill, 1873.
[6] Féré, C, *Revue de Médecine* (Paris), 1883, **3**, 194.
[7] Galezowski, X, *Lancet*, 1882, **1**, 176.
[8] Bradshaw, P, and Parsons, M, *Quarterly Journal of Medicine*, 1965, **34**, 65.
[9] Pearce, J, *Modern Topics in Migraine*, p 31. London, Heinemann, 1975.
[10] Pearce, J, *Journal of the Neurological Sciences*, 1968, **6**, 73.
[11] Graveson, G S, *British Medical Journal*, 1949, **2**, 838.
[12] Friedman, A P, Harter, D H, and Merritt, H H, *Archives of Neurology*, 1962, **7**, 320.
[13] Oppenheim, H, 1890, cited by Whitty, C W M, *Journal of Neurology, Neurosurgery, and Psychiatry*, 1953, **16**, 172.
[14] Buckle, R M, du Boulay, G, and Smith, B, *Journal of Neurology, Neurosurgery, and Psychiatry*, 1964, **27**, 440.
[15] Guest, I A, and Woolf, A L, *British Medical Journal*, 1964, **1**, 225.
[16] Hungerford, G D, du Boulay, G H, and Zilkha, K J, *Journal of Neurology, Neurosurgery, and Psychiatry*, 1976, **39**, 990.
[17] Klee, A, *A Clinical Study of Migraine with Particular Reference to the Most Severe Cases*, Thesis. Copenhagen, Munksgaard, 1968.


# Melanocyte-stimulating hormone?

Pituitary peptides which can darken the skin by dispersing pigment granules within the epidermal melanophores have been named melanocyte-stimulating hormone (MSH). Nevertheless, recent studies have questioned both their identity and their function. In some species (rats, for instance) MSH is a peptide made of 13 amino-acids which have been shown[1] to have the same sequence of the 13 amino-acids on the N terminal of ACTH. Undoubtedly this peptide acts as a pigmentary and sebotrophic hormone[2] in some mammals; but there is no evidence that it exists in the circulation or has any such functions in normal man. While this peptide (named α-MSH) can be obtained from the human pituitary,[3] it is probably an artefact resulting from the degradation of corticotrophin during extraction.

Other peptides with MSH activity containing 18 (porcine, bovine, ovine) or 22 (human) amino-acids have been identified in both the pituitary and the circulation[4] and named β-MSH. Recent studies,[5 6] however, have shown that β-MSH is not an independent hormone but is formed from the enzymatic degradation of the much larger pituitary lipolytic hormones β-lipotrophin (β-LPH) and γ-lipotrophin (γ LPH). These hormones contain 90 or 91 (according to species) and 58 amino-acids respectively and human β MSH is contained within the 37-58 sequence.[4 7 9] There is no clear evidence for an independent pigmentary hormone in man,[10 11] though the lipotrophins may act as prohormones for β-MSH (which also has lipolytic activity).

There are obvious changes in pigmentation in patients with some pituitary diseases (such as Cushing's disease, Nelson's syndrome, pituitary failure) and in other conditions in which corticotrophin (ACTH) concentrations are raised (such as ectopic ACTH syndrome, Addison's disease). Changes in plasma ACTH and β-MSH activity generally occur in parallel.[12] Hypoglycaemia and metyrapone stimulate an increase in the concentration of both hormones, though hypoglycaemia causes a proportionately greater release of ACTH. Lysine vasopressin stimulates release of ACTH alone. Probably these differences reflect the differential effect of these stimuli on the release of ACTH and LPH in man.[13 15]

Recent interest in the regulatory role of the hypothalamus

Br Med J: first published as 10.1136/bmj.1.6060.532-a on 26 February 1977. Downloaded from http://www.bmj.com/ on 19 April 2024 by guest. Protected by copyright.