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Oh! that the Healer's art and skill
Could dissipate this pain, this ill!

ANON.

MIGRAINE



MIGRAINE



Office of Health Economics

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Office of Health Economics

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Introduction

Migraine is typical of the sort of ill defined self limiting condition which takes up much of the time of general practitioners. It involves no risk of mortality but it can cause acute intermittent incapacity to the sufferer, occurring with little warning and at times which may be inconvenient, socially embarrassing and often costly. Perhaps its nature can be best illustrated by a quotation from *Through the Looking Glass* by Lewis Carroll, himself a migraine sufferer, 'I'm very brave really', he went on in a low voice, 'only today I happen to have a headache' (Tweedledum).

Migraine is a condition for which there are no signs which can be objectively measured and doctors must rely solely on a subjective description of symptoms by the patient in order to make a diagnosis. The clinical definition of migraine has been a subject of dispute for many centuries and remains so today. The one symptom that is common to every person with migraine is the recurrence of headache. However, recurrent headaches are rarely the only symptoms of migraine attacks. They are often preceded by warning signs or *aurae* which may vary from patient to patient and from attack to attack. They are usually accompanied by some transient phenomena such as visual, sensory or speech disturbances. They are often, but not always, concluded by a spasm of nausea or vomiting. Nevertheless, it is often difficult to differentiate between migraine and other headaches. There is no clear-cut line whereby a headache can be diagnosed as migrainous or not.

Migraine may be divided into two main sub-groups. First, classical migraine, where the headache is preceded or accompanied by visual *aurae*, sensory or speech disturbances and second, non-classical or common migraine which is not associated with this sort of sharply defined focal neurological disturbance. In both these types the headache is unilateral and may be associated with nausea or vomiting. Common migraine is by far the more prevalent of the two. Other symptoms may include feelings of elation or depression without apparent cause during the twenty-four hours preceding the attacks, total loss of appetite and, especially among women prone to premenstrual tension, a tight feeling affecting the skin. Large quantities of urine may be excreted as the attack is waning. Patients may also experience neurological symptoms such as numbness, 'pins and needles' or giddiness. Table 1 shows a list of warning symptoms that may precede an attack.

Other less common types may occur. Among these is the cluster headache which is characterised by intense unilateral pain involving the eye and one side of the head, associated with symptoms of flushing, nasal congestion and watering eyes. These

Table 1 *Migraine: the warning signs*

Visual disturbances: double vision, difficulty in focusing, temporary partial blindness, dazzling display of coloured lights, spots or lines	Unusual hunger: desire for snacks etc
Dizziness	Yawning
Hallucinations	Trembling
Nausea	Feeling of weakness
Vomiting	Excitability
Numbness	Talkativeness
Tingling sensations	Difficulties in speaking
Sensitivity to noise or light	Pains in neck or shoulders
Depression	Blotchy patches on skin or rashes
Irritability and tension	Unusual pallor, especially in children
Alterations in mood and outlook	Noticeable increase in weight
Feeling of exaggerated well-being	Swelling of fingers, waist or breasts
Uncommon energy and vigour	Increase in frequency or volume of urination

A note of these or any other apparent warning signs may be useful in helping sufferers to begin treatment at the earliest possible moment in the cycle of a migraine attack.

Source *Focus on migraine* (1971). The Migraine Trust.

attacks usually recur once or more a day lasting for 20–120 minutes in bouts which commonly continue for weeks or months but are separated by remissions of months or years. The condition is distinguished from other types of migraine by the absence of warning signs and by the presence of unilateral flushing.

Facial migraine¹ is another variant. As its name suggests, its main features are those of unilateral episodic facial pain associated with the symptoms of either migraine or cluster headache. Two rare forms are ophthalmoplegic migraine and hemiplegic migraine. The former is associated with the occurrence of prolonged double vision and the second with the temporary paralysis of one side of the body.

Because migraine is so little understood, it is perhaps not surprising that myths have grown up about the incidence of the condition and the characteristics of sufferers. There are strong beliefs that migraine is a neurotic disorder. A typical migraine sufferer is generally thought to be highly intelligent, highly strung and a perfectionist. It is also commonly believed to be an hysterical female disorder and it is often thought to occur more frequently among men and women whose occupations involve concentrated work using the eyes. None of these beliefs, however, is supported by hard evidence.

¹ This is not to be confused with trigeminal neuralgia which involves pain along the facial nerves.

History

The word migraine is derived from the Greek word 'hemisrania' literally meaning half a skull, the Greek word itself being derived from the Egyptian language. The earliest known reference is in a papyrus, written in 1200 BC, found in the Tomb of Thebes. It records a magic spell said to be effective against a type of headache known as the half temple. This can be cured by threatening the spirit of evil which causes the malady, followed by threats to the Gods and the whole order of nature. Magic has by now largely been replaced by rationality, but nevertheless medical science has as yet made few significant advances, either in knowledge of causation or in effective treatment.

The many and varied symptoms of migraine have led to many theories of causation. The first to describe its clinical characteristics was Aretaeus of Cappadocia (AD 30-90). He attributed the condition to coldness and dryness. Galen thought it was caused by irritation of the brain by black bile. Serapion, in the eleventh century, attributed the condition to hot or cold substances in the digestive tract being transported to the brain. Tissot (1784) pointed out that as vomiting often concluded a migraine attack, reflex irritation of the gastric nerves caused the headache. Liveing (1873) thought that migraine was a familial allergy closely related to asthma.

A description given by Gowers (1888) includes most of the features now accepted in the establishment of the diagnosis. He wrote 'Migraine is an affection characterized by paroxysmal nervous disturbance, of which headache is the most constant element. The pain is seldom absent and may exist alone, but is commonly accompanied by nausea and vomiting, and it is often preceded by some sensory disturbance, especially by some disorder of the sense of sight. The symptoms are frequently one sided, and from this character of the headache the name is derived . . .'.

