MEDICAL PRACTICE

Clinical Progress

Migraine—Research

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Research into migraine is bedevilled by the lack of an adequate definition, relating directly to the absence of measurable criteria. Though we need not worship the deity of measurement, the absence of objective criteria makes it much more difficult to assess treatment and militates against a fundamental approach to the problem. Nevertheless, a current working definition of migraine is useful in practice. This states that migraine is a paroxysmal headache that lasts hours, sometimes days, interspersed with periods of complete freedom; attacks are invariably associated with some autonomic disturbance affecting either the gastrointestinal tract—anorexia, nausea, vomiting, constipation, or rarely diarrhoea—or the visual system—such as teichopsiae or photophobia. The pain need not be unilateral, belying the original term hemicrania, and frequently is experienced in the midline as a deepseated ache. At some stage during an attack the pain assumes a throbbing quality, accentuated by coughing, sneezing, or head movement. The facial appearance is usually pale, though the occasional patient is suffused—the so-called "red migraine".

Migrainous Neuralgia

Migrainous neuralgia differs from the more common variety described above, because attacks cluster, recurring daily for several weeks; begin in middle age; and are more common in men than in women. Each attack is brief, of 30-60 minutes' duration, and is associated with unilateral injection of the conjuctiva and congestion of the ipsilateral nasal mucosa. Prophylactic ergot is extremely effective in most patients. Despite obvious local vascular changes, the pathogenesis of migrainous neuralgia remains a mystery and its relation to migraine somewhat tenuous.

Neurology owes a great debt to the late Professor Harold G. Wolff, a pioneer of scientific research into headache in general and migraine in particular. His book *Headache and Other Head Pains*[1] is a modern classic that embodies 30 years of devoted research by him and his colleagues. Wolff, however, seemed too committed to the notion that the migrainous aura is caused by spasm of the intracranial vessels and the ensuing headache by extracranial vasodilatation. The fact that many patients feel their pain accentuated by movement or alteration in intracranial pressure—for example, straining or coughing—implies a meningeal component to the pain. Nevertheless, Wolff and his associates used many measurable criteria and laid the foundation for a modern scientific approach.

Art of the Soluble

I believe that the problem of the aetiology of migraine is soluble *if* one assumes the pain to be vascularly mediated. Pharmacological reactions of blood vessels have been extensively studied since the beginning of this century, and many chemicals have been isolated that determine vasomotor responses in physiological concentrations. Furthermore, in the past two decades there have been developed potent vasoinhibitors and sympathetic blocking agents, successfully used in the treatment of hypertension. I propose therefore to review some current trends in migraine research and conclude with a testable hypothesis.

Natural History

Migraine surveys have shown an incidence that usually ranges between 5 and 10%. Though migraine and intelligence are not linked,[2] social status or intelligence influence the likelihood of the patient visiting a doctor, thereby correcting a false clinical

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impression. Another false notion—that migraine is accentuated during the menopause—has been challenged:[3] 18 women noted no difference, two were improved, and only six became worse during this phase of their life.

Many patients give a history of travel sickness or bilious attacks during childhood, but a series of hospital patients is too selected. There is now a real possibility of learning more about migraine in a normal population by analysing the 14,000 children born in the United Kingdom during one week in March 1958. Full medical histories and social details have been recorded on punch cards by the National Birthday Trust Fund. These children were carefully examined at the ages of 7 and at 11 years, and it is hoped will be surveyed again when they reach 16 years. Here is an unparallelled opportunity to learn about the natural history of migraine, perhaps about the genetics of the condition, and even to discover unexpected correlations.

Genetics

The inheritance of migraine is not yet clear. Only hemiplegic migraine, a rare variety, is clearly transmitted by a dominant autosomal gene.[4] A study of migrainous subjects and their parents[5] showed that if both parents were affected then 69% of the offspring had migraine; if one parent was affected the incidence was 44%. But 29% of migraine sufferers had no parental history. This does not tally with a Danish twin study,[6] in which 12 out of 24 monozygotic twins had migraine—whereas only six out of 60 dizygotic twins were affected. Further twin studies seem to be indicated.

Therapeutic Trials

An improvement rate of 60% commonly results from any therapeutic trial in migraine. This surprisingly high success rate suggests that physicians may not have asked: "Why has the patient come now?" In clinical practice most patients have had migraine for years, but a recent increase in frequency or severity of attacks causes the patient to seek advice.[7] This recent exacerbation may be due to or associated with anxiety, depression, or local pains. It is not difficult for a cheerful physician to allay the patient's fears or help depression with optimism. Even placebos have been shown to give a 20% response,[8] indicating that at least some patients have come during an exacerbation of their migraine.

