Drug Treatment of Disease

MIGRAINE: PART I*

BY

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The multiplicity of drugs used in the treatment of migraine is a measure of the ineffectiveness of each when used without discrimination. There is no symptom in which it is more necessary for the treatment to be tailor-made. Though the actual mechanism of an attack is understood (vasoconstriction during the premonitory symptoms and vasodilatation accompanying the pain), the switch which initiates the mechanism is far less clear. Indeed, it would appear that there are several possible switches. Allergy, cerebral oedema, autonomic imbalance, endocrine imbalance, physical or mental strain, or shock, fatigue, sudden sensory stimulation (for instance, by bright light), and water retention have all been incriminated. A family tendency is often manifest. A particular personality pattern is often, but not always, present; many sufferers are tense, overconscientious, meticulous, even obsessional, and, by reason of this, easily frustrated, resentful, and dissatisfied. Though it is extremely unlikely that migraine has ever a purely psychological origin, psychological factors are often prominent in the story, and it is certainly true that confidence in the physician and sincere co-operation in the patient are as important in treatment as drugs or hormones. Often the patient must be willing to make great adjustments in his way of life and even to alter sincerely held beliefs and ingrained habits. The patient demanding only a "wonder drug" will fail to obtain more than temporary relief.

It follows that, before the choice of drug is made, the personality of the patient must first be examined and his habit of life reviewed. The circumstances which tend to cause attacks must be studied. They are not necessarily common to any two patients, for situations which are stressful to one may be calming to the other. Sailing a small boat in a rough sea or climbing a difficult rock peak may bring to the one peace of mind and a cessation of attacks, to the other terror and precipitation of pain. Such studies are possible only to the family doctor, for they require months or years to complete and are beyond the scope of the consultant. The latter may at times be useful in confirming the diagnosis and eliminating other causes of cranial pain: the treatment must remain with the constant medical attendant. Apart from the advice which he can give on work and play, on the avoidance of harmful stress and on submitting gracefully to the inevitable, on the diet when this appears to be unsuitable, an embarrassing richness of drugs lies at his disposal.

DRUGS TO REDUCE FREQUENCY AND SEVERITY OF ATTACKS

1. Ergotamine and Its Preparations

Ergotamine tartrate ("femergin," "gynergen"). $(C_{33}H_{35}O_5N_5)_2,C_4H_6O_6$, is an alkaloid obtained from a fungus, ergot of rye (*Claviceps purpurea*), the pharmacology of which is too well known to need description here. It is effective in migraine by reason of its vasoconstrictor effect. It is probable that its effect is potentiated by the addition of caffeine, as in "cafergot," in which 1 mg. of ergotamine tartrate is mixed with 100 mg. of caffeine. In "migril" 2 mg. of ergotamine tartrate is mixed with 100 mg. of caffeine and 50 mg. of cyclizine hydrochloride, an anti-emetic.

Ergotamine tartrate, whether for prophylaxis or for the treatment of acute attacks, should be avoided: (1) In the presence of peripheral vascular disease, hypertension, and coronary disease. It should be used with great caution in all elderly patients. (2) In pregnancy, when, however, dihydroergotamine, which has only a very slight oxytocic effect, may be given instead, at any rate until the seventh month. (3) In thyrotoxicosis, in which it is unwise to add to the circulatory strain already present. (4) In gross sepsis, hepatic and renal disease, and anaemia.

Ergotamine tartrate may be given by injection, by mouth, or by suppository. None of these can safely be given for prolonged prophylaxis, but they may be useful in aborting the expected attack. Patients frequently know in what circumstances an attack is likely to develop—the interview, the board meeting, the first night in the theatre, the first class at the beginning of term. An injection of 0.25 to 0.5 mg. given the night before is often effective. Some patients prefer dihydroergotamine methanesulphonate 0.75–1 mg. Suppositories are often equally effective (e.g., cafergot suppositories). Tablets are the least effective form of therapy, but are occasionally satisfactory in the occasional patient, either alone or combined with caffeine. The maximum initial dose is three tablets, and not more than 10 should be given in the 24 hours preceding the expected stress.

Toxic Effects.—Prolonged prophylactic treatment with ergotamine is fraught with danger. It is capable of producing such prolonged vasoconstriction that thrombosis and gangrene occur. Graham (1956), in his excellent book *The Treatment of Migraine*, gives an impressive list of toxic effects which have been reported: muscle cramps, joint pains, paraesthesiae, cold extremities, intermittent claudication, raised blood pressure, pulselessness, pallor, cyanosis, thrombophlebitis, peripheral arterial thrombosis, gangrene, precordial pain, abdominal pain, coronary infarction, and cerebral thrombosis. None of these sequels is likely to follow the occasional prophylactic use of ergotamine.

