Migraine in general practice*

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MIGRAINE does not kill. It produces painful, incapacitating attacks that last for hours and which with agonising regularity disrupt the normal pattern of life. This essay deals with the identification and treatment of trigger factors, which in a susceptible individual provoke a disabling paroxysmal headache.

Trigger factors as diverse as stress, hunger, alcohol, fatigue, menstruation, oral contraceptives, food sensitivities, inhalant allergies, travel, bright lights, noise and visual errors have been suggested (Speer, 1971). It is not easy to identify the precise offender or combination of causes. The trigger factor is too often masked by a false, and apparently obvious, cause, so the physician must interrogate, cross-examine and sift all available evidence if he is to isolate the specific causative factor in each patient.

Two vital diagnostic aids for this task are 'frequency charts' (Figures 1–4) and 'attack forms' (Figure 5). These are simple enough for the patient to complete and convey invaluable information to the doctor.

Frequency charts

The frequency chart enables the doctor to establish the day and the intensity of each attack, which is marked by an 'H' or 'h' depending on the severity. Women also mark 'P' (period) for menstruation. The letter 'M' is avoided as it could represent both 'migraine' and 'menstruation'.

Figures 1–4 show the varied but vital information obtained, which can point to factors in the patient's personal life on which more information is required. Cluster headaches becomes obvious immediately. Equally clear is the time of the migraine in relation to menstruation. The 'perfect' 28-day menstrual cycle would suggest that the woman is taking an oral contraceptive.

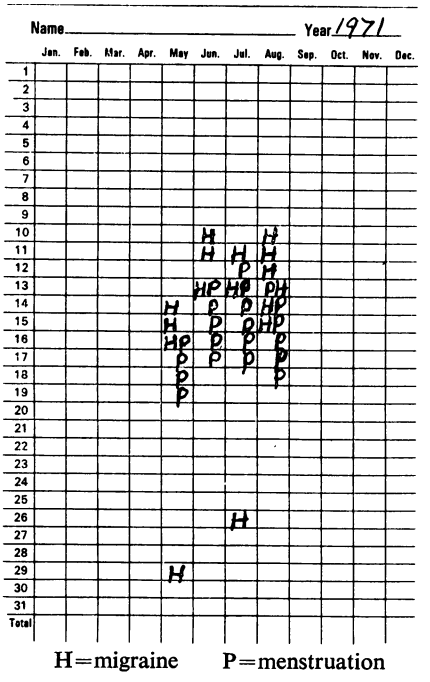

Figure 1
Frequency chart showing menstrual migraine

Patient 1. *Figure* 1—This was a housewife of 45 years with four children. The attacks were essentially premenstrual, occasionally overlapping during menstruation and with mid-cycle attacks. This patient was initially asked if attacks had any relationship to menstruation, but answered in the negative adding "they even come after menstruation," which indeed they did, for they occurred at ovulation.

The frequency charts may show a preponderance of attacks on one day of the week or weekends. If this is suspected the information may be transposed to the days of the week:

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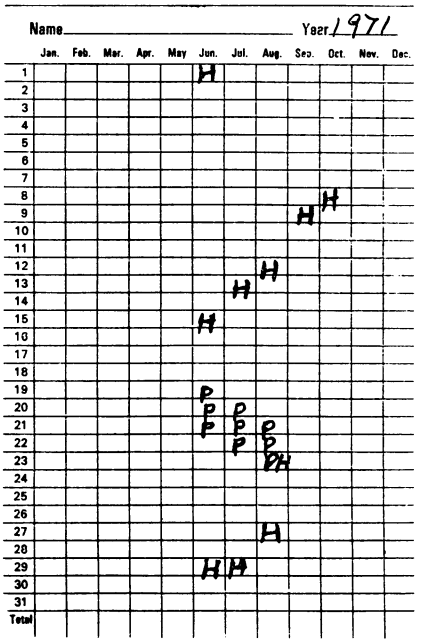
Figure 2

