# Section of General Practice

*President* John Woodall FRCGP

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## Valedictory Address

## Migraine – A Personal View[1]

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At the 1972 meeting of the American Association for the Study of Headache, the Migraine Trust's fifth symposium (*see* Cummings 1973) and the 1972 Dixarit Symposium in Cambridge, I listened to investigators giving the results of many admirably designed double-blind controlled trials, and a plethora of papers discussing the differences between migraine and control subjects in various highly sophisticated physiological tests. Not unnaturally I looked for evidence of progress towards a successful treatment of this perplexing and distressing ailment. However, all that emerged was a unanimity of opinion that ergot still has pride of place as the best drug for relief of an acute attack.

In spite of many theories the cause of a migraine attack is still not clear. The clinical trials of drugs for the relief of migraine are still beset by difficulties. For instance, those patients with only one severe attack every 2–3 months are excluded because of infrequency of attacks, and so the series becomes weighted with those having more frequent attacks. These will tend to include patients whose migraine is precipitated by tension and stress, the very patients whose frequency and severity may be expected to alter in any prolonged trial. Migraine trials have a high proportion of women and yet in all the reported trials I have never found any mention of menstrual history. This is a serious omission, for a woman with a 24-day cycle may have two menstruations during a one-month trial period and only one the following month when a different drug is being evaluated. Many women may record common premenstrual symptoms such as nausea, vertigo and drowsiness as side-effects of the drug, either active or placebo.

If we are to increase progress towards the understanding and treatment of migraine we need a careful analysis of each individual patient. This would require a team of 'migraine detectors' ready to investigate, collect accurate information, interrogate and sift evidence aimed at discovering the initiating cause in each individual case. And no one can better fulfil this role than the GP.

This paper will deal with common and classical migraine, excluding cluster migraine. In 'Focus on Migraine' published by the Migraine Trust there is a list of more than thirty triggers, which can usefully be reduced to six: food sensitivity, hypoglycæmia, tension, depression, water retention and menstruation. The importance of separating these types is that each responds best to a specific treatment regime, although they are not mutually exclusive.

The success of the detector depends on his ability to persevere in the hunt for each patient's 'trigger factor', his ability to cross-examine so that glib causative factors are not too easily accepted and scepticism prevails until six months or more have passed without an attack.

First it is necessary to take a full history, including the time of onset of attacks, family and menstrual history and the factors the patient considers causative. All sufferers enjoy giving an account of the agony suffered during an attack, but it is in the minute study of all happenings during the twenty-four or forty-eight hours before an attack that the vital clue invariably lies.

The most useful diagnostic aids for the detection of trigger factors are frequency charts and attack forms. The frequency charts show at a glance the time intervals between attacks: whether they are occurring in relation to menstruation; on one particular day of the week, or limited to weekends; in teachers at the end of term or in accountants at the end of the month.

[1]Requests for reprints may be sent to
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**Case 1** A 45-year-old mother had a five-month history of hemiplegic migraine. Her chart showed that all twelve attacks had occurred on a Friday. The patient then volunteered the information that following the death of her mother-in-law a year before it had become her duty to visit her mentally ill and paranoid sister-in-law on alternate weekends, entailing a journey of some twenty miles. She had often been received with verbal or physical abuse from her sister-in-law and she dreaded these visits. The migraine was her protection.

Patients are asked to detail the happenings during the twenty-four hours before an attack. The time of onset may give an important lead. Thus, early morning onset occurs in water retention, depression and menstrual migraine. An attack following late wakening, especially at weekends and holidays, may imply hypoglycæmia. Daytime attacks are more often related to stress and food sensitivities. The form is seen as a valuable opening for further probing, especially when it contains such vague statements as 'quarrel', 'shopping expedition', 'chaos at work'.

The itemized food intake is invaluable for detecting food sensitivity and hypoglycæmia, although it should be appreciated that food sensitivity can occur up to 48 hours after intake.