In the twentieth century many theories of causation have been suggested, none of which have been proven. It has been suggested that migraine is a reflexive result of irritative forces elsewhere in the body, the most frequent source being the eyes. Anomalies in the brain and its coverings were thought to be possible sources of migraine (Mingazzini 1926, Fenton 1927), and it has been attributed to stagnation of the blood in the duodenal region (McClure and Huntsinger 1927). Deyl (1900) and Kast (1925) considered that transitory swelling of the pituitary caused migraine by producing pressure on the neighbouring sinus and the nerves connected to it. Sanders (1926) postulated that disorders of the ovary, thyroid or pituitary itself may produce migrainous symptoms. These examples merely illustrate the confusion that

has existed among clinicians and medical scientists in the twentieth century.

More recent observations have shown that migraine is associated with changes in the condition of the blood vessels, or more accurately the calibre of the intra- and extra-cranial arteries. However, it is not yet known whether these variations are a symptom or a cause. A recent editorial in *Hemicrania* (1971) stated 'It must be remembered that there are at least two causes of a migraine attack. There is the primary cause – the often familiar but still obscure diathesis or constitutional predisposition that loads the gun, and the secondary cause that pulls the trigger'. Research is now being directed at both sets of causes, the constitutional inadequacy and the numerous secondary factors that trigger the headache and associated symptoms. Table 2 shows a list of trigger factors that have been reported as initiating migraine attacks in individual sufferers.

Table 2 *Migraine: secondary trigger factors*

Anxiety	Prolonged focusing on TV or cinema screen
Worry	Very hot baths
Emotion	Noise, particularly loud and high pitched sounds
Depression	Intense odours or penetrating smells
Shock	Certain foods eg, fried foods, chocolate, citrus fruits, pastry and cheese
Excitement	Use of sleeping tablets
Over-exertion	Alcohol
Physical or mental fatigue	Prolonged lack of food – fasting or dieting
Bending or stooping, as in gardening	Irregular meals
Lifting heavy weights or straining of any sort	Menstruation and the pre-menstrual period
Change of routine, eg holidays, shift-work, or change of job	Menopause
Late rising, especially at weekends or on holiday	High blood pressure
Travel	Continued use of oral contraceptives
Change of climate	Toothache and other local pains in head or neck
Changes in weather	
High winds	
Bright sunlight, bright artificial light or glare of any kind: fluorescent light	

Source *Focus on migraine* (1971). The Migraine Trust.

Prevalence and incidence of migraine

Recorded prevalence levels for migraine, in common with most other conditions, are largely dependent on the definition of the condition and the proportion of cases likely to become known to the inquiring agency. Most definitions of migraine include three separate symptoms, unilateral headache, often preceded by sensory disturbance and commonly accompanied by nausea and vomiting. However, Critchley (1962) stated that the only criterion necessary to establish a diagnosis of migraine is the presence of recurrent headache, irrespective of any preceding, accompanying or subsequent phenomena. This reflects the inherent difficulty in attempting to arrive at a generally accepted clinical definition of the condition. Migraine is usually diagnosed as a result of a clinical interview and there is no general agreement as to whether one, two or all three of the features mentioned above must be present to establish diagnosis. Therefore, it is possible that migraine may be over-diagnosed by some doctors because their subjective definition of migraine may be more 'elastic'. Similarly, it may be under-diagnosed by others.

In addition, the prevalence of migraine may be underestimated because general practitioners are not aware of all the people on their lists who suffer from migraine. Waters and O'Connor (1971) found in a random sample survey that only 23 per cent of persons diagnosed as having migraine had visited a doctor because of headache during the previous year. Nearly 50 per cent had never consulted a doctor about their headaches at all. A comparison of the studies of Brewis *et al* (1966) confirms this point. The prevalence level for a survey of patients consulting was 0.5 per cent whereas a house to house survey showed a prevalence level of 3 per cent, a six-fold difference. Table 3 shows various prevalence estimates. Those from general practice vary from the figure of 0.5 per cent of the population to over 20 per cent.

For epidemiological purposes, therefore, it is necessary to adopt a similar methodology to Waters (1970 a). By means of questionnaires, he asked a random sample of the population about the individual features of their headaches, with the hope that he could unambiguously isolate the migrainous group from the population by reference to these features. He found that the three features which correlated most strongly with a clinical diagnosis of migraine were, unilateral distribution, accompaniment by nausea and accompaniment by a warning aura (Waters and O'Connor 1971). If the presence of all three factors is taken as a possible definition for migraine then a prevalence of 4 per cent for males and 7 per cent for women can be derived from his figures. Table 4 shows Waters' data by age and sex.

Table 3 *Prevalence of migraine*

<i>Study</i>	<i>Group studied</i>	<i>Prevalence per 1,000 population</i>	<i>Definition</i>
Dalsgaard - Neilson and Ulrich 1970	495 Danish doctors	160	Individual questionnaire asking 'Do you now suffer from migraine'
Childs and Sweetnam 1961	Midland factory employing 4,700 people	90	
Lennox 1941	Medical students and nurses	54	Description of migraine-like syndrome by interviewees
Brewis, Poskanser, Rolland, and Miller 1966	Carlisle, household survey	33 (18 male) (48 female)	
Brewis <i>et al</i> 1966	Carlisle, Survey of GP lists	5	Clinical diagnosis by GPs
Fitz-Hugh 1940	GP list	200	
Fry 1966	GP list	77	GP diagnosis
Logan and Cushion (1958)	Survey of sample of GP lists	53 (27 male) (76 female)	
Walker 1959	GP list	48	GP diagnosis
Waters 1970	Community study in Vale of Glamorgan	56* (39 male) (72 female)	
Waters and O'Connor 1970	Community study in Vale of Glamorgan (Women aged 20-64)	190 (female)	Validation of condition by clinical diagnosis

Source see references.

