MIGRAINE

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To investigate other health and social problems.
To collect data from other countries.
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Introduction

'Choose something common and you will find little is known about it' (Henry Head to the young Dr Russell Brain c. 1920). Although common (8 per cent of the population) and recognised for more than 2,000 years, migraine has rarely commanded significant professional or public attention. It does not shorten life or cause permanent injury. In contrast to many current health problems examined in the Office of Health Economics' series, the morbidity generated by migraine does not give rise to substantial costs borne by the National Health Service.

The 'low profile' image of migraine has also been fostered by several other factors. From a scientific perspective, although investigative techniques have advanced there have been no significant breakthroughs in understanding the aetiology of the disorder. Many theories about causation have been put forward but none proven: hypotheses include, *inter alia*, vasospasm, alterations in the metabolism of the neurotransmitter serotonin, food allergy, abnormalities of the blood-brain barrier, platelets and cerebral hypoxia. The debate over whether migraine is the result of disturbances in the vascular or neurological systems, started in the late 19th century, remains unresolved.

Various popular beliefs have grown up around migraine, for example, that it is a neurotic disorder, which, rather than generating positive concern, have tended to diminish sympathy that might otherwise have been extended to sufferers of the condition. A typical sufferer is popularly thought to be extremely intelligent, highly strung and a perfectionist. It is also perceived by some to be a hysterical female disorder. And others have used the term inappropriately to describe much more minor head pains as a means of giving greater justification to a decision not to do something, such as attend work.

Yet migraine is a much more significant disorder than might be suggested by these erroneous notions. In the first instance, migraine is experienced by a large number of people. Despite the availability of data from the many surveys that have been carried out, precise estimates of prevalence are difficult to obtain because of differing criteria to define cases of the disorder and variations in the proportion of cases likely to become known to the inquiring agency. Nevertheless, if estimates suggesting prevalence rates of between 7 and 10 per cent are correct, then there are currently 3.9 to 5.6 million migraine sufferers in the United Kingdom. This implies that migraine affects twice as many individuals as, for example, asthma, a disease that has featured much more prominently and regularly in both the medical and lay media.

Although migraine does not give rise to substantial financial costs
to the National Health Service, the disorder can impose severe burdens on sufferers themselves. The impact of disease on quality of life and the effectiveness of medical interventions in improving the well being of sufferers are topics that are increasingly attracting the attention of individuals responsible for affecting and managing the delivery of health care as well as the concern of the community as a whole. One of the objectives of this paper is to investigate migraine from these two perspectives.

Finally, it is an appropriate time for an OHE publication to examine migraine because of contemporary and indeed, mutually relevant developments in therapeutic research and the NHS. After a prolonged period in which drug therapy for migraine has made little advance, research has produced promising medicines for the effective treatment of acute episodes of migraine. At the same time, the NHS is becoming increasingly concerned to ensure maximum efficiency in the use of its resources. New medicines, along with other forms of intervention, will therefore more frequently be examined from a value for money viewpoint in addition to being subject to conventional clinical assessments. Against the background of these two developments, this paper examines some of the critical issues involved in assessing the economic and quality of life impacts of therapies for migraine.
The nature of migraine

Migraine is an episodic condition in which headaches recur at irregular intervals, attacks usually lasting approximately one day. The headache develops gradually on one or both sides of the head, the pain being felt deeply often behind one or both eyes. Nausea commonly accompanies the headache and in some cases vomiting occurs. Light can exacerbate the patient’s distress (photophobia) so refuge is often sought in a darkened room. During attacks patients want to be left alone, because noise and movement accentuate the pain, and difficulties in thinking and speaking impair communication. Sleep is desired to escape the discomforts of the attack but the head pain may deny the patient this source of relief. After the episode, the migraineur is usually tired and ‘washed out’ for some hours. Once this phase has passed normal life is resumed until the next attack.

Several attempts have been made to construct accurate definitions for these clinical entities but none has succeeded in attracting universal agreement. The definition of migraine put forward by the Ad Hoc Committee on Classification of Headache (1962) was regarded as unsatisfactory because it employed words like ‘commonly’, ‘usually’, ‘sometimes’ and ‘often’.

More than two decades later Blau (1984) proposed this definition: ‘episodic headaches lasting 2-72 hours with total freedom between attacks. The headache must be associated with visual or gastrointestinal disturbances or both. The visual symptoms occur as an aura before and/or photophobia during the headache phase. If there are no visual but only alimentary disturbances, then vomiting must feature in some attacks’.

The novel feature of this definition was the delineation of the duration of attacks, indicating that migraine headaches do not last minutes; attacks longer than 3 days are classified as status migrainosus, defined by a study of the American Association Study of Headache (Gouch and Diamond, 1983).

The most recent attempt to define migraine, made by the Committee of the International Headache Society (IHS, 1988), recommended the changes of name from ‘Common Migraine’ to migraine without aura, and from ‘Classical Migraine’ to migraine with aura. The criteria laid down by the IHS, shown in Table 1, were intended primarily for use by research workers so that in published papers there is uniformity about the diagnostic criteria employed. The classification will be reviewed at intervals and after trials and, if indicated, modified.

Some aspects of the criteria may still be questioned. It is widely accepted that, for example, migraine need not be throbbing or pulsatile in character. A study by Olesen (1978) found that of 750
Table 1  International headache society criteria for defining migraine

Migraine without aura
The IHS criteria for the diagnosis of migraine without aura state that the patient should experience pain-free intervals between attacks, and at least five of the attacks should have the following characteristics.

Duration:  4-72 hours (untreated or unsuccessfully treated)

Headache character:  At least two of the following must apply:
  • Unilateral location
  • Pulsating quality
  • Moderate or severe intensity (limits daily activities)
  • Aggravation by physical activity

Associated symptoms:  During headache at least one of the following must be present:
  • Nausea and/or vomiting
  • Photophobia and/or phonophobia

A diagnosis of migraine without aura should only be reached if the medical history, physical and neurological examinations do not suggest an organic disorder, or if they do suggest organic disorder but this has been ruled out by neuroimaging procedures or other laboratory investigations.

Migraine with aura
In addition to meeting the criteria listed for migraine without aura, patients with aura should have experienced at least two attacks with at least three of the following characteristics:

i)  One or more fully reversible aura symptoms (e.g. flashing lights, fortification spectra or partial visual field loss; unilateral numbness, weakness or paraesthesiae; aphasia or speech difficulty).

ii) At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occurring in succession.

iii) A maximum aura symptom duration of 60 minutes. If more than one aura symptom is present, the accepted duration is proportionally increased.

iv) The aura is followed by headache within 60 minutes, but occasionally the headache may begin before the aura.

Source: International Headache Society 1988

Patients questioned during a migraine attack, only 47 per cent said the headache was throbbing, implying a pulsatile quality was absent in 53 per cent. Even when a patient does have a throbbing sensation in the head during a migraine attack, it is rare to encounter instances where throbbing is a feature from the beginning; often a pulsating quality occurs only at the height of an attack, or after exertion, for example, vomiting or moving around.
Figure 1 The complete migraine symptoms during various phases of migraine

Source: Blau, 1980
The clinical picture

A complete migraine attack is divisible into five stages (Figure 1), the first being the prodromal phase. Several hours before the headache begins, often during the preceding evening, there are changes of mood and behaviour, tiredness may be experienced as may altered gut activity, sensations of cold and neck stiffness; mood variations range from feeling 'dangerously well' (George Eliot) extrovert, witty, and creative, to feeling low and depressed. Behavioural changes make some patients become highly energetic – undertaking extra housework or feeling on top of the world while others become tired and irritable. These patterns of altered activity emerge slowly and seem more common in those aged 30-40 years perhaps when attacks are longer compared with children, although they can be noted by parents even in youngsters. The term 'complete migraine' has been proposed for migraine with the above warnings (Blau 1980).

The second phase is characterised by the development of an aura (Greek, breeze). A visual disturbance is the most common manifestation lasting 5 to 60 minutes, more usually 20 to 30 minutes: vision may be blurred, a blind spot may develop, or, classically, flashing scintillating lights forming a distinct pattern which migrates across the visual field. For most individuals there is one pattern although some experience different scintillations and spread. The migration takes 5 to 10 minutes, then the pattern persists for 15 to 20 minutes before clearing. The occipital cortex of the brain is the most likely site of origin for these disturbances (Lashley, 1941).

Somato-sensory symptoms begin as numbness in one hand and extend slowly up the arm and may then involve the same side of the face. When this occurs on the right side in a right handed person, dysphasia can impair speech with difficulty in expressing thoughts. Alternation to the contralateral side is characteristic in different attacks. Sensory disturbance of the legs is rare, and motor weakness extremely rare, as a warning. The parietal sensory cortex of the brain and the adjacent speech area in the temporal lobe are responsible for these symptoms.