Sunday	—
Monday	—
Tuesday	1111
Wednesday	—
Thursday	111111
Friday	—
Saturday	—

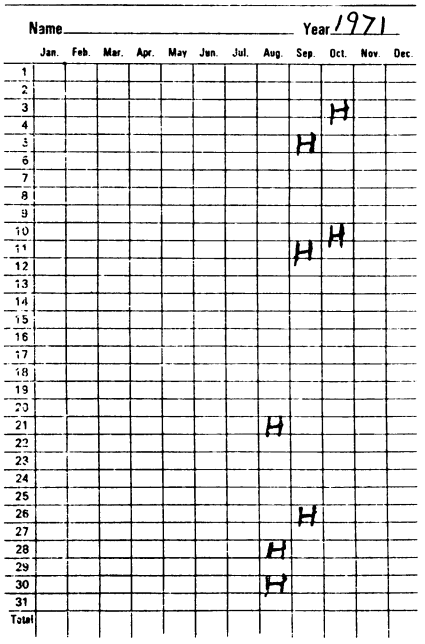
Figure 3

Sunday	1111
Monday	1
Tuesday	—
Wednesday	—
Thursday	—
Friday	—
Saturday	111



H=migraine P=menstruation

Figure 2
Frequency chart showing attacks at fortnightly intervals



H=migraine

Figure 3
Frequency chart showing attacks at weekends and bank holidays

Patient 2. *Figure* 2—This was a single, 27-year-old female secretary. The attacks were at fortnightly intervals originally on Tuesdays, but later on Thursdays. Further questioning as to what Tuesday activity had now been transferred to Thursday, revealed that on Tuesday she went direct from work to her hairdresser, having only a snack lunch. The migraine developed on her way home at about 20.00 hours. When her favourite hairdresser changed her late night to Thursday the patient changed her appointment. Fasting was the trigger factor.

Patient 3. *Figure* 3—This was a male clerk of 42 years, single. The attacks were at weekends and bank holidays, present on rising at 10.00–11.00 hours instead of waking with the alarm at 07.30 on working days. These attacks proved to be related to fasting.

While the last example proved to be due to hunger, other reasons often suggested for weekend attacks can include sheer overwork with domestic chores, shopping, celebration suppers with alcohol, marital and family tensions, eyestrain from cinemas or television viewing.

Patient 4. *Figure* 4—A female teacher, 32 years, with one child, had attacks at the beginning and end of term, precipitated by fatigue and tensions arising out of trying to complete the necessary house decoration before the end of the holidays and the marking of books and school reports before the end of term. The migraine was worse at times of menstruation.

A similar timing of attacks at the beginning and end of school holidays might be

seen among those prone to travel sickness, or in a mother of a large family, who finds the children's exuberance too exhausting during the long, school holidays, such a timing of attacks might suggest apprehension. Tension and fatigue are factors needing consideration.

Attack forms

The 'attack forms' (Figure 5) are given to migraine sufferers, who are asked to complete them immediately they recover from an attack, for the 24 hours before the onset of the attack. The forms give quick and accurate information, which if sought several days later would take time before getting the correct, or possibly inaccurate answer. With three or more completed forms a common pattern should emerge. The questions concerning menstruation are worded so that they cover those having a short cycle of 21 days or a long one of 35 days.

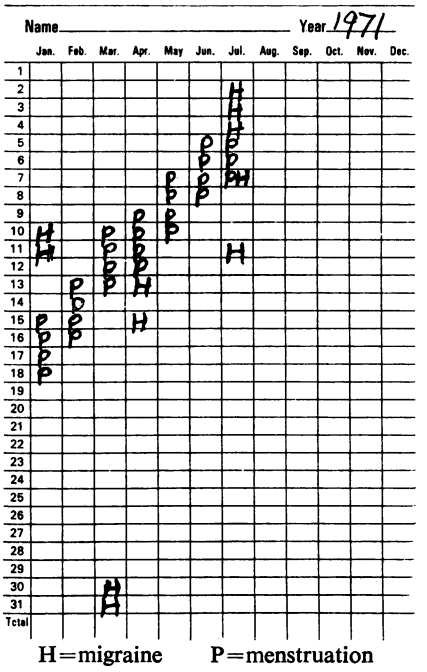


Figure 4
Frequency chart showing attacks at beginning and end of school term

Time of day

Some indication of the cause is suggested by the time of onset of an attack. Menstrual migraine tends to wake the patient in the early hours of the morning or be present on waking. Attacks on waking may be due to hunger and sexual frustration due to failure to achieve an orgasm or premature ejaculation. Attacks starting at midday are common in those who have missed breakfast and been unduly active during the morning, and also those experiencing tensions and frustrations at work. Evening attacks occur among those whose employment entails undue responsibility and those frustrated by rush-hour travel which increases both hunger and fatigue.

