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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it is useless giving it by mouth if he vomits or by suppository if he has diarrhoea. The right dose is the smallest amount that is effective because in larger doses ergotamine tartrate causes nausea and vomiting. The right time is as early in the attack as possible, and the right patient is the one who is having an attack of classical migraine. Probably ergotamine tartrate makes tension headaches worse rather than better. At the City Migraine Clinic we have shown that intramuscular injections of 0·25 mg or 0·5 mg ergotamine are sufficient to control an attack;[38] this is a very much smaller dose than is usually recommended. Many doctors give ergotamine tartrate in doses of 2-4 mg by mouth in an attack and this is perhaps why some people find it an unsatisfactory drug.[39]

The immediate toxic effects of ergotamine tartrate are nausea and vomiting, and it is important that overdosage should not occur as these symptoms are very similar to those of an acute attack of migraine. The maximum dosage of ergotamine tartrate in any one week should not exceed 12 mg, and patients must know how much they are having. There are many different preparations of ergotamine tartrate and so many different names that patients are often unaware that they are taking the same drug in different forms. Cases where patients are taking up to 36 mg of ergotamine tartrate per week in three or four different forms are not unknown. Some patients take so much ergotamine tartrate that they suffer from continuous headache and nausea: then, because their "migraine" is so bad, they take more—and so the vicious circle continues.

Method of Administration

By Mouth.—Ergotamine tartrate tablets *B.P.* 1 mg (Femergin tablets) are probably the best form. Other tablets are Cafergot and Cafergot Q and Migril. All these tablets contain caffeine 100 mg in addition to the ergotamine tartrate, and, though there is some evidence that caffeine facilitates the absorption of ergotamine tartrate,[40 41] most people with a severe headache wish to lie down and go to sleep so therefore caffeine is best avoided. The dosage of ergotamine tartrate should be 1-2 mg; if this is exceeded nausea and headache are likely to be increased. Migril contains 2 mg of ergotamine tartrate and if more than one tablet is taken the side effects are likely to occur.

There is also some doubt whether tablets taken in the acute attack are properly absorbed. Cafergot Q tablets contain 1 mg of ergotamine tartrate and 100 mg caffeine. These tablets should be chewed, and absorption is then thought to take place through the buccal mucous membrane. Unfortunately these tablets are bitter to the taste and, though chocolate flavouring has been used to try and cover this, patients who are nauseated in the attack do not usually find this an acceptable form of medication.

By Suppository.—For a patient who vomits in the attack this is a satisfactory form of treatment as absorption from the rectum is good. Unfortunately Cafergot suppositories contain 2 mg ergotamine tartrate as well as 100 mg caffeine, 0·25 mg belladonna alkaloids, and 100 mg isobutylallyl barbituric acid, and it is difficult to divide the suppositories because they disintegrate easily. Nevertheless, many people find this is the best way of taking ergotamine tartrate, but difficulties may arise in patients who have diarrhoea as a symptom of their attacks.

By Inhalation.—Medihaler-Ergotamine vials contain a suspension of ergotamine tartrate, and the inhaler is calibrated so that each dose contains 0·36 mg ergotamine tartrate. This is rapidly absorbed, either through the buccal mucous membrane or through the highly vascular epithelium of the respiratory tract. It is an effective way of taking ergotamine tartrate because of the rapid absorption and the ease with which the dose can be adjusted. Often one or two inhalations will be enough (0·36 mg or 0·72 mg). Some patients do not find this an acceptable way of taking ergotamine tartrate, but for those who can use it the Medihaler is probably the treatment of choice, though recently some doubts have been cast on the safety of the propellants used in aerosols.[42]

By Injection.—Intramuscular injection of 0·25 or 0·5 mg ergotamine tartrate with an antiemetic such as 50 mg cyclizine lactate is probably the most effective means of treatment of a classical migraine attack. Our recent studies[38] have shown that this is an effective dose and that improvement will occur in two hours in over 90% of patients. Increasing the dose to 1 mg or more is unlikely to have any further effect on the headache and will increase the likelihood of nausea and vomiting. Though this is probably the treatment of choice, many people are unwilling to inject themselves.

Ergotamine tartrate in any form should not be used in pregnancy or in patients with severe cardiovascular disease.

DIHYDROERGOTAMINE

Dihydroergotamine may be given by mouth or by intramuscular or subcutaneous injection for an acute attack of migraine; 1 or 2 mg should be given by injection or 20-30 drops of the oral solution, but for an acute attack ergotamine tartrate is probably more effective.

Antiemetic Drugs

Many patients find that the nausea and vomiting which accompany an acute attack of migraine are as devastating as the headache itself, and it has been found that combining an antiemetic with ergotamine tartrate is an effective form of treatment. Cyclizine hydrochloride, 50 mg by injection (Valoid), thiethylperazine 5 mg (Stemetil), or other antiemetics can be used. Most of these substances are also available in suppository form.

Other Treatments

Several other drugs including sedatives and tranquillizers have been used in the treatment of an attack and are often effective if the patient is able to sleep.

External circumstances are important because any treatment is more likely to be effective if the patient is put in surroundings where external worries and noise are excluded. At the City Migraine Clinic the improvement rate in a classical migraine attack is over 90% in two hours even in patients who say that under other circumstances their headaches may last for 24-48 hours. This improvement rate is due partly to the treatment given—ergotamine tartrate and an antiemetic by an effective route (injection)—but also to the fact that patients are able to lie down in a quiet room where external stimuli such as light, noise, bustle, and worry have been eliminated as far as possible.