Phase three – the most troublesome – is the development of the headache. With or without phase one or two, the headache increases slowly in its severity, usually taking half to one hour. Some waken with a headache fully developed but more frequently patients waken with a 'head awareness' uncertain whether it is an 'ordinary headache' or the beginning of a migraine. This leads to delay in taking analgesics thus impairing the efficacy of early treatment.

The headache starts in different places in different patients and can also vary in its site of onset in the same individual. As the attack progresses the headache increases, the pain becoming more severe and deeper. Additional symptoms slowly develop: nausea which in
some attacks culminates in vomiting (the latter being more common in children), as well as dislike of light and noise (photophobia and phonophobia); intolerance of smells (osmophobia) occurs in about 15 to 20 per cent of patients but is rarely mentioned spontaneously and has to be elicited by direct enquiry. The smells that are disliked include those of cooking, cigarette smoke, paint and petrol (Blau and Solomon, 1985). Other symptoms accompanying the headache include tiredness, yawning, feeling irritable, cold, wanting to be left alone, dysphasia in a few subjects, as well as profound misery and despondency. The headache phase lasts 4 to 72 hours, a major portion of a whole day being most frequent.

Phase four is the resolution of attacks. Sleep is a common way attacks end, although some patients sleep and then awake with the headache still present which then persists for a further half or whole day. In some the recovering sleep is particularly deep while for others one to two hours sleep by day is sufficient to terminate attacks. In children vomiting often ends attacks and in some adults a small meal can initiate recovery. In the majority, however, attacks ‘just slowly fade away’ over a number of hours.

The final stage is the postdromal phase. Patients feel lethargic, tired, washed out, lacking energy and drive, after migraine attacks; concentration and attention spans are limited, speech, bowel function and fluid balance may be altered and head tenderness is common. In some the head pain can briefly recur, after coughing, sneezing or bending down. A few subjects feel ‘high’. These symptoms last several hours, frequently for the major part of the subsequent day. Such ‘hangover’ symptoms are not found in any other headache commonly seen in clinical practice.

**Prevalence**

There have been numerous studies of the occurrence of migraine, giving widely differing estimates. For example, Bruyn (1983) cites 38 studies of the prevalence of migraine in adults in 12 countries, with estimates ranging from one per cent in a city centre general practice in the United Kingdom to 35 per cent in a highly selected sample of hospitalised patients in a neurology department in the USA.

Schnarch and Hunter (1980) argue that two problems traditionally confront investigators who attempt to assess the occurrence of migraine. The first is the lack of standardised diagnostic criteria. Sometimes the criteria are too inclusive, such as ‘severe, frequent, incapacitating headache’ which probably includes severe headache other than migraine. Studies also vary in the time period of the assessment; asking individuals whether they had ever had migraine
**Table 2** Prevalence of migraine in adults *Summary of studies*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Sample-size</th>
<th>Sample-source</th>
<th>Age</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waters</td>
<td>1968</td>
<td>Wales</td>
<td>1718</td>
<td>Random sample from electoral roll</td>
<td>&gt;21</td>
<td>23.2% (F)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>14.9% (M)</td>
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<td></td>
<td></td>
<td></td>
<td>19.1%</td>
</tr>
<tr>
<td>Clarke &amp; Waters</td>
<td>1972</td>
<td>SW London</td>
<td>1519</td>
<td>Patients with GP</td>
<td>15-64</td>
<td>28.7% (F)</td>
</tr>
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<td></td>
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<td>24.1%</td>
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<td></td>
<td></td>
<td>19.5% (M)</td>
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<tr>
<td>Mills &amp; Waters</td>
<td>1973</td>
<td>Isles of Scilly</td>
<td>977</td>
<td>Patients with GP</td>
<td>15-64</td>
<td>23.7% (F)</td>
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<td></td>
<td>19.6%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>15.2% (M)</td>
</tr>
<tr>
<td>Green</td>
<td>1975-1976</td>
<td>UK</td>
<td>14893</td>
<td>Administrative employees</td>
<td>All ages</td>
<td>15.9% (F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>School children</td>
<td></td>
<td>13.1%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Factory workers</td>
<td></td>
<td></td>
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<tr>
<td>Schnarch/Hunter</td>
<td>1980</td>
<td>US</td>
<td>1293</td>
<td>Randomly selected adults (passing</td>
<td>av. 19-21</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>through shopping mall)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schnarch/Hunter</td>
<td>1980</td>
<td>US</td>
<td>26</td>
<td>Clinical patients</td>
<td>av. 19-21</td>
<td>15.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Community Mental Health Centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schnarch/Hunter</td>
<td>1980</td>
<td>US</td>
<td>3616</td>
<td>Randomly selected students MSU</td>
<td>av. 19-21</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>campus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schnarch/Hunter</td>
<td>1980</td>
<td>US</td>
<td>55</td>
<td>Clinical patients</td>
<td>av. 19-21</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MSU counselling centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Migraine Survey</td>
<td>1987</td>
<td>France</td>
<td>2350</td>
<td>General population</td>
<td>&gt;15</td>
<td>11%</td>
</tr>
</tbody>
</table>
is different from asking whether they have had an attack in the last year or previous month. The second problem in assessing migraine occurrence lies in unrepresentative sampling. Because certain sufferers never seek medical treatment, samples of migraine sufferers receiving medical treatment may not be representative of all migraine sufferers in the general population.

A number of studies of the occurrence of migraine in adults are summarised in Table 2. Many of the studies use a variant of Waters’ (1970) Migraine Diagnostic Questionnaire. With this questionnaire, diagnosis is established by the presence of the four most common and clear cut criteria related to migraine: headache in the last year, unilateral head pain during headache, warnings preceding headaches, and nausea and/or vomiting accompanying the headache. Waters’ questionnaire is considered by many to be a practical, standardised method for examining large cross sections of the general population to establish migraine status in a nonbiased manner. However, questionnaires have sometimes been criticised as a method of diagnosing migraine.

In their study, Schnarch and Hunter (1980) estimated migraine occurrence in the general adult sample to be 7.3 per cent, which is comparable with that reported for similar populations in the United Kingdom. In reviewing a wide range of studies, Bruyn (1983) is much more conservative, arguing that ‘an overall percentage of 1.5-2 per cent of migraine sufferers among the population seems realistic’.

Despite the differences in the estimates of migraine occurrence, two features are clear. First, women experience migraine more frequently than men, by a ratio of at least 2:1. Abramson et al (1980) found that both migraine and non-migrainous headache were more prevalent among women, with a peak at age 35-44. In addition, Attanasio and Andrasik (1987) found that attacks in women tended to be more frequent, more intense and of longer duration.

Secondly, in studies where a common definition of migraine has been used, clinical populations tend to report a higher occurrence of migraine than the general population. For example, in a study of college students Schnarch and Hunter (1980) found an occurrence of 2.7 per cent and 4.1 per cent in random samples from two university campuses. This contrasted with an occurrence of 9.1 per cent in students attending a counselling centre. This finding mirrored that for adults (Table 3). A random sample in a shopping centre gave an occurrence of 7.3 per cent, compared with 15.4 per cent in a sample of adult psychotherapy patients at a community mental health centre. This points to the biases inherent in extrapolating from clinical patients, which have formed the basis of ad hoc samples for estimating occurrence in the past.

Another key feature of the epidemiology of migraine is the vari-
### Table 3  Migraine incidence in random and clinical populations

<table>
<thead>
<tr>
<th>Sample/location (N)</th>
<th>Migraine incidence (%)</th>
<th>Migraine subjects consulting physician (%)</th>
<th>Non-migraine subjects consulting physician (%)</th>
<th>Severe headache (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>College students</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random/MSU campus (3616)</td>
<td>2.7</td>
<td>42.9</td>
<td>13.1</td>
<td>34.8</td>
</tr>
<tr>
<td>Random/NYU campus (293)</td>
<td>4.1</td>
<td>16.7</td>
<td>16.0</td>
<td>31.4</td>
</tr>
<tr>
<td>Clinical/MSU counselling center (55)</td>
<td>9.1</td>
<td>60.0</td>
<td>32.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Chi square</td>
<td>7.6991*</td>
<td>84.7624†</td>
<td>19.3568†</td>
<td>5.6252</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random/shopping center (1293)</td>
<td>7.3</td>
<td>71.3</td>
<td>21.7</td>
<td>34.2</td>
</tr>
<tr>
<td>Clinical/community mental health center (26)</td>
<td>15.4</td>
<td>100.0</td>
<td>50.0</td>
<td>76.9</td>
</tr>
<tr>
<td>Chi square</td>
<td>2.5103</td>
<td>10.3797†</td>
<td>11.7578†</td>
<td>20.4548†</td>
</tr>
</tbody>
</table>

* (P<.02)  † (P<.005)  ‡ (P<.001)

Source: Schnarch and Hunter (1980)

...
Figure 2 Prevalence of migraine and non-migrainous headaches by sex and age

Prevalence per 100 persons

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td></td>
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</tr>
<tr>
<td>35-44</td>
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<tr>
<td>45-54</td>
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<td></td>
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<tr>
<td>55-64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-migrainous headaches (NMH)

Males | Females
--- | ---
All NMH |         |
Frequent NMH |   |

Source: Abramson et al, 1980
Diagnosis of migraine

There are no tests for migraine. The diagnosis depends on a careful history obtained from the patient. Questions about the frequency, duration and characteristics of attacks delineate a clinical picture from which it is possible to determine whether or not a diagnosis of migraine is correct. On this basis, diagnosis is reasonably straightforward in most cases, although it is important to distinguish migraine from several other types of headache with which it is sometimes confused.