**Case 2** A 54-year-old male director suspected that dairy foods provoked attacks and he had successfully avoided them for three years, until he was tempted to eat some yoghurt. After twenty-four hours he phoned to tell me that no dire results had befallen him – but a second call the next day informed me that severe migraine had developed after thirty-six hours.

*Food Sensitivities*

The most satisfactory trigger factors to eliminate are in those patients whose attacks result from tyramine sensitivity, and here one must acknowledge the work of Edda Hanington who in 1967 demonstrated the link between migraine and the ingestion of tyramine in susceptible individuals. The commonest foods containing tyramine are cheese, chocolate, wine and citrus fruits, but as the time interval between ingestion and onset of attack is about twenty to twenty-four hours the cause too often passes unrecognized.

**Case 3** A housewife aged 47 attended with three completed attack forms. Together we observed that her migraine had occurred twenty hours after a meal of cheese. Then she suddenly became crestfallen as she recalled that the previous evening she had eaten 4 oz (113 g) of cheddar cheese for supper when she was alone in the house. At 4 p.m. that afternoon her husband phoned to say that she was having her worst ever migraine.

The time interval between the enjoyment of an offending food and the onset of migraine varies between four and forty-eight hours. This interval may lengthen with age.

**Case 4** A woman aged 41 and her 16-year-old daughter were both upset after eating pork, but the daughter developed migraine twelve hours later and the mother after an interval of twenty hours. Moreover the mother recalled that as a child she could not manage pork because it caused bilious attacks. This suggests that in childhood the time interval was shorter, possibly four hours, so the relationship of food to the attack was more easily recognized.

In migraine due to food sensitivities the family history is always positive in both sexes. The mother and daughter who have been quoted gave a family history of migraine in the mother's mother, her maternal grandmother, one brother and 4 maternal aunts.

Recognition of tyramine sensitivity can alter an individual's life pattern, especially in those whose attacks were previously considered to be of psychological origin.

**Case 5** A financial executive, aged 37, suffered from occasional attacks while working in a London suburb. His firm then moved him to central London and there he had frequent migraine. This was attributed to the extra responsibility entailed in his work. After a year he returned to his former office in the suburbs where the attacks were less severe. It was only when thought was given to the possibility of an offending food that it was appreciated that in central London he often had time for only a quick pub lunch of a cheese sandwich and beer whereas in the local office there was time for a proper meal. Now he can pinpoint attacks, which are always due to a dietary indiscretion.

Tyramine sensitivity improves during pregnancy.

**Case 6** A mother aged 34 recognized that attacks were precipitated by chocolate, wine and cheese and was delighted to find that after the first trimester of her second pregnancy she could eat these foods with impunity. As she had planned to limit her family to two she indulged in the best of wines and the most expensive chocolates for the duration of this pregnancy.

If the attacks have been severe, patients are usually most co-operative in avoiding the culprit foods. Indeed, I look forward to an enterprising author writing a cook book on 'Meals for Tyramine-sensitive Folk'. Fortunately it is in these patients that clonidine appears to be most effective (Wilkinson 1969, Sjaastad & Stensrud (1971); it can be started as 0.025 mg b.d. and gradually increased. Incidentally, Youdim *et al.* (1971) and Smith *et al.* (1971) postulate an enzyme defect in tyramine's metabolic pathway, and suggest that it might be dangerous for those with dietary migraine to take monoamine oxidase inhibitors or to use isoprenaline inhalers for asthma.