Probably therapeutic trials will remain inconclusive until measurable criteria become available. It must be self-evident that ergotamine preparations are not the final answer. Many physicians I know take only aspirin or another analgesic for their own migraine. Even those patients helped by ergot find that only after the drug has made them vomit do they obtain relief, and it is well recognized that vomiting can end an attack. Often the drug remains unabsorbed in the stomach owing to gastric stasis. Many proprietary preparations contain a sedative, analgesic, or a stimulant in addition to ergot. All in all, the interpretation of the results of a therapeutic trial for migraine is fraught with difficulties.

Psychotherapy

Psychological mechanisms feature strongly in the layman's mind as a cause of migraine attacks, a view commonly shared by the medical profession.[1,9] It is all too common to blame pervading conditions or the patient for his affliction. This is not a new device; thus Crichton Browne in 1871 writing of his times as "essentially a feverish and fidgety age in which the unappeasable restlessness pervades all classes . . . The result of this ceaseless agitation and ambitious striving is that the nervous system gives way under the strain imposed on it"—(Quoted by Asher[10]). We might well agree with these sentiments 100 years later, were it not that Crichton Browne was attributing general paralysis of the insane to this cause, some years before the spirochaete was discovered.

In practice one knows colleagues, acquaintances, and patients with migraine who are well balanced and not neurotic. Even in neurotic patients an appreciable number of attacks are precipitated by pleasant occasions or by prolonged sleep. This does not imply that there are not psychological causes in some patients some of the time. But it seems preferable to seek biochemical mechanisms that could lead to a rational solution. I know of no properly controlled trial of the efficacy of pyschotherapy for migraine, but it is difficult to visualize how psychotherapy could help to solve the problem.

Biochemistry and Pharmacology

HORMONES

The evidence for a hormonal influence on migraine rests on the following clinical observations: migraine commonly begins at puberty; some women have their attacks strictly related to menstruation; 80% of women have no attacks during pregnancy; and taking the contraceptive pill initiates or increases migraine attacks. Furthermore, the vascularity of the endometrium increases in women who complain of headache while taking oral contraceptives,[11] which is in keeping with the notion that migraine is vascularly determined. Nevertheless, which cranial vessels are influenced by hormones, and how, is as yet unclear, but this could be a profitable line to follow.

5-HYDROXYTRYPTAMINE (SEROTONIN)

It is logical to investigate all known physiologically active vasomotor agents. A. M. Ostfeld[12] has included acetylcholine, bradykinin, histamine, and serotonin among the suitable candidates for consideration in the pathogenesis of migraine. Unfortunately, many hypotheses are unclear whether vasoconstrictors or dilators are responsible, and where the chemicals act. Perhaps this is not the fault of the chemists but of the neurologists.

Investigations of the urinary metabolites of serotonin have shown wide differences in relation to migraine attacks. Some workers have found high values during[13,14] and between[14] attacks, while others[15] have been unable to confirm these findings. Nevertheless on the basis of the serotonin hypothesis, methysergide, a powerful serotonin antagonist, was introduced with noteworthy success in some patients.

TYRAMINE

E. Hanington[16] has put forward a stimulating hypothesis in relation to tyramine. She found that 30% of migrainous patients attribute attacks to specific foods, cheese and chocolate being the most common. The same foods give rise to pressor reactions because they contain the amino-acid tyramine. Hence she has postulated that tyramine triggers dietary migraine. Using lactose as a control substance, Hanington and A. M. Harper[17] have clearly shown that oral tyramine can initiate attacks, though the time after ingestion varies widely for a pharmacological agent. More recently Hanington and her colleagues[18] have shown a defect in the ability of migrainous subjects to conjugate tyramine compared with controls. Though the mechanism by which tyramine may trigger migraine is still unknown, this seems a fruitful approach.

METHYSERGIDE

This powerful serotonin antagonist was introduced in 1959, and thereafter it has been investigated in many therapeutic trials.[8] D. A. Curran and J. W. Lance rendered 20% of 320 patients virtually free from migraine, and an additional 36% had considerable reduction in attacks.[8] Any assessment of this drug is hindered by the inclusion in some trials of patients with migrainous neuralgia. Also the drug's side effects include angina pectoris, intermittent claudication, and retroperitoneal fibrosis, and these limit the use of methysergide to less than six months at a time and then only in the most intractable cases.

CLONIDINE

At present trials are being conducted of clonidine in migraine prophylaxis. This imidazoline derivative has been successfully used in hypertension, though its mode of action is not understood. It was thought to act as a central depressant, but it has been shown that the drug inhibits the vasoconstrictive effect of noradrenaline and the dilatory response to isoprenaline[19].