*Derived from tables 3 and 5 in Waters WE, *Headache*, Vol 9 No 4 Jan 1970.

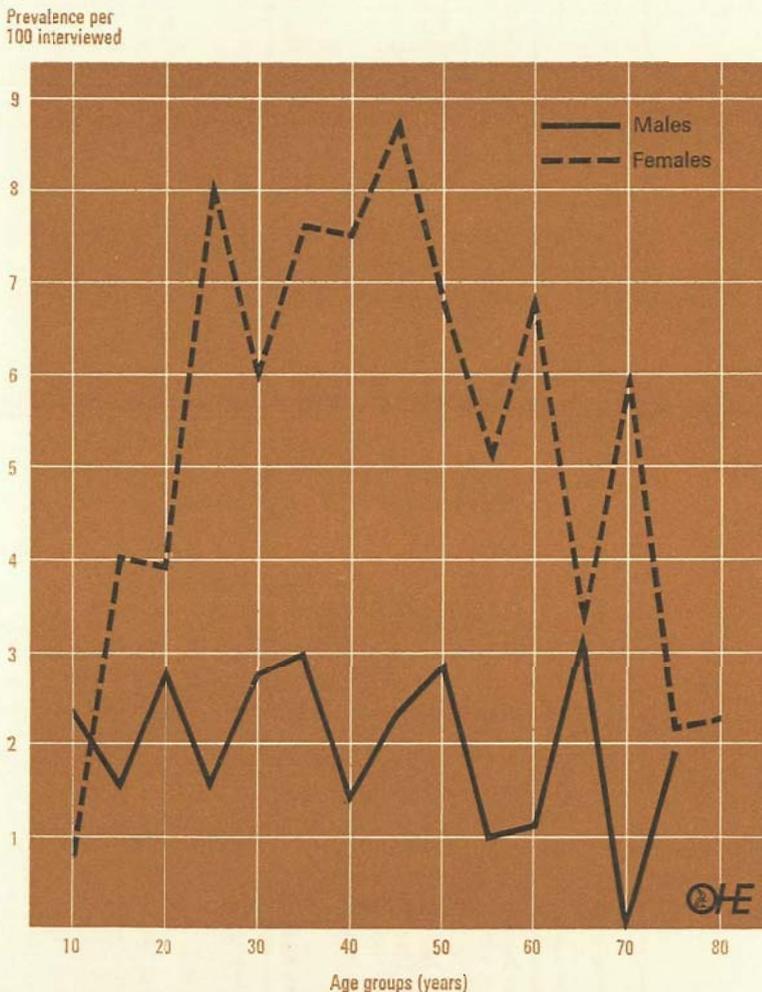
Table 4 *Distribution of subjects with headaches by sex, age and pattern. (Percentage distribution shown in brackets)*

Sex	Pattern	Age (years)	Men				Women			
			15-34	35-54	55+	All ages	15-34	35-54	55+	All ages
	Headaches only		43(43)	42(42)	23(40)	108(42)	41(36)	36(28)	30(31)	107(31)
	Unilateral headaches		31(31)	21(21)	12(21)	64(25)	21(18)	25(19)	19(20)	65(19)
	Headaches with warming		3(3)	8(8)	8(14)	19(7)	8(7)	9(7)	3(3)	20(6)
	Headaches with nausea		4(4)	8(8)	6(11)	18(7)	7(6)	13(10)	10(10)	30(9)
	Unilateral headaches with warming		5(5)	7(7)	2(4)	14(5)	9(8)	7(5)	10(10)	26(8)
	Unilateral headaches with nausea		3(3)	8(9)	0(0)	12(5)	10(9)	22(17)	12(13)	44(13)
	Headaches with warming and nausea		4(4)	0(0)	2(4)	6(2)	6(5)	7(5)	4(4)	17(5)
	Unilateral headaches with warming and nausea		6(6)	5(5)	4(7)	15(6)	13(11)	11(8)	8(8)	32(9)
	Total with headaches		99(100)	100(100)	57(100)	256(100)	115(100)	130(100)	96(100)	341(100)

Source: Waters W E. Community Studies of the Prevalence of Headache. *Headache*. Vol. 9 No. 4, Jan 1970.

However, because many cases with only one or two of the features could also be defined as having migraine, clinical diagnosis of the same population is likely to result in a much higher prevalence level. Thus Waters and O'Connor (1970), attempting

Figure 1 Age specific prevalence of migraine as recorded in a household survey in Carlisle



Source Neurological disease in one English city. Brewis M, Poskanzer D C, Rolland C, Miller H. *Acta Neurologica Scandinavica* Supplementum 24 Volume 42 (1966).

Table 5 *The incidence of migraine among women in relation to the time of day, the day of the week, and the duration of an attack.*

		<i>Time of onset</i>							
	%	0.00- 2	4.00- 13	8.00- 36	12.00- 25	16.00- 15	20.00- 9	Total 100	
		<i>Day of onset</i>							
	%	Sun 18	Mon 7	Tues 14	Wed 15	Thurs 15	Fri 14	Sat 19	Total 100
		<i>Duration (hours)</i>							
	%	0- 28	4- 32	8- 26	12- 9	16- 5	Total 100		

Source Waters W E and O'Connor P J. Epidemiology of headache and migraine in women. *J of Neurol, Neurosurg Psychiat* Vol 34, p 149 1971.

to test the validity of diagnosis by questionnaire, calculated the prevalence of migraine among women as high as 19 per cent according to normal clinical diagnostic procedures.²

One estimate of the age and sex-specific prevalence of migraine is shown in Figure 1. The data are from a household survey in Carlisle (Brewis *et al* 1966). It is uncommon before the age of five but increases in prevalence through childhood to reach a plateau in adult life and middle age. Migraine is not usually a burden of old age. In childhood both sexes are affected alike, but in adult life women are far more likely to suffer from migraine than men. Fry (1966) reported that migraine was related to menstruation in 23 per cent of female sufferers and De Witt (1950) gave the figure as 60 per cent. Waters and O'Connor (1971) found that migraine headaches were significantly commoner during menstruation, the highest incidence being during the first few days of menstruation. They also found that migraine attacks were significantly more frequent in the week after menstruation than in the rest of the menstrual cycle.