Migraine, tension headache and localised head pain, constitute 90 per cent of headaches referred by family practitioners for consultants' opinion. Each of these three headaches has its own characteristics, causes and treatments, and therefore needs differentiation from each other. Diagnosis is not difficult when these headaches occur separately; when combined they present a diagnostic challenge, especially when a drug-induced headache further complicates the picture.

Tension headaches can occur very frequently (5-7 days per week) and last from awaking till sleep. It is 'a pressure not a pain', felt like a band round the head, or a weight on the vertex, or 'all over the head', often without variation throughout the day, although it may be exacerbated by emotional stress. Analgesics have no effect although those affected often take 2 pain relieving tablets 2-4 times daily - and continue to do so for weeks or even months. To make the diagnosis with confidence requires evidence of anxiety (difficulty in attaining sleep), or depression (difficulty in staying asleep), or a combination, agitated depression. Treatment consists of an explanation, stopping ineffective analgesic consumption and is then directed towards the underlying causes.

Localised head pain is usually unilateral and clearly indicated by the patient's index finger outlining the radiation from the neck over the same side of the head to the temple, or in the reverse direction. The pain can occur daily but has a periodicity, from waking for several hours, or from late afternoon till going to sleep. Analgesics partly or completely relieve the pain in 20-60 minutes. When the pain arises from the neck muscles or joints, patients are aware of local neck tenderness and 'creaking or grating' as well as head turning limitation, for example in reversing the car. Unilateral head pain can also arise from jaw malalignment, a clicking jaw joint, or impacted wisdom teeth. Pain on one or both sides of the forehead can arise from the paranasal (frontal) sinuses. Treatment is directed to the underlying cause, although different specialists' opinions may be necessary before the cause is established.

Episodic cluster headache, although rare, is one of the most severe
pains that can be experienced (Kudrow 1980). Because there is effective therapy, its accurate and early diagnosis is essential. A typical history is a man (4:1 is the male to female ratio), in his 40's or 50's who has bouts of pain for 6-10 weeks at annual intervals. During a cluster his headaches occur nightly, usually wakening him in the early morning hours, with remarkable regularity. The pain is always situated in one eye, building up slowly over a few minutes, when he will get out of bed and pace the bedroom. Looking in the bathroom mirror, he sees that the affected eye is red, the eyelids swollen and tears can come from the eye. The ipsilateral nostril is blocked. The pain becomes so severe that he does not know what to do with himself. He may press on the forehead and the eye with his hands, at times he wants to 'bash his head against the wall' – so intense is his pain. After about three-quarters of an hour, the pain disappears, leaving him shaken; a dull ache round the eye may remain for a few hours longer. Attacks can occasionally occur during the day, usually provoked by drinking alcohol, so that during this spell it is usually avoided. Between these cluster periods he enjoys good health.

The cause of cluster headache is not understood but may involve vasodilation and oedema of the internal carotid artery, as it runs in the carotid canal on the base of the cavernous sinus, giving rise to nerve compression. Between clusters the patient is symptom free, although a rare variant is chronic cluster headache where attacks occur more irregularly but persist for months or years.

**Pathophysiology of migraine**

The underlying cause of migraine remains elusive. Case histories commonly suggest an inherited disorder. Dalsgaard-Nielsen (1962) found a family history of migraine in 90 per cent of women sufferers, with a 73 per cent parental incidence (57 per cent maternal and 16 per cent paternal). Migraine also occurred in 27 per cent of siblings and in 15 per cent of the patients' own children. An earlier study by Goodell and colleagues (1954) showed that 69 per cent of children suffered from the condition when both parents were affected. There is therefore reasonable evidence to support a migraine predisposition being transmitted from parent to offspring but the precise mode of inheritance is unclear. The condition is not gender-linked but an autosomal dominant gene with incomplete penetrance (i.e. not always expressed) has been proposed.

Few doubt the genetic basis of migraine, but dispute about neurological or vascular aetiology has continued for over 100 years. Sir William Gowers (1888), in his famous neurological text book, quoted German authorities who supported spasm of cranial vessels.
while others favoured vascular dilatation giving rise to the concept of two migraine varieties – the ‘sympathetico-tonic’ and the ‘sympathetico-paralytic’ which nowadays would be called adrenergic and cholinergic. Gowers credited Dr Latham of Cambridge who proposed that ‘the early symptoms of the paroxysms are due to spasm, and the headache due to dilatation of the vessels’. This was the forerunner of Wolff’s (1963) theory for which he accumulated a great deal of experimental support. The theory suggested that migraine attacks were initiated by cerebrovascular spasm causing the aura by ischaemia of the visual cortex; the subsequent headache phase was believed to arise from extracranial vasodilatation, the pain being due to vessel distension.

This explanation is inconsistent with a number of observations. For example, Wolff’s classical vascular theory predicts that patients should have a flushed face during migraine attacks yet many patients exhibit intense pallor during such episodes. To overcome this contradiction Heyck (1969) proposed that arterial blood was by-passing the capillary bed via arteriovenous anastomoses (shunt vessels) directly into the venous system. Thus he explained the skin pallor and the diversion of cerebral blood flow accounted for the headache because of resultant ischaemia and accumulation of substances causing pain.

Heyck measured the arterial and venous oxygen content of neck vessels in migraine patients during an attack. He found a significant reduction in the normal differences of oxygen concentration between the two sides of the circulation. The difference was re-established following the administration of ergotamine causing long-lasting vasoconstriction, thereby lending support to his theory.

The existence of arteriovenous shunts in the human dura mater has subsequently been demonstrated by other workers (Rowbotham and Little 1965; Kerber and Newton 1973). However, it is difficult to equate the shunt theory with the differing findings in cerebral blood flow in the two types of migraine. It may be that arteriovenous shunting is the consequence, not the cause of migraine attacks and Heyck’s theory therefore remains a tentative explanation.

A large amount of research has focused on intracranial vasomotor changes during migraine attacks using radioactive Xenon-133. However, after 25 years of endeavour the results are completely contradictory: a 30-40 per cent increase is claimed by one group (Meyer et al, 1987), a 30-40 per cent decrease by another (Lauritzen and Oleisen, 1984) and more recently a 30-40 per cent error in the technique has been ascribed to Compston Scatter (Skyhøj-Olsen and Lassen, 1989).

The great advocate of the neurological basis for migraine pathophysiology was Liveing (1873) whose monograph ‘On Megrim, Sick
Headache and Some Allied Disorders: A Contribution to the Pathology of Nerve Storms' is a classic still worth reading. Gowers (1888) favouring a neurological aetiology, considered migraine to be 'a primary derangement of the nerve cells of the brain'.

A neurological explanation of migraine is supported by a number of observations and pieces of evidence. First, premonitory symptoms that occur several hours before an attack—such as alterations in mood and gut activity and excessive tiredness—as well as the visual warning or the somato-sensory aura of numbness ascending from hand to face, cannot be explained on a vascular basis. Second, Fisher (1971) an international authority on cerebrovascular disease, stated that neither the migration of the visual aura nor the scintillations (teichopsiae) have been observed in strokes or transient ischaemic attacks of the brain. Third, migraine headaches begin and develop slowly yet most vascular phenomena are sudden in their onset. Finally, many of the common precipitants of migraine such as stress and hunger stimulate the nervous system directly rather than blood vessels. Gower's (1888) analogy with blushing is appropriate in this context: the primary disturbance is cerebral and the secondary response is the facial flush.