ALCOHOL AND SLEEPING TABLETS

Many people with migraine avoid all forms of alcohol because they know that an attack may ensue some hours later, usually the following morning. Some beverages—for instance, red wine or port—are more likely than others to produce migraine, and hence it has been suggested that some alcoholic drinks contain "toxic" contaminants. I know of no serious investigations using alcohol, potent though it is in producing migraine.

A sleeping tablet may also induce migraine, the pain being present when the person wakens the following morning. This makes one wonder whether attacks of migraine precipitated by alcohol or sleeping tablets are related to the depth or length of sleep, when carbon dioxide accumulation or relative anoxia can affect the intracranial circulation.

Precipitating Factors

The study of precipitating factors is not fundamental but enables advice to be given to patients so that the number or severity of attacks may be reduced. Induced attacks using these triggering factors also provide a foundation for research in a condition which cannot be studied in animals. Moreover, the analysis of precipitating factors should lay the myth that all migraine is psychogenically determined.

Physical factors.—These include exposure to excess heat, cold, noise, flashes of bright light, or prolonged focusing on a cinema film, television screen, or down a microscope. Intense odours may also cause migraine.

Dietary factors.—Cheese, chocolate, and alcohol are well-recognized precipitating factors and possible mechanisms for this have been discussed. Missing meals may initiate attacks and a low fasting blood glucose level may activate a vascular response.[20] This concept has gained support from the observation that some migraine sufferers have lost their attacks when they developed diabetes, while others have had attacks precipitated by insulin-induced hypoglycaemia.[21] Since immunology has become an established scientific discipline, we have heard less of the "allergic" basis for migraine.

Sleep.—Sleeping too long is a recognized cause for headache and migraine too. A possible mechanism has been mentioned.

Local Pains.—Local pains in the head or neck arising from the upper cervical region, from ocular or dental causes, may provoke migraine. Treatment for the local condition, assessed on its own merits, may return the patient to his former frequency of attacks.

Electroencephalography

In the past many unexplained neurological phenomena were labelled "epileptic" and there has been no difficulty in finding a greater proportion of electroencephalographic abnormalities in people with migraine than expected in normal population.[22] Though the old adage that "migraine affects the intelligent and epilepsy the less fortunate" is incorrect, it does suggest that the two conditions are not closely allied. This is borne out in clinical practice.

The approach of measuring cortical responses to photic stimulation is relevant to the problem, because, as mentioned previously, attacks are triggered by bright light and because photophobia during an attack is common. F. L. Golla and A. L. Winter[23] found three types of specific electroencephalographic responses using flashing lights at 20 cycles per second. These findings have been confirmed to some extent,[24] but more recently a highly complex technique has shown that during a migraine attack there may be a twofold to fivefold increase in the cortical evoked visual responses.[25]

Vascular Approaches

The pain of migraine has been attributed to vasodilatation because the headache is throbbing and temporary relief may be obtained by compressing the superficial temporal artery. Because of the latter clinical observation it was suggested that the headache was due to extracranial vasodilatation. Pulsations of the superficial cranial arteries were recorded by M. M. Tunis and H. G. Wolff,[26] but critical examination of their tracing (Fig. 4) shows that the pulsations measure exactly the same height 36-72 hours before the onset of headache as during an attack. Hence the pain of migraine cannot be due solely to extracranial vasodilatation. So much theorizing has been based on this piece of evidence that careful reappraisal seems warranted.

E. Skinhoj and O. Paulson[27] have measured cerebral blood flow by intracarotid injection of Xe-133 during and between attacks of migraine. Three patients were examined: in the first, during a dysphasic aura, the overall flow was reduced by 67%; the second, examined during the headache phase, had a mixture of very slow and rapid perfusion in each of the 16 areas tested; the third showed increased flow in the internal carotid system. A more suitable method for investigating migraine is rebreathing Xe-133,[28] because this technique is painless and repeatable. M. D. O'Brien and N. Veall[29] at first claimed that the flow was reduced during migraine, but later O'Brien[30] stated that the flow was reduced during the *early phase* of the attack in seven patients. One awaits the findings from a larger series.

A simpler approach is the response of the conjunctival vessels. Wolff and his colleagues[31] found that the changes were restricted to the side of the headache. We re-examined these observations[32] and noted that the blood-vessel calibre was altered in each of 11 persons during a migraine. These changes were invariably bilateral, and involved arterioles, capillaries, and venules. Six subjects responded by vasoconstriction and the remaining five by dilatation. The conjunctiva became oedematous in three out of the 11 persons. Because the conjunctival blood supply is derived partly from the external and partly from the internal carotid circulation, these findings allow one to question Wolff's hypothesis and also to raise several further questions: in particular, are there abnormal intracranial vascular reactions during migraine? Perhaps two widely differing vasomotor responses occur in people with migraine—one with dilatation that responds to ergot, and the other with vasoconstriction which does not.