Because reliable epidemiological studies of migraine are so few and limited in content it is not possible to estimate the incidence of new cases each year. For the same reason it is not possible to say whether the incidence is increasing or decreasing.

Attempts have been made to obtain data on the incidence of attacks in relation to the time of day, day of the week, and the duration of the attack. The data of Waters and O'Connor (1971)

² The Migraine Trust quotes a round figure of 10 per cent prevalence in Britain. Thus the number of sufferers could be estimated at over five million.

are shown in Table 5. Over one third of the attacks started between 8.00 hours and noon and 40 per cent between noon and 20.00 hours. These findings are very different from those of Ostfeld (1963) who recorded most attacks between 4.00 and 8.00 and between 20.00 hours and midnight. There is no explanation why one study recorded most attacks during working hours and the other most attacks during the night. Although the figures of Waters and O'Connor are for women only, this could not account for such a large discrepancy.

Table 5 shows that more migraine attacks among married women occurred on Saturday and Sunday, which they attributed to having their children at home all day. The lowest incidence of attacks was on Monday. These findings are similar to the results for women given by Barrie, Fox, Wetherall and Wilkinson (1968). There is no published information concerning the frequency of attacks or their pattern because both vary widely from patient to patient.

The characteristics of migraine sufferers

Because the causes of migraine have not yet been determined, literature on the condition has often been concerned with the characteristics of the sufferers, which might provide clues to cause. However, much of this literature has been based on clinical impressions or the study of the medical records of general practitioners. It is only recently that a random community survey has been performed in South Wales with a view to testing these impressions. The findings have been reported by Waters and others (1970-71). Groups of individuals with headache, unilateral headache, those with all the classical symptoms of migraine and a fourth group who had not had a headache in the previous year, were identified by a questionnaire administered to a random sample of the population. All four groups were then assessed according to their intelligence, social class, ocular disorders and levels of blood pressure with the intention of demonstrating any association between these variables and the symptoms. The first-degree relatives of all four groups were also questioned as to whether they suffered from migraine. Few of the widespread

clinical impressions were able to stand up to rigorous testing of this sort.

Intelligence

Lennox (1941) believed migraine affected 'brain-using' more than muscle-using persons. This view is often stated, sometimes in the more specific form that patients with migraine are more intelligent than the average. However, Waters (1971 b), found no evidence of a relationship between intelligence and migraine. The distribution of intelligence scores were similar in all the four groups he examined. The myth of higher intelligence among migraine sufferers can probably be attributed to higher consultation rates among more intelligent people, related to their lower threshold of tolerance.

Social class

Fothergill (1784) found 'sick headache' mostly in the 'middle and upper ranks of life' and Lennox (1941) said that it was commoner among the professional classes. A study by the Research Committee of the Council of the College of General Practitioners (1962) found a social class gradient in the recorded prevalence of consultations for migraine, decreasing with social class. However, as with intelligence, this may merely reflect different thresholds of tolerance and attitudes to treatment. More broadly based epidemiological data do not confirm the existence of a social-class gradient. An epidemiological study among Swedish school children with migraine showed no demonstrable differences in social class of migraine sufferers when compared with other children of ages 7 to 13 years (Bille, 1962). Again, Waters (1971 b) found no evidence of an association between social class and the prevalence of migraine when this hypothesis was tested in his random sample survey.

Although Waters' (1971 b) study showed no relationship between migraine and social class or intelligence, it did show a tendency for more of the intelligent individuals and those from social classes I and II to consult a doctor because of their headaches. Therefore the clinical impression, that migrainous patients who actually attend doctors are more intelligent and of a higher social class than the average, is in accord with objective evidence. The implication from this study is that migraine sufferers consulting their doctors are a self-selected group and are not typical of all migraine sufferers. Waters also states 'If patients with migraine attending their general practitioners are selected it is reasonable to assume that sufferers attending

neurological or migraine clinics may show greater differences from unselected individuals with migraine'. Thus conclusions from studies based on clinic patients must be treated with even greater reservations if attempts are made to relate them to the population as a whole.

Familial prevalence

Liveing (1873) was the first to state that migraine is a familial condition. Subsequent studies have strengthened this impression – for example Lennox (1941), Walker (1959) and Childs and Sweetnam (1961). However, the methods used to verify the hypothesis are suspect in all these studies. There are two main difficulties involved in analysing them. First, the definition of migraine is never consistent between any two studies and second, the possibility of bias cannot be ignored. Migraine is a condition in which the diagnosis of borderline cases is difficult and some authors include a family history of migraine as part of their definition. If borderline cases were diagnosed as migrainous or non-migrainous according to familial history it could be possible to provide a tautological demonstration that migraine is an inherited family trait.

However, Waters (1971 b) concluded that 'the data from the first degree relatives of probands with migraine, headache, and without headache in the previous year suggest that the prevalence of migraine was highest in relatives of migraine sufferers. The differences between the prevalence of migraine in the families of those three groups, however, were not as large as might be expected from other reports in the literature. In fact, in this study they do not reach the usual levels of statistical significance'. Even if migraine is more prevalent in certain families, it does not logically follow that the condition is passed on as an inherited trait. Members of one family tend to share the same environment and therefore the condition, or the perception of the condition may well be acquired or triggered as a result of environmental factors.