*Hypoglycæmia*

There are those whose attacks are precipitated by long intervals without food or preceded by an

unprovoked and insatiable hunger. Inaccurately these are usually referred to as 'hypoglycæmia' although their fasting blood sugar is usually no lower than controls, and insulin-induced hypoglycæmia only rarely provokes an attack of migraine. It seems that in these individuals there is a metabolic abnormality with insulin resistance (Hockaday *et al.* 1973) and a defect in breakdown of liver glycogen (Pearce *et al.* 1973). Many who claim attacks are precipitated by fatigue are included in this group. They include those who miss a meal when working overtime, the ones who continue gardening until the last glimmer of light has gone and those who are determined to finish their decorating before stopping for a meal. Attacks among those following a low carbohydrate diet and during religious fasts are precipitated by hypoglycæmia. Those who are unable to sleep on at weekends because they wake up with an attack should consider the possibility of hypoglycæmia, and try the effect of a late night snack. Hypoglycæmia is commoner during the premenstruum (Billig & Spaulding 1947) and on the postcoital day. The possibility exists that fasting as a cause may be masked by an apparently obvious psychological precipitant (Case 7), or by, fatigue or tension (Case 8).

**Case 7** A housewife aged 42 had a light fish supper on Friday at 7 p.m. On Saturday she rose at 7 a.m., had no breakfast, and went shopping 8–10 a.m. Then a hurried change for her son's wedding, leaving home at 11.30 a.m. Severe migraine with vomiting developed at 2.30 p.m. after 18½ hours without food.

**Case 8** A woman aged 45, mother of three children, part-time clerk. Attacks occurred on Thursdays. She attributed the attacks to fatigue and tension, as after leaving work at midday on Thursday she would drive twelve miles to her favourite supermarket, buy a week's shopping and then drive home in time to pick up her daughter from school and take her to the weekly dancing lesson. Admittedly it was a tight schedule, accompanied by fear that traffic delays might prevent her completing it, but it was noticed that apart from early morning tea and mid-morning coffee she had no food until 4.30 p.m. The previous evening meal was at 9 p.m. so she went nineteen hours without food, taking only drinks.

Those with a tendency to hypoglycæmia should be advised to take frequent snacks at intervals of three hours, thus enjoying mid-morning coffee, afternoon tea and a bedtime snack, in addition to the regular three meals daily. Incidentally, could this offer an explanation of why migraine patients admitted to hospital for investigations so often lose their migraine while on a regular hospital diet? Those who are worried lest these extra snacks increase their weight should be advised that non-fattening foods at frequent intervals will suffice. Otherwise they can be taught to divide their total daily calorie allowance into six snacks instead of three meals.

*Tension*

In using the term 'tension' I include anxiety, worry and stress. Often the migraine occurs a day or two after a time of extreme stress, thus after examinations are safely over, after one has coped magnificently with a domestic crisis and at the end of a hard week's slog. Or the stress may be of the happy variety such as a win at the pools or unexpected promotion.

Although tension is a trigger factor, too often it is blamed when other causes are responsible, as in the tyramine-sensitive financial executive or the mother with her Thursday migraines from hypoglycæmia.

I do not regard travel as a trigger factor in itself; too often on closer observation it is found to come into the category of either hypoglycæmia or tension. Consider the holiday departure – getting up at 5 a.m., hurried packing and leaving an hour later, a long journey to the airport and a further hour's wait there. The snack in the plane comes after an interval of several hours. On the other hand all too often the flight itself is accompanied by tension and fear, for let us not forget that we are mostly dealing with the first generation enjoying an annual holiday abroad. Even the long car journeys at home frequently entail a missed meal, worries about the job to be tackled on arrival, or mere tension from motorway driving and fear of accidents.

When tension is the trigger factor tranquillizers will reduce the frequency of attacks, or a course of relaxation or meditation or other restful therapy may be tried. A wise spouse can usually tell when the partner is leading up to an attack and this is the ideal time to use a tranquillizer.

*Depression*

Depression as a trigger factor differs from tension. In the interval between attacks, the patient gives the typical picture of apathy, anorexia, insomnia and pessimism. In this state small incidents are sufficient to provoke a major migraine attack. Depression is the trigger and not, as often claimed, the result of migraine. I cannot agree with the sentiments expressed in one letter of introduction, where the doctor described the patient as 'tense, introspective and intelligent', and added: 'If totally deprived of her migraine, which acts as a safety valve, she might well develop a depressive illness.' These patients respond to antidepressants which produce both an elevation of mood and a marked reduction in the frequency of migraine.