Recognising stress

Tension and stress situations vary greatly in each individual. Reasons given for special worry, overwork or shock included:

"Signed agreement for new flat."
"Emotional upset due to argument."
"Kitchen painted, overwork and shopping."
"Favourite uncle died suddenly—heard yesterday."
"Tooth removed."

Unusual activity and being extra tired was attributed to:

"Travelling 100 miles to mother."
"Visit to West End."
"House decorating."
"Car broke down—had to push it."
"Christmas stock arrived—chaos in shop" (Shop assistant).

These statements should be looked upon as a useful opening for further amplification at the next interview. The statement "travelling 100 miles to mother" required further questioning to determine whether motion sickness or a traumatic confrontation with mother was the more significant factor.

Name..... Date .....
Day of week .....
Time of onset.....
Duration.....
Day of cycle..... Days before next menstruation.....
During the 24 hours *before* the attack:—
(1) Did you have any special worry, overwork or shock?
(2) What had you done during the day?
Normal work?
Unusual activity?
Extra tired?
(3) What food had you eaten and when?
Breakfast ..... Time.....
.....
Mid-morning..... Time.....
.....
Lunch..... Time.....
.....
Mid-afternoon..... Time.....
.....
Supper ..... Time.....
.....
Evening..... Time.....
.....
Bedtime ..... Time.....
.....

Figure 5
Migraine attack forms for the patient

Food intake

Hanington's work (1967) has revealed the inability of some sufferers to digest certain foods, especially those containing tyramine. This section of the 'attack form' pinpoints those whose attacks result from food sensitivity or hunger. Particulars in this section can rarely be obtained with any accuracy if sought several days later. Common foods which are suspect include cheese, milk, yoghourt, eggs, chocolate, fish and wines. If a migraine develops at 16.00 hours it is far easier to blame it on events of that day instead of the cheese or chocolate eaten on the previous evening.

Fasting is a more common precipitating factor than is generally realised. Often it is only when the foods taken are itemised that it is appreciated there was an interval of six hours without food.

Elimination of trigger factors

Having identified an individual's trigger factors the next step is their elimination. Migraine affects marital and family relationships so the spouse should be invited to join the discussion. Together, ways must be found of overcoming tensions, eliminating offending foods and avoiding long intervals without food.

If migraine has resulted from an oral contraceptive, it is unlikely that a change of formulation will prove permanently helpful, and the physician should be ready to suggest alternative methods. If personality problems or sexual difficulties exist this may call for further discussions or reference to a psychiatrist.

Food sensitivity

Attacks of migraine precipitated by certain foods appear to be due to an inborn error of metabolism. Youdim *et al.* (1971) and Smith *et al.* (1971) postulate an enzyme defect in the tyramine metabolic pathway, and suggest that it might be dangerous for those with dietary migraine to take monoamine-oxidase inhibitors or use isoprenoline inhalers for asthma.

Food sensitivity may be suspected as a factor if there is a family history of migraine among members of both sexes. If the family history is limited to the female line then menstrual migraine is a possibility. Those with food sensitivities often show in their life span the full evolution of migraine, the bilious attacks in childhood gradually merging into migraine in adult life and finally, visual aura without migraine in later life.

Patient 5—A female teacher, 38 years, had bilious attacks in childhood and, later, migraine precipitated by white wine, sherry and chocolate. Her eight-year-old son and four-year-old daughter were both liable to bilious attacks after chocolate or trifles (containing sherry). No doubt as these two children grow up, their bilious attacks will gradually alter and take on the classical picture of migraine.

One 48-year-old housewife appreciated that migraines were always more frequent when attempting a slimming diet. It was revealed that the offending food was cheese, which was taken more liberally when conscientiously attempting to avoid the starchy and fattening foods.