Ocular disorders

In view of the close topographical and nervous connections between the eye and the brain it is not surprising that headaches have frequently been said to be associated with visual defects. Refractive errors are often said to be a cause of migraine (Duke-Elder, 1949) and their correction has been claimed to result in considerable improvement in 90 per cent of patients with migraine (Friedman, 1954). Prolonged eye strain, especially in

the presence of an uncorrected error of refraction, is considered a precipitating factor in migraine (Williams, 1966). The views expressed have been based largely on clinical experience and are most likely to be the result of the examination of a highly selected series of patients.

The results of Waters' (1970 c) survey give little evidence to support the hypothesis that visual acuity and ocular muscle imbalance are frequently causally related to headaches. This investigation found no relationship between either corrected or uncorrected visual acuity and muscle imbalance and migraine. Only one statistically significant result was found, namely that individuals with hyperphoria³ with near vision are more likely than others to have migraine.

One reason why the association between migraine and ocular disorders may have been supposed to exist is that a high percentage of the general population suffer from migraine (10 per cent plus) and an even greater number⁴ have visual defects. Therefore, there is a good statistical chance of both conditions being present in the same person. It is sometimes stated that the correction of a refractive error will cure a patient of migraine headaches. However, no hard evidence exists to verify the truth of this hypothesis. Indeed, Drews (1957) found that the use of plain (window glass) lenses in patients who did not need glasses for refractive errors greatly helped their headaches.

Occupation involving close vision

It is often assumed that the number of hours spent in activities which require close vision is related to migraine. Taylor *et al*, (1970) reported on an investigation into the prevalence of migraine and headache in photogravure colour retouchers. These skilled craftsmen do fine and close work touching up photographic negatives in front of fluorescent screens. For some years it had been thought, within the printing industry, that these men suffered excessively from migraine. This impression was originally based on the number seeking medical attention in one large firm and was strengthened by the results of a self-administered questionnaire arranged by the union in which all retouchers were asked a direct question, 'Do you suffer from migraine'?

Taylor *et al* (1970) found no evidence that the prevalence of migraine differed between the group of colour retouchers and the

3 A tendency for the visual axis of one eye to rise above that of its fellow.

4 34 per cent had unaided visual acuity of 6/9 or less in the South Wales survey (Waters 1970 c).

two control groups, even though the retouchers were more aware of migraine, having had their attention drawn to the condition by the union questionnaire. In his survey, Waters (1970 c) found that the prevalence of migraine was not related to the amount of time individuals spent in activities requiring close vision on any one day of the week.

Hypertension

Walker (1959) reported that in 300 consecutive patients over the age of 40 years the prevalence of migraine rose as blood pressure increased. However, Robinson (1969) found that certain symptoms, and particularly headache, made general practitioners more likely to measure a patient's blood pressure. This is likely to lead to an underestimate of the prevalence of high blood pressure among patients without headaches. Therefore, results based on the records of general practitioners, as was the main part of Walker's (1959) study, may contain bias.

Waters' (1970 a) study, based on representative samples of individuals with migraine, unilateral headache, headache and individuals without headache in the year preceding the survey, found no evidence of any difference in the distribution of either systolic or diastolic blood pressure in these four groups.

In summary, none of the major factors which have been associated with migraine have on close investigation been confirmed as being more common among people who suffer from migraine than among people who do not.

The treatment of migraine

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. Here again, objective evidence on the effectiveness of treatment is patchy. Some controlled trials have been conducted but in many of these there is the danger that the extension of conclusions from one sample of patients to the general population, or to different

sub groups, may not be valid. As an illustration, the majority of people with migraine are not at any one time receiving medical advice. Since it is possible that the people who are not in contact with the medical profession may tend to have experienced poor response to therapy, results from patients consulting doctors may not accurately reflect the general usefulness of any new therapy.

If it is possible to discover the 'trigger' factor of any particular patient's migraine then preventive action may take the form of avoidance of the stimulus (Table 2). It may be tension or other psychological factors in the sufferer's environment that act as the predisposing or trigger factors and relaxation therapy, or any combination of treatment which has the same effect, may be of considerable value. Some support for this may be inferred from the good results obtained by the City Migraine Clinic where care and general support play a large part alongside whatever specific therapies are felt appropriate.

If preventive therapy without the use of chemotherapy does not bring relief there are three categories of drugs that can be used, first analgesics, second anti-emetics and third, drugs which have a specific action on migraine. To date, no randomised controlled trials have been undertaken to determine the relative efficacy of either analgesics or anti-emetics in the alleviation of the symptoms of migraine. However, it is likely that aspirin and paracetamol, which are both available without prescription, are used to treat more migrainous headaches than all other drugs. Some migrainous persons have a history of bilious attacks or travel sickness during childhood. In some of these cases anti-emetics may be useful. However, no hard evidence exists from which satisfactory conclusions as to the effectiveness of the first two categories of medicines, and the effectiveness of self medication for migraine in general, can be drawn.

The third category, those which have a specific response in patients, consists mainly of drugs containing ergotamine tartrate. Since ergotamine tartrate was first used in the treatment of migraine over 40 years ago it has steadily gained favour and is now regarded as the single most useful drug in the treatment of attacks (Wolff 1963, Dunlop 1969). Indeed, relief by ergotamine is often considered a useful criterion in the diagnosis of migraine (Friedman and Merrit, 1959; Ostfeld 1963) as it is said to give little relief to other headaches. Critchley (1962) stated 'migraine characteristically comprises a recurrent and incapacitating handicap which is typically ergotamine-sensitive. However, ergotamine can produce toxic side effects and if vomiting takes

place early in an attack the orally taken drug is useless. To overcome this the drug is sometimes given by injection or inhalation or taken orally combined with an anti-emetic.