The neurological explanation is not however as straightforward as it might at first appear. The brain itself does not contain pain fibres, yet headache can arise from hunger, alcohol, pre-menstrual tension, alteration in sleep patterns or stress. Hence there must be some way that pain fibres situated in the meninges or outside the skull can induce pain when the brain is disturbed. A further major problem is that migraines often start after, rather than during, stress. It is difficult to conceive how neurotransmitters, the messengers between nerve cells, which are rapidly released can initiate sensations of pain six or more hours after the stimulus has gone. Nevertheless this delay is a characteristic of 'hangover headache', or of muscle stiffness that occurs after the previous day's exercise. Although clearly not an explanation, these observations show that delayed biological phenomena exist.

Combining vascular and neurological explanations, Moskowitz (1987) has hypothesised that a disturbed interaction between the trigeminal nerve (the major pathway of sensation to the head and face) and cerebral blood vessels occurs during migraine attacks: animal experiments showed that stimulation of the trigeminal ganglion produced a vascular reaction in the brain coverings, the meninges, where blood vessels become permeable, giving rise to local oedema which Moskowitz termed sterile inflammation. This 'trigemino-vascular theory' is attractive because the initial stimulus comes from the nervous system causing blood vessels to respond with regional dilatation. The pain of migraine may well be meningeal as demonstrated
by Blau and Dexter (1981): 49 of 50 subjects examined during a migraine attack had evidence of meningeal pain – coughing, head shaking, and straining accentuating the pain. However, it should be emphasised that extrapolation from animal data to man may not be valid and experimental evidence of the type described above can only support, not prove, a theory. Further, the observations in migraineurs during attacks are only circumstantial.

Other hypothesised causes of migraine

In addition to the vascular and neurological explanation for migraine, many other possible causes of the condition have been put forward. The ‘Chemical Theories’, expound the involvement of certain neurotransmitter substances in migraine including tyramine and octopamine, although the precise location of their action – in the brain, blood vessels or both – remains uncertain. The strongest evidence for a causal role centres on the neurotransmitter serotonin (5-hydroxytryptamine or 5HT).

Clinical observations in 1961 (Sicuteri et al, 1961) showed that some migraine patients have increased urinary levels of the 5-HT metabolite 5-HIAA (5 hydroxyindoleacetic acid) during an attack. It subsequently became clear that platelet 5-HT levels fall, and plasma and urinary 5-HT levels rise during migraine attacks in as many as 85 per cent of patients (Anthony and Lance, 1975). Furthermore, reserpine, which depletes 5-HT and other monoamines from nerve terminals, produces migraine-like headaches in migraineurs (Anthony et al, 1969). The infusion of 5-HT itself ameliorates reserpine – induced headaches and migraine, albeit accompanied by severe side-effects (Kimball et al, 1960). Lastly, drugs acting at 5-HT receptors are known to be effective anti-migraine agents, particularly ergotamine and more recently developed 5-HT1-like agonists (Perrin et al, 1989; Byer et al, 1989).

Another theory suggests that the primary abnormality of migraine lies in the blood platelets of these patients: the platelets of migraineurs may be more sensitive to 5-HT releasing agents than normal control subjects and also more susceptible to spontaneous aggregation when 5-HT is released. However, the platelet theory is contradicted by the finding that anti-platelet agents like dipyridamole exacerbate, rather than improve, migraine. In addition, increased platelet aggregability is found in other conditions such as diabetes. It is also difficult to explain how a primary abnormality involving platelets can account for the episodic nature of migraine, or how stress reaches platelets.

Many other theories of migraine causation exist. For example, it has recently been shown that levels of brain magnesium – important in the maintenance of vascular tone and central neurotransmitter
### BOX 1 Precipitants of migraine

1. Lack of food or delayed meals
2. Various foods:
   - Alcohol
   - Cheese
   - Chocolate
   - Citrus Fruit
   - Coffee
3. Sleep excess and lack of sleep
4. Menstruation
5. Local pains
   - Eye
   - Sinuses (nasal)
   - Neck
6. Environment
   - Heat
   - Cold
   - Light
   - Smell and smoke
7. Travel
8. Allergy
9. Stress
10. Smoking

release – are low during migraine attacks. Others have linked migraine with allergy and hypersensitivity to certain foods.

It is evident that much remains to be discovered about migraine inheritance, the primary site of the pain experienced by sufferers and the underlying mechanisms involved. Nevertheless, the polarisation between the neurogenic and vascular theories appears to be diminishing and more research may yield new discoveries which, set alongside existing knowledge, could result in deeper understanding of migraine pathophysiology.

### Trigger factors

Although the mechanism(s) underlying migraine have yet to be elucidated, for some patients certain dietary, physical or emotional stimuli can trigger migraine attacks (Box 1). Among dietary triggers, cheese, chocolate, alcohol (especially red wine) and citrus fruits are the most frequently identified factors triggering migraine attacks in some subjects. Other precipitants include too little or too much sleep, excessive heat, light and noise as well as excitement, stress and fatigue. Identifying and then avoiding provoking factors to minimise exposure to these triggers, offers an additional approach to the management of the condition. Blau and Thavapalan (1988) found a reduction in migraine episodes over a two month period among a group of 23 migraineurs from 107 to 48 attacks following recognition and avoidance of relevant trigger factors.

However, it should be pointed out that triggers do not invariably provoke attacks. This observation suggests the probability that no one factor is solely responsible for setting-off an episode of migraine; there may also be an internal ‘threshold’ above which specific trigger factors are likely to provoke an attack (Blau, 1990).
The management of migraine

Some patients need advice and support over months or years. Attacks characteristically start during the teens or twenties and persist until late middle age. Thus a study of 52 migraineurs found a mean age of 55.5 years at which subjects 'lost' their migraine (defined as freedom from attacks for 2 years or more). Yet some patients found that their attacks persisted until their 60s and 70s although some compensation for these sufferers was that the frequency of episodes generally diminishes with age (Blau, 1987).

Management of patients with migraine will depend on frequency, severity and duration of attacks. In general, managing migraine involves drug and non-drug based strategies. Focusing on the latter, avoiding trigger factors clearly offers a means of reducing attack frequency. In this regard many magazine articles and books have been published linking, for example, diet and migraine with a view to helping sufferers identify and exercise control over some of the principal food and drink related causes of their attacks.

Other non-drug approaches, acupuncture, chiropraxis, and physiotherapy to the neck have varying degrees of efficacy in cases where migraine attacks are triggered by neck pain. The latter, more common in the middle aged or elderly, can also be relevant in younger patients sitting in one position for prolonged periods, for example typists operating a visual display unit, or telephone operators and professional musicians who hold the head in a fixed position. Neck exercises, sitting comfortably, and not remaining in one position for too long, can reduce neck pains that trigger migraine attacks.

General tension resulting in head and neck muscle contraction is a feature of anxiety states which induce migraine attacks. Relaxation techniques may therefore reduce the number of migraine attacks, but what is relaxing for some, like jogging, can be stressful to others. Relaxation methods include yoga, meditation, biofeedback techniques, the last being popular in the United States where patients learn to relax aided by skin thermometry (a relaxed person has warmer hands than a tense one), or transcutaneous electromyography, which measures muscle contraction.

Herbal therapy is another 'remedy' favoured by the lay public because of common fears about the safety of 'drugs'. (People often do not realise that many medicaments were initially derived from plants including aspirin, quinine and digitalis.) Feverfew is an example of a herb used historically as an analgesic for head and joint pains which has been investigated in a number of trials during the last decade and shown to be efficacious in migraine prophylaxis for some patients (Johnson et al, 1985).
In some women migraine attacks occur in association with menstruation. In such cases guidance from a gynaecologist or endocrinologist can be useful particularly in reducing premenstrual tension.

Eating breakfast or lunch can prevent some migraines that begin during the morning or the afternoon respectively. An experiment in Aberdeen showed that in children who woke with migraine a proportion of attacks could be prevented by having ‘breakfast before going to bed’ – an example of lack of food provoking migraines (Box 2). The opposite may also work: physicians at Great Ormond Street Hospital for Children in London have pioneered a low antigenic diet which was evaluated in a controlled double-blind trial (Egger et al, 1983). The investigators claimed a great improvement in migraine but the diet was only tried for three to four weeks. In addition to migraine other conditions like epilepsy, asthma, eczema, rhinitis, aching

BOX 2 Migraine in childhood

It is surprising to many, including doctors, that migraine affects children even beginning as early as between the ages of 1 and 4 years. A unique study of 73 school children in Sweden spans 30 years (Bille, 1989). The average age of onset was aged 6. Up to 11 the prevalence in boys and girls was the same. After puberty an increase was evident in both sexes but greater in girls. Providing strong evidence for a hormonal factor in females. Of the whole series 38 per cent persisted with migraine attacks but 62 per cent remained free from attacks for more than 2 years, although in one-third of the latter attacks recurred after an average of 6 years. Follow-up 30 years later, the subjects now aged 37-43, showed that 53 per cent had migraine with the females being more affected than the males.