Having suggested to one patient that as chocolate appeared the suspect food she should avoid it, she returned a month later to tell me her father was also liable to migraine provoked by chocolate and for this reason had abstained from chocolate for years. Indeed she recalled, as a child, trying unsuccessfully to tempt her father with chocolates. A mother of two children whose migraines were provoked by chocolates recalled that during the last trimester of both her pregnancies she found to her delight that she was able to eat chocolate with impunity.

Some patients appear to have specific sensitivities to different wines and not necessarily all types, thus four mentioned white table wine, six red wine and two sherry, but they had no difficulties with other wines. Over indulgence in alcohol is always liable to result in a severe headache. Patients with this should be advised to be more temperate and avoid drinking on an empty stomach. Over indulgence is not the same as sensitivity to sherry or wine when the advice must be to abstain from the offending drink altogether.

Some patients bring their completed forms with their own explanation of the provoking food.

Patient 6—A male clerk, 32 years, had attacks which were most frequent on Mondays, although not limited to that day. On listing the food it was noted that attacks always followed a meal of cold roast meat. His wife varied the meat including pork, beef and lamb, but attacks continued. Then his favourite brand of pickles was eliminated and attacks of migraine ceased.

There may be more than one provoking cause.

Patient 7—This was a housewife 23-years-old, with no children. Her frequency chart suggested menstrual migraine, although a few attacks occurred at other times. Following progesterone therapy the menstrual migraines improved, but she continued to have occasional attacks. It was then noticed that chocolates were the offending food, and elimination completely eased the migraine. Later she returned with her own explanation. Her sensitive husband appreciated her sufferings and so bought a box of chocolates each time menstruation was due.

In the last 22 patients seen the offending food which had produced at least three attacks per patient proved to be cheese in nine, yoghourt in four, chocolate in four, wine or sherry in four, and eggs in one. The interval between the ingestion of cheese and the development of migraine varied between 17 and 24 hours, although this was as short as eight hours in a 54-year-old housewife, who had a meal of both cheese and sherry. The intensity of the attack appeared to be proportional to the amount of food consumed.

When a specific food has been incriminated it must be eliminated from the diet, which means that the patient must become familiar with every form in which it can be presented. Few appreciate that quiche lorraine or mornay sauce contain cheese, shop-bought ginger cake often contains chocolate for colouring or that trifles may contain sherry. On the other hand there is the woman overheard at a party refusing pineapple juice because "sweet foods cause migraine." It was the tyramine in chocolate which provoked her attacks, not the sugar or sweetening agents. This familiarity with the offending food is vital if the patient is on a reducing diet.

Ziamis and Hanington in 1969 suggested the use of clonidine ('Dixarit', 'Catapres') which reduces the responsiveness of cranial blood vessels to the vasoactive monoamines like tyramine and its metabolic derivatives. The results of clonidine have proved excellent in those with dietary migraine (Wilkinson, 1969; Sjaastad and Stensrud, 1971). In normotensive patients there does not appear to be any hypotensive effect, although in some it causes drowsiness, making the preparation unacceptable. After two or three months on clonidine it is sometimes possible for the patient to take small quantities of the offending foods without precipitating an attack.

Fasting

There are some susceptible individuals in whom a long interval without food will provoke an attack of migraine. Normally a lowered blood sugar triggers off a feedback mechanism for the mobilisation of glucose thus reversing the hypoglycaemia. It is possible that in these susceptible individuals the feedback mechanism operates at too low a blood-sugar level or that the individual is hypersensitive to this emergency mechanism.

Many of my patients had gone for more than 12 hours without a substantial meal, trying to manage on a cup of tea or coffee or possibly some fruit. Often the husband had eaten the same food at the same interval but was unaffected. Once an attack has been provoked it is too late for food, nor is it desired, and the patients are adamant that they do not feel hungry. Women rarely recognise this process in themselves for they have become conditioned to suppressing the sensations of a rumbling stomach and may even pride themselves on their self-control.

The length of time any individual can manage without food while leading an active life varies tremendously. Man can go longest. They are rarely affected by this reversible hypoglycaemia, which is most marked in women during their paramenstruum. It is well recognised that many orthodox Jewesses experience headaches during their fasts, and headaches are often given as the reason for stopping weight-reducing diets.