In an attempt to determine the effectiveness of ergotamine, Waters (1970 b) conducted a controlled clinical trial testing oral ergotamine against a placebo. Fifty-one per cent of cases reported some benefit with ergotamine but 58 per cent reported benefit with the placebo. The difference was not statistically significant but there was a statistically significant difference between ergotamine and the placebo in their detrimental effects. Significantly more subjects felt their condition had been worsened by ergotamine. This relatively small trial, therefore, found no evidence that oral ergotamine in doses of two or three mg was more effective than a placebo. However, Waters stressed the following qualifications to this conclusion.

First, patients vary in their response to drugs and a standard regimen of two or three mg may be the most effective dosage level for only a small proportion. The technique of a controlled trial may not in this case be sufficiently flexible to achieve the benefits that might be achieved in clinical practice. Furthermore, there are contradictory results from an American survey by Ostfeld (1961) who found five mg dosages of oral ergotamine to be significantly more effective than a placebo. However, the subjects may not have been representative of the migrainous population as a whole and also, a high dose would seem inappropriate for general routine therapy because of toxic side effects. The second reservation is that Waters' trial was a small one and numbers were not large enough to yield statistically valid conclusions for each of the sub groups of patients who may have responded differently to ergotamine.

Third, oral administration of ergotamine is considered to give less reliable results than if the drug is taken parenterally. Sublingual administration is often recommended, though in a small controlled trial (Crooks *et al*, 1964) no evidence of a beneficial effect was found. Oral administration has the advantage of convenience. Finally, it may be relevant that over 80 per cent of all ergotamine tablets prescribed in England and Wales contain caffeine. This is because caffeine is said to increase absorption of ergotamine but there is no hard evidence to support this hypothesis.

There are also some drugs which, unlike ergotamine, are used for their prophylactic properties. Methysergide has been used to control the risk and intensity of attacks satisfactorily in a high proportion of cases, but it is associated with the risk of

Table 6 Response to clonidine among 27 patients followed up for 12 months

Attacks	Attack frequency (mean attacks per month) in:		
	12 month follow up with clonidine	Double blind trial clonidine period	Double blind trial placebo period
Severe	0.90	1.22	1.51
Moderate	1.68	2.08	2.42
Mild	2.28	3.22	3.02
Total	4.86	6.52	6.95
Weighted Score	8.34	11.04	12.40

Source Shafar J, Tallet E R and Knowlson P A (1972) *Lancet* 1, 7747.

bizarre side effects. Another more recently introduced prophylactic drug, clonidine, has virtually no known side effects. It was developed originally as an antihypertensive agent, but, in view of the theory that tyramine and possibly other vaso active amines might play a part in migraine triggered by certain types of food, Zaimis and Hanington (1968) suggested that clonidine might be useful in the treatment of patients suffering from dietary migraine. In the event, however, a controlled trial (Shafar *et al* 1972) has demonstrated that clonidine is of value in patients with relatively frequent migraine of any aetiology, though tyramine-sensitive patients are, as a group, somewhat more responsive.

Table 6 shows the effect of prophylactic treatment among 27 patients who agreed to a twelve month follow up. It illustrates the point that although results of active treatment are significantly better than placebo administration, only a proportion of attacks can be avoided. The mean frequency of attacks was, in the case of clonidine, reduced by about one third by the end of follow up period.

One more point of interest is illustrated by this trial. Those persons who benefited significantly from prophylactic treatment said that the primary value to them lay in avoidance of domestic disruption, absence from work and interference with social life. It was the control of risks which was appreciated above all and this must clearly be the objective of further pharmacological and other research designed to improve migraine therapy.

The cost of migraine

The costs of any illness are commonly divided into three categories. First the cost of the prevention, diagnosis and treatment of the condition. This is a direct cost, involving the consumption of health and welfare resources that could have been spent on other goods or services within or outside the health services. Second, the indirect cost to the community as a whole of the lost productivity caused by the illness. Third, there are the personal costs of hardship and disability to the individual and his family.

Table 7 shows the cost of migraine to the National Health Service for the UK in 1970 and this is compared to expenditure for the whole of the service in 1970. Migraine was found to absorb £2.8 million in those sectors of the NHS where available data allowed refined calculation. As migraine is seldom a reason for hospital admission, the cost of hospital in-patient treatment is only £0.5 million. Unfortunately NHS statistics do not permit an analysis of the cost of out-patient treatment attributable to migraine. Treatment for the condition can be obtained from the neurology departments of major hospitals and there are eight hospitals which hold special migraine clinics. These clinics are small departments of the neurology clinics and provide treatment for acute cases of migraine. In general practice in 1970, £0.7

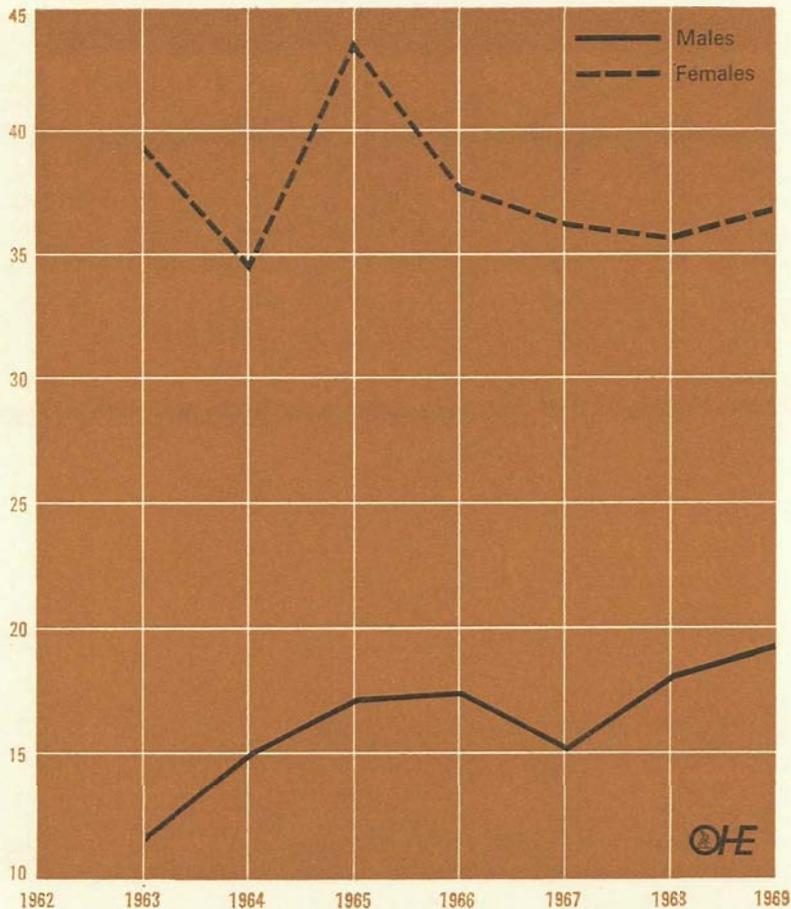
Table 7 *The cost of migraine to the National Health Service, UK 1970.*

