MIGRAINE IN A RURAL PRACTICE (1958–1963)

A five-year study of a controlled clinical trial

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"IF ONE should search for a human ill which has manifest itself most widely during all times and among all peoples, there can be little doubt headache would achieve this undesirable distinction" (A. H. Riley, 1932). According to Riley, Aretaeus of Cappodocia, at the end of the first century A.D., isolated from the general group of headaches a type distinguished by its paroxysmal nature, its severity, its one-sidedness, and its association with nausea, the crises of pain being separated by intervals during which the patient is free from all discomfort. About half a century later Galen introduced the term 'hemicrania'. During the following centuries the word was gradually modified to include 'hemigranea', 'emigranea', 'migranea', 'megrim', and finally 'migraine'.

Clearly migraine is one of the oldest described conditions, and yet today no satisfactory treatment has been found. Even the incidence of migraine has been difficult to establish, and there is a wide variation recorded in the literature. Sweetnam (1962) in a survey of 150 practices reports an incidence of 0.4 per cent. Childs and Sweetnam (1961) found an incidence in a factory population as high as 18 per cent. Other workers like Lennox (1941) report 3.5 per cent; Fry (1955–56) 3.5 per cent; Walker (1959) 4.85 per cent; Grimes (1931) in America, 8 per cent; and the *Journal of American Medical Association* (1955) reported 10 per cent. In this practice, which is largely a rural one, 92 cases were found over a period of five years (1958–1963). This represents an incidence of 0.89 per cent. There are a number of reasons for this variation of incidence, the chief being that different methods of finding cases have been used; and the fact that there must be a group of migraine sufferers who have accepted this malady as incurable and have long since given up seeking treatment.

Although migraine has been recognized for such a long time and no effective treatment or prophylactic has been found, it has not

been neglected. Friedman and Sheldon (1961) have reported that over 400 prophylactic treatments have been described, such as UML-491, Friedman and Sheldon (1961); reserpin and phenobarbitone and placebo, Grahame (1960); methyltestosterone, Moehlig (1955); psychotherapy, Hunter and Ross (1960); surgical procedures, Knight (1962); urea and other diuretics; antihistamines: chorionic gonadotropin, Leyton (1943); use of histamine, Horton (1941); prostigmine, Pelner and Aibel (1942). Of all these perhaps the discovery of ergotamine in 1928 has been the most important.

While no completely satisfactory treatment or prophylactic has been found the mechanism of the migraine attack is now fairly well understood. This is chiefly due to the work of Goltman (1935–36) and the work of Wolff (1948) and others in the U.S.A. That is, the prodromal symptoms are due to vasoconstriction of the extracranial branches of the external carotid artery and " the intense headache phase " is due to vasodilatation of these arteries. Wolff has shown that the intense pain is due to the stretching of nerve endings in the arterial wall. What is still elusive is the precipitating mechanisms or factors. It has been postulated that there is a hereditary or personality diathesis and this, when combined with certain conditions or stimuli, produce the attack. These conditions may include " allergy, cerebral oedema, autonomic imbalance, physical and mental strain, shock, fatigue, sudden sensory stimulation, and water retention " (Graham, 1962), and possibly some endocrine imbalance.

This paper is the result of a five-year study of 92 cases of migraine who were found in this practice. The migraine syndrome was defined as the periodic headache, usually unilateral in onset but which may become generalized. The headaches are usually associated with nausea, irritability, photophobia, vomiting, scotomas, hemianopia, unilateral paraesthesia and speech disorders. There were 30 male and 62 female cases giving a male to female ratio of approximately 1:2. This group was compiled by a search through the case records of the practice, and by my two partners referring all cases of migraine to me. Of this group, the first 48 patients (22 male and 26 female) were subjected to an uncontrolled trial of two drugs, chorionic gonadotropin and prostigmine bromide. The details of these treatments are set out later. The results from this trial were so encouraging that a further group of 44 patients (eight male and 36 female) were subjected to a double-blind trial using the same drugs and the same dosage.