The difficulty of investigating a patient with migraine in hospital is well-appreciated by research workers, who find that once the patient is hospitalised her tendency to migraine disappears. Is this due to the regular meals, augmented with an early morning tea, mid-morning coffee, afternoon tea and bedtime drink?

The precipitating effect of fasting is well-illustrated by the following two case histories:

Patient 8—This was a female medical auxilary, 54-years-old. She rose at 07.30 hours on Saturday, had coffee and an 'Energen' biscuit. She was anxious not to gain weight after having stopped smoking. At 12.45 in a restaurant a severe migraine developed before starting a meal.

Patient 9—This was a male sales representative, of 34 years. Sunday 08.00 hours breakfast of porridge, egg and bacon, toast and coffee. He played 18 holes of golf. No further food or drink was taken until 18.00 hours when he developed a classical migraine.

The Sunday morning headache is perhaps the best example of fasting migraine (patient 4). Here the patient has an early evening meal on Saturday night, followed by an energetic evening and a long lie in bed on Sunday morning. The remedy is a late

night snack before retiring, and if necessary some cereal and milk by the bed, ready to be eaten on waking.

The possibility of fasting migraine as a causative factor may be masked by an apparently obvious psychological cause (patient 10), or by fatigue or tension (patient 11).

Patient 10—This was a housewife of 42 years. On Friday she had at 19.00 hours a light fish supper. On Saturday she rose at 07.00 hours, without breakfast, shopping 8–10.00, then she hurriedly changed for her son's wedding, left home at 11.30. Severe migraine with vomiting developed at 14.30 hours after 18½ hours without food.

Patient 11—This was a mother of three children, a part-time clerk. Attacks occurred on Thursdays. She attributed these attacks to fatigue and tension, as after leaving work at midday Thursday she would drive 12 miles to her favourite supermarket, buy a week's shopping and then drive home in time to collect her daughter from school and take her to a 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 16.30 hours. Her evening meal was at 21.00 hours so she went 19 hours without food, with only drinks.

For fasting migraine, the patient should be advised to take frequent snacks at three-hourly intervals, thus enjoying midmorning coffee, afternoon tea and a bedtime snack, in addition to the regular three meals per day. Those who are worried lest these extra snacks increase their weight should be advised that non-fattening foods at frequent intervals will also suffice. Otherwise they can be taught to divide their total daily calorie allowance into six snacks instead of three meals.

Many women regularly manage without breakfast and do a morning's work but only during the paramenstruum does the fasting become critical and they develop a migraine at midday. These women with fasting migraine predominating in the paramenstruum show a good response to progesterone, which causes a rise in the glucose tolerance curve.

The Review of Physiological Chemistry (1969) by H. A. Harper explains that the menstrual hormones, oestrogen and progesterone, are responsible for the transport of the glucocorticoids attached to the globulin in the plasma. "Progesterone is one of the few steroids with a high affinity for this free active fraction." Glucocorticoids maintain the liver glycogen and help to maintain blood sugar levels (Singer, 1972). This probably accounts for the tendency for women to develop hypoglycaemia during the paramenstruum and may also cause headaches in women on oral contraceptives.

Tension headaches

Some attacks are triggered off at times of special responsibility or decisions, such as having to speak in public or preparing for a holiday. While it may not be possible to eliminate these stresses completely, they may be eased by the timely administration of a mild sedative, e.g., diazepam 5mg. t.d.s. for a few days before the event. Here the spouse is often alert enough to remind the patient when tension is likely to arise and take the necessary precautions. Attacks precipitated by travelling may be prevented by remedies for motion sickness, such as promethazine or hyoscine.

Relaxation therapy is a simple, harmless method worthy of trial when tension is a prominent feature in the patient's personality and a determining factor in the timing of attacks. Hay and Madders (1971) found among those attending evening classes in relaxation therapy 69 per cent reported a decrease in frequency, severity and duration, furthermore "almost all patients reported a feeling of wellbeing which cannot be objectively measured." The local branch of the Migraine Society is usually ready to help patients referred to them for relaxation.

Fatigue

Over-exertion, which could have produced undue fatigue sufficient to precipitate an attack, was frequently mentioned. However, a closer examination of the 24 hours

immediately prior to an attack often revealed other factors. Missed meals were common, thus one housewife was determined to finish decorating the room before preparing supper and another wanted to use every minute of daylight in the garden and so did not realise that six hours had passed without food.