<i>Health Service sector</i>	<i>Cost attributed to migraine £m</i>	<i>Total cost of sector, £m</i>	<i>Per cent attributed to migraine</i>
Hospital Service in-patient* cost (current)	0.5	976	0.05
General Practice	0.7	174	0.4
Pharmaceutical Service	1.6	209	0.8
Dental and Ophthalmic Services	Nil	131	Nil
Sub Total	2.8	1,490	0.2
Other services, including local authority health services. Hospital out-patient costs. Hospital capital expenditure. Miscellaneous. (No basis for allocation of costs to migraine)	Not available	668	Not available

Source OHE estimates.

*Excludes significant out-patient expenditure of migraine for which there is no basis for estimation.

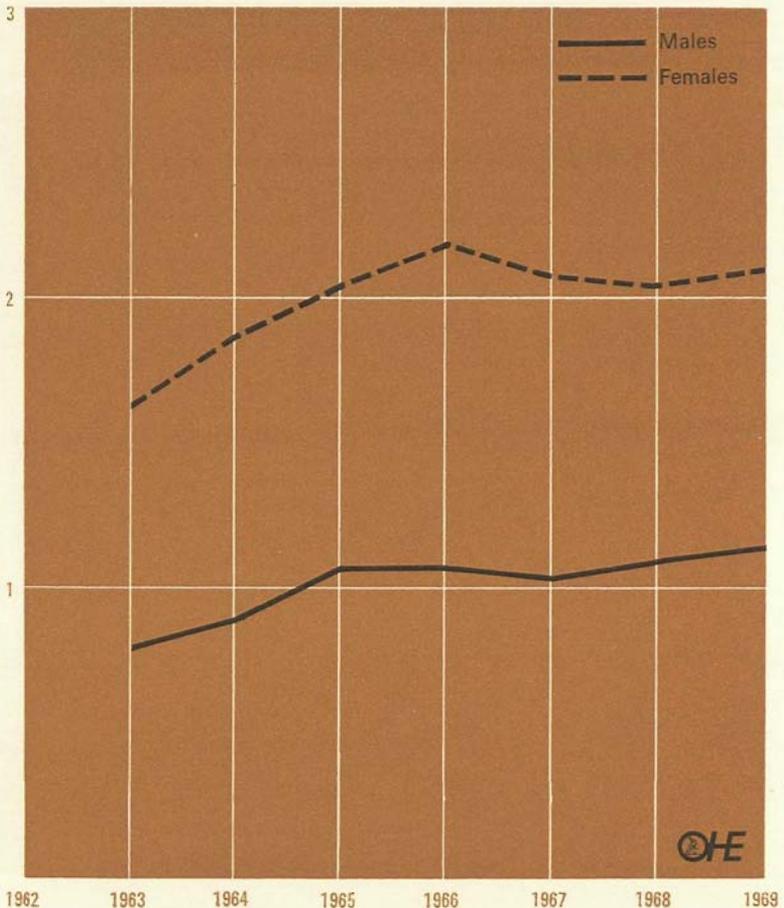
Figure 2 Days of certified incapacity recorded against migraine – expressed as a rate per year per thousand population at risk 1961/62 to 1968/69.



Source Digests of statistics analysing certificates of incapacity. DHSS.

million of expenditure can be attributed to GP consultations specifically for migraine and prescription costs in the same year came to £1.6 million. In total, in those parts of the NHS where costs can be estimated, migraine accounted for only 0.2 per cent resource expenditure. Since self medication plays such a large

Figure 3 *Spells of certified incapacity recorded against migraine – expressed as a rate per year per thousand population at risk 1961/62 to 1968/69.*



Source Digests of statistics analysing certificates of incapacity. DHSS.

part in treatment of migraine, private purchases of analgesics are likely to add a considerable amount to this total, though the sums involved are not known.

The second category of costs to the economy covers the loss of working time through migraine. One indicator of this can be

derived from sickness benefit statistics. However these figures include only absences of three days or more for which sickness benefit is claimed. One day absences, which are typical of migraine, are thus excluded. Also, many sufferers seek to conceal their migraine because they regard it as a sign of weakness or fear that it will be regarded as such. Other gaps in sickness absence data are described elsewhere (OHE 1971). Bearing in mind these reservations, 295,000 man days and 167,000 woman days were recorded as lost through migraine in Britain in 1968-69. This is little more than 0.1 per cent of all recorded days of sickness absence. Figures 2 and 3 shows the trends of both days and spells of certified incapacity over the last six years for which figures are available, expressed as rates per thousand population at risk. The median length of absence recorded against migraine is about eight days and there is little long term absence from work.