In the first part of this study a search was made for any common factor(s) in the total group of 92 patients which might support the hypothesis that there exists a hereditary or personality diathesis and this, when combined with certain conditions or stimuli, produces the attack.

The second part deals with the results of treatment in the two trials.

Description of patients

Age at onset. The greatest number of cases (36 per cent) had their first attack in the age group that includes puberty, and the next largest group was the 20–30 year range, so that 72 per cent suffered their first attack before 30 years of age. The average age of onset was 25 years, and this compares with Sweetnam and Child's figure of 23 years, which they found in their migraine survey of a factory population (table I).

TABLE I
AGE AT ONSET OF MIGRAINE

Age groups	*Number*
0—10 ..	11 cases
11—20 ..	33 „
21—30 ..	24 „
31—40 ..	15 „
41—50 ..	7 „
51—60 ..	1 „
60 and over	1 „
Total	92

Family history of migraine. It has been thought from time to time that migraine might be familial, and so those migraine sufferers who had a family history of migraine were compared with a control group of 92 non-migraine patients who were matched for age and sex (table II).

The proportion of migraine sufferers who had a family history of migraine (53 per cent) was similar to that found by Walker (55 per cent) in his survey. The incidence was almost five times greater in the migraine group than in the control group, this being comparable to the ratio of six found by Sweetnam (1961).

Travel sickness. The possible connection between travel sickness and migraine was studied by contrasting with the incidence of the former in the control group with that in the migraine group (table III).

There appears to be no great difference between the two groups. This result is very different from that of Sweetnam (1961) who found

TABLE II
NUMBER WITH A FAMILY HISTORY OF MIGRAINE

Group	*Men*	*Women*	*Total*
Migraine	14	35	49
Control	3	7	10

TABLE III
NUMBER OF PATIENTS WITH TRAVEL SICKNESS

Group	*Male*	*Female*	*Total*
Migraine	6	26	32
Control	6	15	21

that the incidence of travel sickness amongst migraine sufferers, was nearly four times as great as for non-migraine patients.

Exciting factors of attack. In almost all the cases the patients themselves had long decided what the factor was which initiated the attack (table IV).

Emotion and menstruation are by far the chief " initiators " in the opinion of the sufferers.

TABLE IV
PRECIPITATING FACTOR

Emotion	40
Menstruation	38
Travel	8
Food, fat, chocolates, etc.	8
Alcohol	7
Lying in bed	4
Fatigue	4
Bright light	3
Reading	2
Sitting in draught ..	1
Stooping	1
Dusts (including Hay Fever Time)	1

Hypertension. There is some evidence in the literature of a possible connection between migraine and essential hypertension. Taking as the high level of normal a systolic of 150 mm. Hg. or over, and a diastolic of 100 mm. Hg. and over, the migraine group were compared with the control group and it was found that 14 in the migraine group and 16 in the control group suffered from hypertension. The difference between these two groups is therefore negligible. Gardiner (1940) stated that 80 per cent of hypertensive patients gave a migraine history, and Walker (1959) stated that of the total registration at the Mayo Clinic migraine was five times as frequent in hypertensive patients as those in whom hypertension was not recorded.

Migraine personality. The migraine personality takes the form of being unusually ambitious and preoccupied with achievement and success. Sufferers are tidy and meticulous, and always striving after perfectionism and efficiency. They live all the time worrying about the next attack, that it might come when they have some important business or social engagement. Quite a number feel intensely well the day before an attack, and often say that they could " clean the house from top to bottom ". They learn to regard this feeling of exhilaration ominously. Hunter and Ross (1960) said it was more important to ask " who or what is you headache rather than when or where ". Table V shows that this type of personality was found almost three times as often in the patients who suffer from migraine.