Fatigue may be used to explain an attack during the premenstruum when lethargy, irritability and depression are characteristically present. Occasionally a restless energy, which may reach almost manic proportions, can occur immediately before menstruation and the women will then state that their attacks always come when they 'overdo things,' for it is easier to blame the happenings on the day of attack, rather than the menstruation which is due tomorrow.

Menstrual migraine

Menstrual migraine has been recognised since Hippocrates attributed its symptoms to "the agitated blood seeking a way of escape from the body." Greene (1963) estimated that 20 per cent of women suffer at some time from menstrual migraine. Of the 2,000 patients attending the City of London Migraine Clinic 61·5 per cent were women. Pregnancy brings complete or partial relief of migraine to 80 per cent of sufferers (Friedman and Merritt, 1959), even though it often returns during the puerperium.

Three types of menstrual migraine can be differentiated:

Tension headache, which is characteristically preceded by a period of increasing depression, lethargy and irritability for one to 14 days. Occasionally on the day immediately before menstruation there may be restless energy.

Water retention headache, in which the attack is preceded or accompanied by weight gain, swollen ankles, bloated abdomen or breast tenderness. The pain may be concentrated behind the eye which appears stony hard during an attack due to the temporary premenstrual rise in intra-ocular tension (Dalton, 1967). Or there may be nasal obstruction with vacuum headache due to engorgement of the sinus mucus membranes (Dalton, 1964).

Fasting headaches which have already been described.

Menstrual migraine usually responds well to progesterone although not to progestogens (Greene and Dalton, 1953; Bradley *et al.*, 1968). Many workers including Sacks (1970) in his book *Migraine* still fail to differentiate between progesterone and progestogens, so it is not out of place to stress the difference.

Progesterone is synthesised in the corpus luteum of the ovary, the adrenals and the placenta. The ovarian progesterone passes in the blood to the uterus where it causes proliferation of the oestrogen-primed endometrium. Any synthetic compound capable of performing this function on the endometrium is termed a *progestogen.* But progesterone is also synthesised in the adrenals, being converted from cholesterol and then synthesised further to become the precursor of all known corticosteroids. This adrenal progesterone does not appear in the blood in any quantifiable amount for it is immediately converted to corticosteroids (Harper, 1969). Again, as mentioned earlier, progesterone participates in the transport of glucocorticoids. The synthetic progestogens, either oral or long acting injections, cannot be used by the adrenals for the synthesis to corticosteroids nor the transport of glucocorticoids. Indeed Johansson (1971) has shown that progestogens lower the progesterone plasma level.

The functions of corticosteroids are numerous, but aetiologically it seems that during the premenstruum when there is a relative or temporary insufficiency of adrenal progesterone there may be an upset of the corticosteroids concerned with:

1. Electrolyte metabolism, which could result in premenstrual depression, irritability and tension migraine.
2. Water regulation, resulting in water-retention migraine.
3. Glucose metabolism resulting in fasting migraine.

Progesterone therapy

Singh *et al.* (1946) were the first to report successful treatment of menstrual migraine with progesterone, but this method is not universally practised. Too often, the oral progestogens have failed and so progesterone has not been tried. Also progesterone therapy was previously hampered by the need for frequent intramuscular injections, but Nillius and Johansson (1971) demonstrated that adequate absorption occurs by the rectal and vaginal routes, although the dose required is increased fourfold and the duration of action is shorter. The use of progesterone suppositories and pessaries has revolutionised the treatment of menstrual migraine.

Progesterone suppositories, pessaries and injections were tried on 51 sufferers, whose menstrual migraine had been confirmed by a frequency chart for a minimum of three months. The initial route of administration was chosen by the patient, but if this proved unsuccessful another route was tried.

After a minimum period of three months' treatment the optimum treatment was suppositories 29, pessaries 12, injections 11 and other medication nine. The suppositories caused diarrhoea in two. The pessaries were disliked by five because of the vaginal discharge, and a further three found insertion difficult. One woman developed an urticarial rash following injections, but was able to tolerate the suppositories.