At the City of London Migraine Clinic 1 in 10 new patients is aged 16 or under. Children are just as able to describe their symptoms as adults. Management requires reassurances of parents, one or both of whom usually have migraine, and are determined that their offspring should be better cared for than they were. It is striking how many can be alleviated by greater food intake: ‘breakfast before bed’ for those who waken with a headache; ‘a proper breakfast’ when migraine begins during the morning, or an adequate mid-day meal if migraine start during the afternoon. School lunches are unappetising at times and all too often replaced by a bag of crisps or a bar of chocolate.

It appears that growing children need more substantial and regular meals, particularly when they are thin and active in sport – organised or in the playground. Commonly a mother says: ‘I am glad you have told him (or her) to eat properly; he might listen to you, doctor’. Perhaps it was not a good idea to abolish school milk with its carbohydrate, protein and fat content.

Drug therapy is the next step although aspirin should be avoided for those under 12 years old. Paracetamol is useful in aborting attacks if taken early and the school-matron or a teacher needs to be advised. Prophylactic drugs are rarely needed and generally disliked by parents and children; when necessary prophylaxis should only be prescribed for short periods (Forsythe and Hockaday 1988).
limbs and behavioural problems were also claimed to have been improved. Clearly the diet needs to be tried for a longer period of time in migraine to see if it remains effective.

Avoiding certain types of alcohol or total abstinence is a method of preventing migraines well-known to patients and probably does not require formal evaluation under trial circumstances. Allergy testing has been employed by different groups to identify the types of food it might be beneficial to avoid. However in addition to this advice, patients are often recommended to take vitamins and inorganic chemicals, but without controlled trials, it is difficult to know how efficacious these therapies are in the short or long term.

**Drug therapy**

Medicines employed in the treatment of migraine fall into two categories – those used to alleviate headache and other symptoms immediately before or during an attack and those used to reduce the frequency and possibly the severity of attacks. In providing an overview of medication for migraine in its first publication on migraine in 1972, the Office of Health Economics suggested that ‘therapy for migraine, whether prophylactic or designed to alleviate symptoms when they occur, is as yet of limited effectiveness. There is no single therapy which will prevent the majority of attacks in the majority of people and although there are a number of therapies which have been shown to reduce the incidence and intensity of symptoms it is only a minority of people with migraine who can expect to have their condition wholly or largely relieved by any one of these’.

Many of the mainstays of migraine therapy at the time of the 1972 OHE publication on migraine are still used in treating patients today, although the objective evidence on the efficacy of many of these compounds has grown significantly in the subsequent two decades. The number of clinical trials been undertaken in recent years supports this view but it is hazardous to extend trial conclusions from specific cohorts of sufferers to wider migraineur populations. However, new medicines are gradually becoming available and clinical trials have shown the potential for greater efficacy.

(a) **Acute therapy**

Simple analgesics – aspirin or paracetamol – are the most frequently employed medicines in the treatment of migraine attacks. The mode of action of each of the drugs in migraine is unknown but aspirin is likely to involve peripheral analgesic or anti-inflammatory activity on painfully distended blood vessels by prostaglandin inhibition; it may also have a central analgesic effect. Paracetamol has both analgesic and antipyretic properties but, unlike aspirin, does not affect platelets. Both medicines are available as preparations combined
with antinauseants such as metoclopramide which may aid absorption. As current 'frontline' therapy aspirin and paracetamol have the advantages of low direct and indirect costs (both drugs being available without prescription) and are moderately effective in treating attacks. However, although controlled clinical trial data are in short supply and, even where available, sometimes difficult to interpret, it is clear that neither drug is effective in all attacks or in all patients (Wilkinson et al, 1978).

Ergotamine is widely used to treat migraine attacks. It has various pharmacological actions but vasoconstriction of cranial arteries is believed to account for its effectiveness in migraine. Ergotamine has been employed in the condition since the late 19th century but only became a rational therapy following Graham and Wolff's studies in the 1930s and 1940s suggesting a vascular origin for migraine attacks (Graham and Wolff, 1938).

As with the simple analgesics, it is not possible to specify accurately the effectiveness of ergotamine. Drug trials have largely been uncontrolled and have varied substantially in such key considerations as dosage regimen, measures of efficacy, drug formulation and definition of migraine. Despite the confusion created by these variations, ergotamine is used by many clinicians as the most effective acute treatment for migraine currently available. In these patients with infrequent attacks, who benefit by ergot, it remains the drug of choice but requires careful medical supervision because it has a number of important disadvantages. It is occasionally associated with side effects such as nausea and vomiting, perhaps due to a direct dopaminergic action on the emetic centre. With prolonged and excessive use, some patients may develop signs and symptoms of chronic ergot toxicity – involving more frequent or worsening headache which is unresponsive to ergotamine – drowsiness, nausea and vomiting, numbness and coldness of extremities, muscle pains and anorexia. Finally, the drug is contraindicated in the presence of a number of common conditions including coronary disease, peripheral vascular disease, hepatic/renal dysfunction and hypertension.

Some nonsteroidal anti-inflammatory drugs (NSAID), more widely employed to alleviate the pain of arthritis and related disorders of the musculoskeletal system, have also gained a place in treating migraine. It is thought that inhibiting prostaglandin synthesis may partly explain the efficacy of these drugs in migraine. In addition, drugs like naproxen (although not licensed for use in migraine in the UK) inhibit platelet aggregation and serotonin release from platelets as well as exert potent anti-inflammatory and analgesic effects. The relative significance of each of these actions in migraine remains unclear.
Various other pharmaceutical preparations have been used to treat acute episodes of migraine. The sedative and anti-emetic properties possessed by chlorpromazine, for example, have led to investigations of its potential benefit to migraine sufferers but it is not widely used.

However, perhaps one of the most interesting prospects for the treatment of migraine lies in the developing understanding of the role of 5-hydroxytryptamine (5-HT) in the aetiology of the condition.

A variety of observations undoubtedly implicate the endogenous biogenic amine, 5-HT in migraine pathogenesis. Indeed, 5-HT itself, administered intravenously, has been shown to be capable of abolishing attacks of migraine (Kimball et al., 1960). However, 5-HT acts at a variety of 5-HT receptor types and its wide range of actions (Bradley et al., 1986) makes its clinical use unacceptable.

It is apparent that many of the drugs used in the treatment of migraine interact with 5-HT receptors in some way. Most of these are receptor antagonists, and have clinical value in some patients. Since evidence supports the view that an acute migraine attack is caused by a low 5-HT state, selective 5-HT receptor agonists might be considered to be more likely to provide therapeutic benefits as treatments for an acute attack.

Sumatriptan, an analogue of 5-HT synthesised in the UK pharmaceutical industry, is a highly selective agonist at a '5-HT1 like' receptor subtype which mediates vasoconstriction predominantly in cranial vessels.

Recent clinical studies have demonstrated sumatriptan to be an effective acute anti-migraine agent (Perrin et al., 1989; Byer et al., 1989). A high degree of specificity contrasts markedly with the ergot alkaloids which stimulate or block a wide range of 5-HT receptors.

It may be that this new class of anti-migraine preparation produces selective vasoconstriction of the vessels which are dilated and distended during migraine headaches, thereby aborting attacks.

(b) Prophylactic therapy

Preventative drug therapy is generally indicated in those with two or more attacks per month. Ideally, therapy should be reviewed after one month to determine how effective it has been, and then at three monthly intervals to ascertain for how long the drug needs to be taken. To date, however, no prophylactic treatment has succeeded in completely eliminating migraine attacks – the best results have been an approximate halving of attack frequency in up to 50 per cent of patients.

The principal classes of medicine used in migraine prophylaxis are beta blockers, 5-HT antagonists and calcium antagonists. Most experience with beta blockers has been with propranolol. The dis-
covery of propranolol's effectiveness was made by chance: a patient treated with the drug for angina, reported relief of long standing headaches. The mechanism of action of propranolol in migraine was originally attributed to beta-blockade in cerebral or extracranial vessels, with resultant vasoconstriction. However, propranolol also has 5-HT antagonist and anxiolytic properties which may contribute to its anti-migraine effect. It is estimated that about one-third of patients have a good response to propranolol with a greater than 50 per cent reduction in the number of attacks (Weerasuriya et al, 1982, Tfelt-Hansen et al, 1984).