*Water Retention*

Water retention migraine is preceded by weight gain, bloatedness and œdema of the eyes, face or

ankles. During an attack the pain may be concentrated behind one or both eyes, and the intraocular tension in the affected eye may be raised 1–3 mmHg above its normal. Or there may be nasal obstruction with engorged sinus mucous membrane producing a vacuum sinusitis. During attacks these patients, usually women, may notice a marked diuresis and the loss of a pound or two in weight. Attacks are most frequent in the premenstruum, but occasionally are limited to ovulation. This is the migraine which responds to prophylactic diuretics, which can be taken before the anticipated time of an attack, or when the patient begins to feel bloated or puffy.

*Menstruation*

The recognition of menstruation as a trigger factor becomes obvious when using a frequency chart. When 75% of attacks occur during the four premenstrual days then menstrual migraine can be diagnosed. It is in this group that overlapping of trigger factors occurs; tension, depression and water retention need special mention in this connexion. In a recent series the distribution throughout the menstrual cycle of 512 headaches in 52 women with menstrual migraine showed that 36% occurred in the four premenstrual days and 30% during the first four days of menstruation.

These are the most worth while of all types to identify as their response to progesterone is excellent. In a recent study (Dalton 1972) I reported on 65 women whose menstrual migraine was treated with progesterone either by pessaries or suppositories in doses from 50 to 400 mg daily. The response was good in 60%, moderate in 23% and poor in 17%.

Migraine developing or increasing in severity while the patient is on the oral contraceptive pill always has menstruation as a trigger factor.

The question may well be asked: why does progesterone bring relief of menstrual migraine yet progestogen in the 'pill' causes migraine? There is a fallacious belief that synthetic oral progestogens are the same as progesterone. They are not. Their chemical formula is different (Harper 1969). Let me recall some facts of progesterone physiology, in addition to its ability to cause proliferation of endometrium and maintenance of pregnancy it is now appreciated that progesterone is formed as an intermediary in the biosynthesis of corticosteroids in the adrenals and that progesterone can displace cortisol from the binding protein in the blood. There is evidence that increased monoamine oxidase levels occur in the tissues, particularly in the endometrium, which correlate well with progesterone blood levels. Monoamine oxidase is related to the menstrual cycle with a tenfold increase during the luteal phase.

Synthetic progestogens cause endometrial proliferation, but cannot mimic these other progesterone functions. Indeed Johansson (1971) has shown that progestogens lower the progesterone blood level.

So it is evident that in cases of migraine produced by the 'pill' no improvement will be obtained by altering the œstrogen-progestogen ratio by trying another pill. A far more satisfactory result is obtained by assisting the couple to choose an alternative method of contraception.

Each of these different trigger factors has its own treatment. But it is important to realize that in women these trigger factors are all influenced by the hormonal changes of menstruation and pregnancy. All types of migraine usually disappear during the second half of pregnancy, when progesterone levels are high. However, those in whom it does not disappear have an unduly high incidence of toxæmia of pregnancy and in these women the progesterone level is low (Dalton 1960). On the other hand migraine returns with a vengeance during the puerperium following the abrupt loss of placental progesterone. Tyramine sensitivity decreases during late pregnancy. Hypoglycæmia and altered glucose tolerance occur in the premenstruum and pregnancy. The frequency of tension, depression and water retention in the premenstruum is universally recognized.

From all this evidence it is seen that progesterone plays a part at tissue level in the etiology of migraine, possibly in the final common pathway of the biochemical changes mediated by the various trigger factors. Modern knowledge has revealed the importance of progesterone in both sexes although in any series of migraine patients women exceed men in number. Migraine sufferers appear to have an increased arousal to stressful stimuli. Cortisol levels are remarkably increased in stress situations.

Thus, clinical observation implicates progesterone, but our biochemists and histopathologists have not yet unravelled its precise role in the jigsaw of events which culminate in the disabling scourge of migraine.

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