The dosage and time schedule differed for each individual, being determined by the timing of symptoms and length of menstrual cycle. The same guide lines were used as with the timing of progesterone injections (Dalton, 1964), with the usual course being from the fourteenth day for two weeks. Those with shorter or longer cycles than 28 days had the course adjusted accordingly. If ovulatory migraine occurred, treatment was begun on the tenth day.

When treatment postponed the timing of the attack from the paramenstruum to the postmenstruum, then progesterone was continued throughout menstruation. If only partial relief occurred after the first month of treatment the dose was increased in the following month, whereas if there had been complete relief the dose was halved. The most frequently successful dosages were suppositories 200 mg die, pessaries 200 mg b.d. and injections 100 mg die.

Many learned to adjust their own dosages, increasing at times of stress or when a migraine appeared imminent. Menopausal women could sometimes anticipate that they were likely to experience a missed menstruation in one month and would postpone treatment.

Somerville (1971) used progesterone injections 50 mg or 75 mg for only seven days premenstrually in six patients with menstrual migraine. He abolished the expected attack in one patient and decreased the duration of the attack in four. Unfortunately he did not alter the dose or duration of the progesterone course during the subsequent months or his results might have shown greater improvement. Nillius and Johansson (1971) have shown that the effect of daily progesterone was cumulative, and therefore it is usually wise to start administration at mid-cycle to have a high enough plasma level during the late premenstruum.

Women with water-retention migraine will be helped by diuretics during the premenstruum either alone or with progesterone therapy.

Conclusion

Migraine is a symptom. Management depends on a meticulous search in each individual for the provoking cause followed by its elimination or specific treatment. However, as long as unselected cases of migraine are subjected to trials of treatment suitable only for one type, the problem of migraine will continue and the efforts of the Migraine Trust will remain unfruitful.

Addendum

Progesterone pessaries and suppositories are available in this country on National Health Service prescriptions and are retailed by Locatell Chemist, 100 Stoke Newington Church Street, London, N16. In the United States they are available from Mr Milton Caplan, 424 Equitable Building, Baltimore 21202, Maryland.

REFERENCES

Bradley, W. G., Hudgson, P., Foster, J. B. & Newell, D. J. (1968). *British Medical Journal*, **3**, 531–533.
Dalton, K. (1964). *The Premenstrual Syndrome*. London: William Heinemann Medical Books.
Dalton, K. (1967). *British Journal of Ophthalmology*, **51**, 692–695.
Friedman, A. P., Merritt, H. H. (eds.), (1959). *Headache: Diagnosis and Treatment*. Philadelphia: F. A. Davis & Co.
Greene, R. (1963). *Journal of the Royal College of General Practitioners*, **6**, Suppl. No. 4, 15.
Greene, R. & Dalton, K. (1953). *British Medical Journal*, **1**, 1007–1014.
Hanington, E. (1967). *British Medical Journal*, **2**, 550–551.
Harper, H. A. (1969). *Review of Physiological Chemistry*. California: Lange Medical Publications, Los Altos.
Hay, K. M. & Madders, J. (1971). *Journal of the Royal College of General Practitioners*, **21**, 664–669.
Johansson, E. D. B. (1971). *Acta Endocrinologica*, **68**, 779.
Nillius, S. J. & Johansson, E. D. B. (1971). *American Journal of Obstetrics and Gynaecology*, **110**, 470–477.
Sacks, O. W. (1970). *Migraine*. London: Faber & Faber.
Singer, B. (1972). *British Medical Journal*, **1**, 36–39.
Singh, I., Singh, I. & Singh, D. (1947). *Lancet*, **1**, 745.
Sjaastad, O. & Stensrud, P. (1971). *Acta Neurologica Scandinavica*, **47**, 120–122.
Smith, I., Kellow, A. H., Mullen, P. E. & Hanington, E. (1971), *Nature*, **230**, 246–248.
Somerville, B. W. (1971). *Neurology (Minneap.)*, **21**, 853–859.
Speer, F. (1971). *Headache*, **11**, 63–67.
Wilkinson, M. (1969). *Lancet*, **2**, 430.
Youdim, M. B. B., Carter, S. B., Hanington, E., Sadler, M. & Wilkinson, M. (1971). *Nature*, **230**, 127–128.
Zaimis, E. & Hanington, E. (1969). *Lancet*, **2**, 298–300.