The Future: Testable Hypothesis

Does the future look hopeful? I believe, yes. Interest in migraine is evidenced by the activities of the Migraine Trust in Britain, and the American Association for the Study of Headache and the Scandinavian Migraine Society abroad. Much scientific research is in progress, shown by annual migraine symposia organized by the Migraine Trust, and papers abstracted in Hemicrania.

As long ago as 1888 Hughlings Jackson[33] appreciated that "The use of hypotheses is the method of science. To suppose that we can make discoveries by the Baconian method is a delusion. No discovery, we are told by good authority, has been made on that method. A hypothesis, otherwise a supposition, is not a conclusion, it is only a starting point for methodical observation and experiment, the endeavour being not only to prove it, but to disprove it."

I propose therefore to conclude with a testable hypothesis.

The pain during migraine arises from perivascular nerve endings of the meningeal vessels; two divergent vasomotor responses occur—constriction or dilatation; specific vasoinhibitors of each variety of response will prevent or relieve the pain.

On the basis of this hypothesis we can formulate, and perhaps attempt to answer, these questions:

(1) Which cranial vessels are responsible for the pain? Intracranial or extracranial; arterial, capillary, or venous?
(2) How are these vessels affected? Uniformly or not; dilatation or constriction?
(3) Why are the affected vessels hypersensitive? Too much or too little constricting or dilating agents; or greater reactivity to normal vasoactive circulating agents?
(4) Does counteracting the vascular response relieve or prevent migraine?

The answer to some of these questions could bring us nearer to a solution, but if not we must elaborate further testable hypotheses.

Migraine—Treatment of Acute Attack

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Recently the International Committee on Headache has classified migraine into two main groups, classical and non-classical migraine. In the first group the attack is preceded or accompanied by transient focal neurological phenomena, such as visual, sensory, or speech disturbances. In non-classical migraine these sharply defined neurological disturbances do not occur. In both types the headache is usually unilateral and may be associated with nausea and vomiting, and the attacks may be mild or completely incapacitating. Though these are the main types, other varieties of migraine may occur, including cluster headaches, hemiplegic, ophthalmoplegic, and facial migraine. Treatment of the acute attack is similar for all types.

Characteristically an attack of migraine occurs early in the morning, the patient usually waking up with a headache. Nevertheless, the headache may occur at any time. Sometimes people are able to predict when their headaches will occur. There seems little doubt that the earlier an attack is treated the more likely it is to be amenable to the treatment. This is the first thing which must be impressed on the patient as all drugs—including ergotamine tartrate—are more effective if given in the first three or four hours of the attack, and even more effective if given during the prodromal period.

Three main types of drugs are used in the treatment of a migraine attack: analgesics; drugs which have a specific action in migraine; and antiemetics.

Analgesics

Probably more patients with migraine are helped by simple analgesics than by any other type of therapy, and these should be tried before any other treatment is given. The drugs most commonly used are aspirin and paracetamol, either in the simple *B.P.* form or as more expensive proprietary preparations, and may be taken alone or in combination with other substances. Aspirin is best taken in soluble form as this reduces the danger of possible gastric bleeding. The dose of aspirin is 300-600 mg, taken at the beginning of the attack and again two hours later if there has been no improvement. Paracetamol is also an effective treatment and recently at the City Migraine Clinic we have obtained good results using Paragesic.[38] This preparation combines paracetamol 500 mg, caffeine 10 mg, and a small quantity of pseudoephedrine in an effervescent tablet, and probably the good results obtained were due to the ease of absorption of this product. We hope that aspirin may soon be available in an effervescent form.

One advantage of analgesics is their relative lack of side effects, but the dangers of gastric bleeding with aspirin and of blood dyscrazias with paracetamol should not be forgotten. If a simple analgesic has been used and found to be helpful it is better to stick to it. Children very rarely require anything but analgesics and on the whole do not respond well to ergotamine tartrate; this is possibly because the dose of ergotamine is usually too large. Nevertheless, many patients vomit early in their migraine attack, so it must be borne in mind that any drug taken by mouth is ineffective if the patient vomits. There is also some evidence that the rate of gastric absorption and gastric motility are decreased in an acute attack of migraine.

Drugs With Specific Action

ERGOTAMINE TARTRATE

It has been said that if a headache does not respond to ergotamine tartrate it is not true migraine. Though this is probably not completely true, undoubtedly ergotamine tartrate is an extremely useful drug for migraine. Nevertheless, in too large a dose it has toxic effects, so it is important to give it in the right form in the right dose to the right patient at the right time. The right form is the one in which the patient can absorb the drug;

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