Among the 5-HT antagonists, pizotifen has undergone a large number of placebo controlled trials which, despite wide differences in terms of design, dose, treatment duration and efficacy assessment, generally show a 50 per cent or better reduction in the number of headaches for more than half of the trial patients (Fozard 1988).

In the same drug class, methysergide has been shown by a series of double blind cross-over trials against placebo to achieve a 50 per cent or greater reduction in the frequency of migraine episodes for between 27 and 57 per cent of patients (Lance et al, 1963). Its action is likely to reflect not only antagonist activity at receptor sites but anti-inflammatory and vasoconstrictor effects as well. Short and long term adverse effects associated with the drug's use have meant, however, that methysergide has tended to be reserved for patients who are refractory to other treatments. Its use is limited to a maximum of five months followed by a drug free interval of at least one month (a 'drug holiday') because of the danger of retroperitoneal fibrosis.

Calcium antagonists, nimodipine, nifedipine, flunarizine, constitute the third group of medicines employed in migraine prophylaxis (although none of these is licensed in the UK for migraine treatment). These agents block the entry of extracellular calcium into vascular smooth muscle and were introduced for the treatment of hypertension and vasospastic angina. The potential of calcium antagonists in migraine prophylaxis was explored because vasospasm has been thought to be important in migraine (at least in migraine with aura) Gelmers, 1983; Amery et al, 1985).

Much of the work investigating the potential value of calcium antagonists in migraine has involved flunarizine, a compound not available in the United Kingdom. Trial results suggest, in broad terms, that it produces a similar response to propranolol (Amery et al, 1985). Evidence concerning calcium antagonists which are available in the UK such as nifedipine and verapamil is more limited and it is not possible at this stage unequivocally to state exactly how effective the two drugs are in migraine prophylaxis, or how these benefits stand in relation to side effects.
A number of other drugs have been employed to try to prevent or reduce the occurrence of migraine attacks. Among these clonidine was first proposed as a potentially prophylactic agent in 1969 because it is thought to diminish the responsiveness of peripheral vessels to constrictor and dilator stimuli, thereby preventing the vascular changes associated with migraine. The efficacy of clonidine has recently been questioned. But it reduces menopausal flushes which patients find disturbing as well as interrupting sleep – each can provoke migraine attacks. Other drugs used prophylactically include aspirin and naproxen which appear moderately effective (Johnson et al, 1985).

**The economic burden of migraine**

The economic burden of migraine comprises three elements. First, there are the health service costs resulting from sufferers seeking therapy. Secondly, there are the broader costs to the community in lost production resulting from sufferers ceasing work, or working inefficiently following an attack. Finally, there are the more intangible disbenefits to individuals resulting from a reduction in the quality of life. These are discussed in turn.

The health service costs for migraine can relate both to the therapy received during or immediately following an attack, or longer term maintenance therapy including prophylaxis.

A number of published studies have asked sufferers from migraine and other headaches how often they consulted a doctor. For example, in a study of 402 Swedish school children in the age groups 7, 11 and 15 years, Egermark-Erikson (1982) found that 6 per cent of the children had consulted a physician for their headache. Schnarch and Hunter (1980) argue that there may be considerable cultural variance among those who seek treatment for less severe headache, whereas the same percentage of migraine sufferers in these cultures seek medical help. In comparing their study of randomly selected adults in the USA with one on a similar population in Britain (Henryk-Gutt and Rees, 1975) they found that the proportions of migraine sufferers seeking medical treatment for their headaches were very similar (71.3 per cent versus 72 per cent). However, only 8 per cent of non-migrainous headache sufferers in Britain consulted a physician, compared with 21.7 per cent in the USA.

In one of the most recent and largest epidemiological studies of headache in the USA, Linet et al (1989) conducted a population-based telephone interview study of 10,169 Maryland residents ages 12 to 29 years old. They found that for males of all ages, 14.6 per cent had consulted a physician for headache at some stage, 6.5 per cent
within the last year. The figures for females were higher, 27.9 per cent having consulted a physician at some stage, 15 per cent during the last year. Unfortunately, separate figures are not given for migraine sufferers, of which there were 3 per cent of males and 7.4 per cent of females in the population studied.

In England the last National Morbidity Survey (OPCS, 1986) reported 12.8 consultations for migraine per year for each 1,000 patients on a GP's list. This would suggest approximately 700,000 consultations a year in the United Kingdom. The average cost of a consultation, updated to 1989-90 prices (OHE, 1989) is £8.17, so the total annual cost of GP consultations for migraine is approximately £5.72 million. In addition to this sum, a further £15.7 million is spent in the primary care sector on the two million prescriptions for antimigraine medicines written by general practitioners each year.

Hospital admission does not at present play a large role in the management of migraine. The Hospital Inpatient Enquiry for 1985 indicates that 3,080 people were admitted in England, of which 2,040 were female and 1,040 male. Possible reasons for admission include further investigations, adjustments to drug therapy and the seeking of psychiatric opinion. The mean duration of hospital stay was 4.8 days, with a median of 2 days. Given an average daily cost of hospital stay of £130 (updated to 1989-90 prices), this would suggest a cost for hospital inpatient care of between £800,000 and £1,920,000 per annum for England, or £912,000 and £2,190,000 per annum for the whole UK.

Few reliable data are available for the number of hospital outpatient attendances attributable to particular diseases. However, most patients admitted are likely to have a specialist consultation before admission and one or two consultations subsequently. With an average cost of a specialist consultation of approximately £40 in 1989-90 prices, and an average of 2.5 consultations per inpatient case, this would suggest a total annual cost for outpatient care of around £350,000 for the UK.

The total cost to the NHS of treating migraine, is therefore relatively modest at about £23 million per annum. Assuming a prevalence rate of 8 per cent, which implies a migraineur population of 4.5 million in the United Kingdom, it may be estimated that the annual cost of the disorder to the NHS is equivalent to only £5 per sufferer. The small magnitude of this sum, which may, for example, be compared with more than £200 per head per annum in the case of asthma (Action Asthma, 1990), reflects the fact that there is relatively little the NHS can effectively offer the migraine patient at the present time.

The second category of economic burden from migraine relates to the lost production if individuals are forced to cease work, either temporarily or in the long run. A number of published studies have
assessed this, both for migraine and headache more generally. Jones and Harrop (1980) studied the impact of migraine in a food company employing 2,000 workers. Approximately 6 per cent of the workforce were seen to be affected by migraine. During the period April 1979 to December 1979, 111 separate incidents were reported to the medical department, with 281 working days lost, which implies an average annual loss of 420 working days through migraine (about 0.20 days per worker year). Of these individuals experiencing an attack at work, the authors claim that the majority could return to their place of work within 1 hour following simple treatment, with no subsequent problem caused to their health, either through migraine or accident.

There are some indications in the literature that the occurrence of

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Males (n=4394)</th>
<th>Females (n=5055)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most recent headache occurrence, week*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>57.1 (2510)</td>
<td>76.5 (3865)</td>
</tr>
<tr>
<td>4-51</td>
<td>32.6 (1433)</td>
<td>18.5 (937)</td>
</tr>
<tr>
<td>≥52</td>
<td>10.3 (451)</td>
<td>5.0 (253)</td>
</tr>
<tr>
<td>Frequency of headache†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>43.0 (1889)</td>
<td>23.6 (1191)</td>
</tr>
<tr>
<td>1</td>
<td>27.1 (1192)</td>
<td>28.1 (1420)</td>
</tr>
<tr>
<td>2</td>
<td>18.8 (827)</td>
<td>25.4 (1286)</td>
</tr>
<tr>
<td>3</td>
<td>5.0 (220)</td>
<td>8.9 (448)</td>
</tr>
<tr>
<td>4†</td>
<td>6.1 (266)</td>
<td>14.0 (710)</td>
</tr>
<tr>
<td>Migraine prevalence†</td>
<td>3.0 (146)</td>
<td>7.4 (390)</td>
</tr>
<tr>
<td>Work or school absence due to most recent headache†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>91.7 (2302)</td>
<td>85.9 (3322)</td>
</tr>
<tr>
<td>Part of day</td>
<td>6.1 (153)</td>
<td>10.2 (394)</td>
</tr>
<tr>
<td>Full day</td>
<td>1.8 (46)</td>
<td>3.7 (143)</td>
</tr>
<tr>
<td>Missing data</td>
<td>0.4 (9)</td>
<td>0.2 (6)</td>
</tr>
<tr>
<td>Mean (SEM) intensity of pain†</td>
<td>4.5 (0.04)</td>
<td>4.9 (0.03)</td>
</tr>
<tr>
<td>Mean (SEM) duration of headache, h</td>
<td>5.9 (0.23)</td>
<td>8.2 (0.25)</td>
</tr>
</tbody>
</table>

* Totals include subjects who experienced at least one headache in the 5-year period before interview.
† Characteristics of most recent headaches that occurred within 4 weeks before interview.
‡ Scale of 1 to 10: 1 indicates mild; and 10 excruciating pain.

migraine may be related to type of work, although this is partly con­founded by the different age/sex compositions of workers in differ­ent job categories. In the study by Jones and Harrop cited above, there was a slightly higher rate of reporting migraine among day-pattern workers. In a study of headache in a random sample of 200 persons in Finland, Nikiforow (1981) found that the proportion of headaches of the vascular type was highest in managerial and service occupations and among housewives.