Finally, there are the personal costs of migraine to the individual and his family. Although the individual may be symptom free almost all of the time there is a constant risk of an attack. The fact of being 'at risk' can play a major part in the lives of migrainous persons 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 anticonvulsant drugs, treatment to control the risk of migraine is as yet ineffective or only partially effective in the majority of cases. Because attacks can occur at any time there are occasions where personal costs can be inordinately high, for example during examinations or other crucial events. Many migraine sufferers also talk of a sense of shame when an attack is imminent and when they realise they must withdraw immediately from their normal activities. Finally, although there is no statistically demonstrable excess risk of death and although insurance premia are not loaded, there are certain occupations from which migrainous persons are debarred because of the risks of sudden incapacity. For example, they may not become airline pilots.

Although usually of good health between attacks, the migraine sufferer may live in a world of uneasy anticipation. Attacks may occur with little warning at times which may be inconvenient, socially embarrassing or even dangerous. The fear of such situations, of appearing unreliable or inconsistent at work or neglecting children at home, can lead to a vicious circle of worry, tension and increasing frequency of attacks.

Discussion

Because of the inadequacy of existing knowledge on migraine few positive conclusions can be drawn and few policy recommendations can be made. Only a minority of persons suffering from migraine at any one time attend their general practitioner for treatment or advice and only a very small minority seek further specialist treatment. However, there would be little value in discussing the reasons why some consult their doctor and why some do not, or which are the most appropriate levels of the health service at which to provide treatment or advice, since the health service cannot as yet offer proven effective treatment in the majority of cases. The problems of migraine are not as yet soluble by organisational or administrative initiatives. More effective treatments are required first and for this reason a discussion of alternative policies must centre around a delineation of those areas in which research is likely to be of the greatest final value to people with migraine.

Many of the conclusions of recent research have been of a negative nature. None of the clinical impressions which have moulded conventional wisdom have been verified when tested by epidemiological surveys covering a representative sample of the population. There do not appear to be any easily measurable characteristics which are typical of people with migraine. Thus the work of Waters and others in South Wales found no social class or intelligence gradient among migraine sufferers. It also cast considerable doubt on the theory that migraine is an inherited condition and there seems to be no hard evidence associating the prevalence of migraine with refractive errors or hypertension.

What exists at present is a few tentative hypotheses on the causation of migraine and also a number of treatments, mainly pharmacological, whose effectiveness varies widely according to different assessments, but none of which is able to prevent or alleviate the majority of attacks among the majority of sufferers. Research to bring effective therapy to all persons with migraine could be developed in four major directions. First, empirical research with various combinations of existing drugs and preventive measures such as relaxation therapy and avoidance of trigger factors can suggest new treatment regimes. The work of such institutions as the City Migraine Clinic tends to follow these lines. Much of their work tends to be experimental and they have contact with a large population of migrainous persons, many of whom visit the clinic during an attack. However, in view of the dangers of invalid conclusions through reliance on clinical impressions from unrepresentative samples,

it is important that any new treatment regime should be rigorously evaluated under controlled conditions.

Second, further epidemiological research may elicit causes through statistical associations between the incidence of attacks and any hypothetical causative variable. Here again, however, past experience has shown that good research methodology is of crucial importance.

Third, pharmaceutical companies may use their resources in the search for new treatments. This search throws into relief the economic problems of pharmaceutical research. At present, with the paucity of clues, research must necessarily be highly speculative and risky. As the cause is unknown the work would have to be quite fundamental and therefore expensive. It is significant that clonidine emerged from research primarily concerned with hypertension, not migraine. If pharmaceutical firms are to be encouraged specifically to follow what leads there are in respect of migraine this will involve them in expenditures which are of a totally different order of magnitude from the total amount spent at present by all interested parties. The average R & D investment to produce one new pharmaceutical compound is now estimated to be between £5 million and £10 million⁵, and this average is likely to be exceeded in the difficult search for a fully effective migraine treatment. Clearly firms must be assured of an adequate return, if in the event they are successful, if they are to invest sums of this order or above. At present, the sales of pharmaceutical preparations specifically for migraine under the NHS amount to about £1 million at manufacturers' price levels and probably do not exceed £25 million on a world-wide basis. The reward for a successful R & D investment would therefore have to come eventually from a much extended market **which would be created if more effective treatments** were found, especially if these were prophylactic. If the true prevalence of migraine is in the order of 10 per cent then the potential demand for effective prophylaxis would be very much greater than the demand for medicines prescribed for migraine at present

Finally, basic research into the causes of migraine may be undertaken in universities and in MRC and health service laboratories. This type of research has often been supported by financial aid from the Migraine Trust though this is on a relatively

⁵ If the British pharmaceutical industry's annual research expenditure between 1962 and 1967 is divided by the number of new pharmaceutical chemical entities marketed by British companies between 1965 and 1970. Thus allowing an average three-year lag between R & D spending and eventual marketing, the average figures for recent years yield an estimated R & D investment of £7.5 million per drug.

small scale, amounting to £27,000 in 1971. It is worth noting, in this connection, that migraine, like any other condition, is world wide. Given that relatively little is spent on migraine research and that the research now being undertaken is somewhat fragmented, there is a strong argument for an international institution to help co-ordinate research and act as a focal point for all parties interested in migraine. In Britain the Migraine Trust already fulfils this function but an international body could also play an important part in mobilising and exploiting the limited resources available for research into migraine. Different countries have different approaches, depending on their institutions and their history, and there is every reason why Britain, where migraine is the particular sphere of neurology departments, should gain from the experience of countries such as America, where psychiatrists tend to be much more involved in the diagnosis and treatment of migraine. The balance between clinical medicine and a much more rigorous scientific approach also varies from country to country and if the major priority at present lies in well directed research then a change in Britain's balance towards the latter approach should ultimately prove beneficial to patients.

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