The acute toxic effects are likely to be more difficult to control. In some patients, they are less likely to occur when dihydroergotamine methanesulphonate is used, even though twice the dosage may be needed. Whichever preparation is given, a dose high enough to stop the headache commonly causes nausea and vomiting. These side-effects may sometimes be prevented by giving dimenhydrinate ("dramamine")

*Part II, with list of references, will be published next week.

or chlorpromazine ("largactil"). Prednisolone (5 to 25 mg.) given before the ergotamine may be highly effective, relieving not only the nausea but the prostration of the attack if it is not altogether prevented.

2. Diuretics

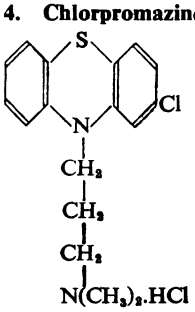
The administration of these drugs is undoubtedly a most useful prophylactic measure in patients whose attacks seem to be related to water retention. Urea is the most useful diuretic, because it retains its efficacy and may be administered for life if necessary. It is best given in doses of 10–20 g. three times a day after food, dissolved in a little hot water flavoured with lime juice.

Urea (or carbamide, $CO(NH_2)_2$) is a natural product of the metabolism of protein and is completely without toxic effect. It often reduces the incidence of attacks of migraine and in occasional cases altogether prevents them. It is a much-neglected remedy.

3. Carbachol

Carbachol, *B.P.* syn. carbamylcholine chloride, $[H_2N.CO.OCH_2.CH_2.N+(CH_3)_3]Cl-$ ("moryl"), is a cholinergic drug, and the rationale of giving it between the attacks is obscure. Yet its value is attested by several authors and by my own experience. It is given in a dosage of 2 mg. three times a day, and in some patients undoubtedly increases the intervals between attacks. It is contraindicated in the presence of cardiac failure and peptic ulcer.

4. Chlorpromazine



The main use of chlorpromazine (largactil) is to offset the toxic effects of ergotamine tartrate. 25 mg. should be given by mouth or by injection a quarter to half an hour beforehand. It can also be given as a suppository of 50 mg. Its use in acute attacks will be described later. "Stemetil" is a chemically related proprietary remedy which has not yet had an extended trial. As a prophylactic 10 mg. is given morning and evening.

(To be concluded)

What vaccinations do you need to travel abroad? The answer is to be found in the new publication of the World Health Organization (W.H.O.), *Vaccination Certificate Requirements for International Travel*, which lists the vaccinations imposed or recommended by some 180 countries and territories from Aden to Zanzibar. Land, sea, and air travel around the world comes under the International Sanitary Regulations promulgated by W.H.O. in 1952. Their aim is to ensure maximum security against the international spread of disease with minimum interference with world traffic. Under these regulations, certificates of vaccination against only three diseases—cholera, smallpox, and yellow fever—may be required. The necessity for one or more of these vaccinations varies according to the country from which the traveller comes and the itinerary he intends to take. The now famous yellow booklet of vaccinations, "The WHO International Certificate of Inoculation and Vaccination," has become as important for the traveller as his passport.

A FOETAL TISSUE BANK

PROBLEMS AND PROSPECTS

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Two of the most fruitful branches of recent research have been concerned with tissue-transplantation immunity and with the effects of radiation on the body. Where these have overlapped there has developed the study of bone-marrow replacement, which, in this new age of radiation, is of obvious practical importance. It is hoped that by transplantation of fresh marrow cells after massive accidental irradiation lives may be saved and, in a similar way, that the scope of high-dosage radiotherapy could be extended.

At an early stage it became apparent that, for donor material, foetal cells might hold definite, even decisive, advantages over adult cells but that other factors might counterbalance these (see Table). Clearly more information was required.

Immunological Considerations

It can be stated as a principle that grafts of living cells exchanged between unrelated members of a species are destroyed after a short interval by an immune response of the host's lymphoreticular system—the homograft reaction. The main exceptions to this rule occur where either the graft is "insulated," as in the cornea, or where the host's immune system is ineffective

Advantages and Disadvantages of Foetal and Adult Haemopoietic Cells for Transplantation

	Adult	Foetal
Quantity	Unlimited. (1) Donor (2) Cadaver	Limited
Quality:		
Activity	Normal adult proportions	Erythro > thrombo > leucopoietic
Stem cells	Low proportion	High proportion
Lymphoid cells ..	Small numbers in marrow	Precursors accompany haemopoietic cells in spleen and ? liver
Tolerance:		
Of graft by host ..	Normal homograft reaction unless modified by radiation, etc.	Homograft reaction possibly slightly delayed
Of host by graft ..	Seldom achieved. Usually "secondary disease"	Better than adult but sometimes "secondary disease"
Genotype availability	Wide range available either (1) fresh from donors or (2) stored from cadavers	Limited to stored tissue

owing to immaturity (in the foetus), disease (agammaglobulinaemia), or damage (irradiation, nitrogen mustards, etc.).

The dose of whole-body radiation needed to suppress the immune mechanism is very high, exceeding the dose which, without marrow replacement, would be fatal. With doses in this range, therefore, marrow replacement becomes simultaneously both possible and essential to survival. This is the basis of bone-marrow replacement therapy. After marrow-assisted recovery a rather complicated situation may develop. The following