Other population surveys have examined the impact of headache on work or school. Linet et al (1989), surveying the previous four weeks, found that work or school absence (used as an objective measure of disability) resulting from a subject's most recent headache was substantial, with 1.2 per cent to 4.5 per cent (varying by age and sex) of subjects indicating absence for an entire day and 3.4 per cent to 2.5 per cent for part of a day (Table 4). On the other hand Nikiforow and Hokkanen (1979) concluded that work absence was not a common occurrence as 'only 263 of 2,018 respondents (13 per cent) who suffered from headaches were absent from work one or more days during the previous year. Self-employed persons had a higher percentage of absence than other employed categories, and the rural self-employed and rural housewives had the highest per-

Table 5  Effect of headache on daily activities

<table>
<thead>
<tr>
<th>Effect of headache on daily activities</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No. 224 (%19)</td>
<td>223 (%27)</td>
</tr>
<tr>
<td>Affected, but able to continue</td>
<td>No. 264 (%22)</td>
<td>253 (%30)</td>
</tr>
<tr>
<td>Sometimes forced to rest</td>
<td>No. 89 (%8)</td>
<td>50 (%6)</td>
</tr>
<tr>
<td>Usually forced to rest</td>
<td>No. 202 (%17)</td>
<td>121 (%15)</td>
</tr>
<tr>
<td>Usually forced to rest or lie down</td>
<td>No. 171 (%14)</td>
<td>56 (%7)</td>
</tr>
<tr>
<td>Usually forced to lie down</td>
<td>No. 184 (%16)</td>
<td>85 (%10)</td>
</tr>
<tr>
<td>Not stated</td>
<td>No. 53 (%4)</td>
<td>43 (%5)</td>
</tr>
<tr>
<td>Total</td>
<td>No. 1187 (%100)</td>
<td>831 (%100)</td>
</tr>
</tbody>
</table>

Source: Nikiforow and Hokkanen (1979)
centage of absence. Twenty two per cent stated that headache did not affect their work, 26 per cent were able to carry on by easing their pace of work and 47 per cent were forced to rest or lie down during an attack (Table 5). However, migraine appeared to have a greater level of interference with daily activities than non-vascular headaches; 64 per cent of respondents with vascular headaches were forced to rest on some or all occasions.

At the aggregate level the economic impact of migraine can be assessed by considering the days of certified incapacity. The Department of Social Security data show 43,800 days of sickness and 276,900 days of invalidity in the year ending April 1989. Based on average weekly earnings of £220 for full-time adult workers in manufacturing and certain other industries a crude estimate of the annual lost production would be around £14,000,000, with annual benefit payments of approximately £2,700,000. However, as stated earlier much of the impact of migraine on productivity will not be captured in this way, since many sufferers remain at work during an attack. Others, such as housewives, are not eligible for sickness benefit payments since they are not in full-time paid employment.

The intangible costs of migraine are even harder to assess and there have been few studies of how migraine affects the quality of life. The study by Nikiforow and Hokkanen, referred to above, gives some indication of the impact on daily activities during an attack, but there may also be a longer lasting effect on quality of life. Barat and Lake (1983) surveyed patient attitudes about headache. The life stresses most frequently implicated in headache were inability to relax, demands of self and depression. The most frequent emotional reactions during headache were frustration, anger, tension or nervousness and depression. Patients' main coping strategies were medications (75.4 per cent of patients), rest (68.3 per cent), fighting the headache (38.9 per cent) and keeping busy (32.1 per cent). The study also considered a number of the social stigmas associated with headache but shed very little light on the degree of restrictions on patients' activity as a result of headache.

Van den Bree et al (1989) explored the correlations between headache, quality of life and stress-coping behaviour in adolescent male students in The Netherlands. Quality of life was measured by questions on satisfaction with life in general, health, school, relationships with boy and girlfriends, home situation and autonomy. Negative correlations were found between headache duration and intensity versus satisfaction with autonomy, and between headache intensity versus satisfaction with health only. It also indicated that satisfaction with health was the most important quality of life variable for headache intensity, although this did not necessarily imply that the other quality of life variables did not contribute to this parameter.
Economic evaluation of migraine therapy

As health care budgets become increasingly stretched in the face of competing demands for their use, there is growing interest in the economic evaluation of health care interventions. Economic evaluation assesses whether alternative programmes and treatments represent good value for money by comparing their costs with their benefits. In the case of medicines the government has suggested that the pharmaceutical industry can make a contribution by demonstrating the economic value of its products. It has also pointed out that any economic assessment should not be limited to the costs of the medicines themselves, but should also include consideration of other health care costs and the benefits to patients in terms of improved quality of life (DH, 1990).

The relevant costs and consequences to consider when undertaking an economic evaluation of health care interventions were outlined in

Figure 3 Components of economic evaluation

<table>
<thead>
<tr>
<th>INPUTS</th>
<th>HEALTH</th>
<th>OUTPUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOURCES CONSUMED</td>
<td>CARE PROGRAMME</td>
<td>HEALTH IMPROVEMENT</td>
</tr>
</tbody>
</table>

POSSIBLE MEASUREMENTS

- C = Direct Costs
- C₂ = Indirect Costs (Production Losses)
- C₃ = Intangible Costs
- In Natural Units (Health Effects)
- In Utility Units (Quality Adjusted Life-years)
- U

- E = Associated Economic Benefits
- B₁ = Direct Benefit
- B₂ = Indirect Benefits (Production Gains)
- B₃ = Intangible Benefits

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an earlier OHE publication (Drummond, Teeling Smith and Wells, 1988). Three types of benefit are typically attributed to successful therapy: (i) the savings in other health care resources owing to the patient’s improvement in health (direct benefits), (ii) the gains in productivity owing to the patient, or someone who is caring for him, being able to return to work (indirect benefits), and (iii) the value of improved health for its own sake (intangibles) (Figure 3).

Economic evaluations have now been undertaken for a wide range of health care interventions. However, it is clear that such an evaluation for migraine therapy would present a major challenge. First, it was pointed out earlier that the NHS expenditures on migraine therapy are relatively small when compared to other diseases. Therefore the potential for substantial direct benefits to the NHS from effective therapy is low. Of course in a truly comprehensive economic evaluation the costs borne by sufferers from the disease, in expenditures on OTC medicines, should also be considered. However, since new medicines for migraine will, of necessity, be prescription only medicines, an expansion in their use will have the effect of transferring some of the costs from the private to the public purse.

Whereas some estimations can be made of the NHS costs, measurement and valuation of the indirect benefits of migraine therapy are likely to be even more difficult. These benefits relate only to averted morbidity since migraine is not a fatal disease. The normal method of valuing indirect benefits is to use the gross earnings of individuals. (This is taken to represent the productive value of workers to the economy.) However, it was pointed out above that migraine is most prevalent amongst females, many of whom may not be in paid employment. Therefore a value would need to be imputed for the important role many women play at home. Also it could be argued that since many migraine attacks last for a limited period, any lost production could be made up at a later stage, or that rather than ceasing work completely, sufferers carry on at reduced productivity. This makes measurement extremely difficult.

This leaves the intangible benefits as the main possibility for demonstrating the value for money from migraine therapy. Drummond et al (1987) point out that owing to the difficulties in valuing the intangibles in money terms, there has been increased interest in assessing the impact of therapy on the quality of life of the patient. Some quality of life scales, such as the chronic respiratory disease questionnaire developed by Guyatt et al (1987), are disease-specific. They have the advantage that, being targeted at the disease in question, they are most sensitive to changes in the patient’s condition. However, they do not allow comparisons to be made between interventions for different diseases. Currently no such scales for migraine
exist in the published literature, although some are under development.

Other scales are more generic. For example, the Nottingham Health Profile (Hunt et al 1986) has been used to assess the health status of patients with a number of diseases. It gives assessment on six dimensions: physical mobility, pain, sleep, energy, social isolation and emotional reactions. While such scales enable broader comparisons to be made of the health status of patients with different diseases, they may not be sensitive enough to detect the apparently small improvements in the overall condition of a migraine patient. In addition, the episodic nature of migraine would make measurement difficult, although, as is argued later, migraine sufferers may experience a continuous reduction in their quality of life, even between attacks.

Many scales like the Nottingham Health Profile give scores on a number of dimensions which are not weighted one with another. Economists tend to favour utility measures, such as those produced by the time trade-off or standard gamble method (Drummond et al,

Figure 4 Impact on quality of life of effective migraine therapy

Notes: Therapy reduces the length and intensity of attacks. The individual's general quality of life is higher if therapy controls attacks effectively.
1987). These give a single estimate of the quality of life of an individual, on a scale from zero to unity. The main attraction of this approach is that it allows, in conjunction with data on length of survival, the calculations of the quality-adjusted life-years (QALYs) gained by therapy.

In recent years it has become fashionable to produce rankings of health care interventions in terms of their cost per QALY gained. The implication is that interventions near the top of the list represent better value for money, in that a unit of health (the QALY) is obtained at a lower cost. It has therefore been argued that information on the relative cost per QALY from health care interventions should be used in assessing the relative priority for expansion of services (Williams, 1985).

In assessing where migraine therapy is likely to fall in such rankings, it is necessary first to consider the impact that successful therapy would have on the patient's utility. This is an empirical matter and to date no such measurements have been made. However, it is possible to outline the general approach that would be required. Figure 4 shows, in a schematic fashion, the impact that successful therapy would have. In particular it can be seen that, in this example, therapy does not only improve quality of life during an attack, whether by making it less prolonged or less severe, but also improves the quality of life between attacks.

As assessment of the likelihood of continuous reductions in quality of life can be obtained by considering the utility scales used in the construction of QALYs. For example, the scale developed by Kind et al (1982) considers two dimensions disability and distress (Table 6). It is likely that many migraineurs experience at least slight disability as assessed by this scale, since fear of an attack may cause them to rearrange their social life. Similarly the multiattribute utility function developed by Torrance et al (1982) considers the dimensions of physical function, self care and role activity, social-emotional function and health problems. At least 3 of these could be affected by migraine.

Indeed, for many migraineurs it is likely that the largest number of QALYs will be gained as a result of the continuous, rather than the transient, quality of life improvement. The two are obviously related. An individual with frequent or particularly severe attacks is more likely to experience a significant continuous reduction in the quality of life. Empirical investigation is obviously required to quantify the size of these changes. However, the general approach is important to outline as migraine may be regarded by many as a self-limiting condition. Each attack is, of course, self limiting, but the same may not be true of the quality of life reduction, depending on the intensity and frequency of the attacks and the individual's reaction to them.
<table>
<thead>
<tr>
<th>Disability rating</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>i     No disability</td>
<td>1.000</td>
<td>0.995</td>
<td>0.990</td>
<td>0.967</td>
</tr>
<tr>
<td>ii    Slight social disability</td>
<td>0.990</td>
<td>0.986</td>
<td>0.973</td>
<td>0.932</td>
</tr>
<tr>
<td>iii   Severe social disability and/or slight physical impairment</td>
<td>0.980</td>
<td>0.972</td>
<td>0.956</td>
<td>0.912</td>
</tr>
<tr>
<td>iv    Physical ability severely limited (e.g. light housework only)</td>
<td>0.964</td>
<td>0.956</td>
<td>0.942</td>
<td>0.870</td>
</tr>
<tr>
<td>v     Unable to take paid employment or education, largely housebound</td>
<td>0.946</td>
<td>0.935</td>
<td>0.900</td>
<td>0.700</td>
</tr>
<tr>
<td>vi    Confined to chair or wheelchair</td>
<td>0.875</td>
<td>0.845</td>
<td>0.680</td>
<td>0.000</td>
</tr>
<tr>
<td>vii   Confined to bed</td>
<td>0.677</td>
<td>0.564</td>
<td>0.000</td>
<td>-1.486</td>
</tr>
<tr>
<td>viii  Unconscious</td>
<td>-1.028</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Notes: healthy = 1.0; dead = 0.0
* not applicable
Source: Kind et al, (1982)

The discussion of potential QALY gains above emphasises the importance of length of duration of a disease in the calculation of QALYs. Implicitly the QALY assumes a constant proportional trade-off between length and quality of life. That is, the loss of utility of 0.1 in each of 10 years is considered equivalent to the loss of one year of healthy life. Therefore very bad health states may not have much impact on the overall QALY score if only experienced for a short period, even if individuals consider them so bad that they would avoid them at all costs!

Also, the rankings of cost per QALY, whilst being useful for informing health care priorities, say nothing about how much a QALY is worth. Therefore an alternative approach, of asking individuals how much they would be willing to pay to avoid pain and discomfort, may also be worth considering. This approach may be particularly useful in eliciting individuals’ valuations of the benefits of migraine therapy, where severe pain and discomfort may be experienced for a short period of time.
Conclusion

Migraine does not place substantial demands upon the National Health Service. The estimates contained in this paper suggest a total cost of just £23 million per annum which is equivalent to only 0.09 per cent of total NHS expenditure. Instead, the burden of migraine is borne principally by sufferers in terms of impaired quality of life and by the national economy as a consequence of sickness absence from work.

In both of these areas, there is insufficient information to derive a comprehensive and accurate estimate of the magnitude of the burdens involved and further research would be valuable. Nevertheless, focusing on sickness absence, a simple extrapolation from the study by Jones and Harrop (1980) would suggest that among the economically active male population alone there are nearly 4 million days of sickness absence from work attributable to migraine in the United Kingdom each year. In terms of the value of potential productivity foregone this magnitude of absence could represent an annual cost to the economy of about £200 million. Furthermore, this sum is likely to be an understatement since female absence is excluded as well as any allowance for the reduced productivity of individuals who remain at work during a migraine attack.

Considerable anecdotal evidence exists for the impaired quality of life experienced by migraine sufferers but, once again, quantitative data are in limited supply. It is obviously difficult to provide an overview of the personal and social impacts of the disorder because of the wide variations in the frequency, severity and duration of attacks experienced by different patients and by the same patients at different times. Nevertheless, it is clear that patients experience not only the severe physical symptoms and social disruption of acute episodes but also the discomfort of being vulnerable to largely unpredictable future attacks. The fact of being 'at risk' can play a major part in the lives of migraineurs and the personal costs of attacks themselves can be compounded by a continuing knowledge of the likelihood of recurrence. This is similar in nature, though of a different order, to the personal costs of epilepsy. However, while about three quarters of epileptic fits can be controlled in about three quarters of epileptics with the use of anti-convulsant drugs, treatment to control the risk of migraine is as yet ineffective or only partially effective in the majority of cases. This observation was contained in the 1972 OHE paper on migraine and is still largely valid today.

More effective therapy clearly represents the way forward to reducing the personal and broader economic costs of migraine. At present, acute treatments are aimed at alleviating symptoms and in some cases stemming attacks but reported effectiveness varies con-
siderably — reflecting, *inter alia*, the difficulties of assessing therapeutic efficacy in migraine, especially the problems of how and when to measure pain — and none is able to alleviate the majority of attacks in the majority of patients. With regard to prophylactic therapy, no treatment has completely abolished migraine attacks, the best results indicating an approximate halving of attack frequency in up to 50 per cent of patients.

Looking to the future, there are however grounds for optimism. Research has suggested that a naturally occurring chemical in the brain called serotonin (5-HT) plays an important role in the genesis of migraine attacks through its influence on the widening and narrowing of the blood vessels around the brain. Further laboratory and clinical investigation conducted in the UK pharmaceutical industry has subsequently resulted in the development of a new chemical entity which appears to be able to abort migraine attacks through its effect on 5HT1 receptors.

The development of effective medicines is however becoming extremely expensive and in common with the previous OHE publication on migraine it is appropriate to conclude this paper with some observations on the economics of pharmaceutical innovation in this therapeutic area. The process of bringing a new chemical entity from the laboratory bench to the prescription medicine market now requires an investment of £100 million or more and expenditure on this scale has inevitably to be reflected in the price of new medicines. At the same time, however, pressures confronting the National Health Service have created a greater need for the service to maximise the value for money from available resources. To this end the NHS is looking increasingly at the costs and benefits associated with different types of therapeutic intervention. In this context perhaps one of the most important points to emerge from this paper is that the benefits do not necessarily accrue to the NHS although it is indeed the health service that must pay the cost. Consequently, economic analyses in some therapy areas such as anti-migraine treatment which confine their attention to the cost-benefit implications for the NHS alone will fail to reflect the potentially substantial gains from innovation which fall to the national economy and, more importantly, to sufferers.
References