TABLE V
NUMBER POSSESSING A
' MIGRAINE PERSONALITY '

Group	*Male*	*Female*	*Total*
Migraine	16	41	57
Controlled	4	16	20

Clinical trials

The second part of this study deals with two clinical trials. Because

there was a seemingly large number of patients who alleged that their migraine began around puberty; or that there was a very definite connection with menstruation; or that the attack ceased during pregnancy or began afterwards; also because a number of patients gave a history of an allergic diathesis either for themselves or in the family history, it seemed reasonable that migraine might have a hormonal or allergic element in its make up. This idea is not new, for Leyton (1955) described this theory and its practical application consisted of the combined treatment with regular injections of chorionic gonadotropin and oral administration of prostigmine bromide. Patients therefore received treatment by both routes.

Scheme of dosage (Leyton's scheme modified)

(A) Chorionic gonadotropin (Antuitrin 'S'—Parke, Davis & Co.)

Patients start with a test dose of 50 units to discover if there is any sensitivity. Occasionally a migraine attack is precipitated, sometimes patients complain of an itchy area at the site of injection, and sometimes they claim a feeling of elation which lasts for 24 hours following injection, but in nearly all cases the upper limit of dosage, i.e. 950 units, can be reached without any side effects. Two days after the initial dose, providing no reaction has occurred, a second dose of 100 units is given. After this the dosage is increased by 100 units at twice weekly intervals until 500 units are being given twice a week. This dose is maintained for two weeks, when the frequency is reduced to once weekly (500 units) for a further two weeks and then a final dose of 950 units is given a fortnight later. This completes the full contents of the original ampule.

(B) Prostigmine (Pelner and Aibel, and modified by Leyton)

Before starting desensitization by prostigmine it is necessary to determine any sensitivity to this compound by carrying out a histamine intradermal test. If the intradermal test is negative, then the patient is started on a prostigmine desensitization course; if there is a positive reaction, then the condition is likely to be a 'histamine headache' and desensitization by histamine is indicated. The regime is that a 15 mg. tablet of prostigmine bromide (Roche) is dissolved in 1 oz. of water (Aqua Chloroform is added as a preservative). The dosage scheme is one drop of this mixture taken in water three times the first day; thereafter the dose is increased by 1 drop per dose per day, i.e. 2 drops three times the second day, 3 drops three times the third day, until a total of 50 drops is being taken three times a day. The dose is maintained at this level for a further two weeks, when it is reduced to once daily, and kept at this level for two months. It is very necessary to impress on the patient the need for keeping a personal record of the dosage each day. There can be side effects to this drug, i.e. exacerbation of headaches, giddiness, occasional faintness, dryness of the mouth, and nausea. When this occurs it is necessary to keep the dosage within the range of tolerance.

Uncontrolled trial

An uncontrolled trial was started on the first group of 48 patients. These patients were subjected to a six-month follow-up and only those who had no further attacks at the end of the six-month period were claimed as 'cured', because as Graham (1956) has pointed out "migraine is notorious for responding temporarily to any new or encouraging form of therapy". Among the 48 patients, 23 were

cured, 13 showed improvement, and 12 were not improved. This was very encouraging, but because migraine is a psychosomatic disease it is essential that in any attempt to assess the effectiveness of these drugs, the technique of a double-blind trial, with full statistical control, be followed.

Controlled trial

A controlled trial was therefore carried out on a second group of 44 patients according to the following scheme:

> If A = Antuitrin 'S', P = Prostigmine, and O = Placebo then four combinations are possible. That is, A+P; P+O; A+O; and O+O.

This group of patients was divided into four sub-groups of 11 patients each, using a key which was known only to my partner. By using 44 cards from a pack, 11 cards from each suit, and each suit representing a 'treatment' combination, patients were randomly allocated to the four treatment groups. I 'applied' to my partner for the actual material, i.e. 'injection and drops' which he prepared from the above plan. I carried out the course of treatment. As in the first trial, a six-month follow-up was carried out and only those who had no attacks were regarded as cured.

The results of this trial are shown in table VI.

TABLE VI
RESULTS OF CONTROLLED TRIAL

Treatment	*Cured*	*Improved*	*Not improved*	*Total*
A + P	3	6	2	11
A + O	4	5	2	11
O + P	5	5	1	11
O + O	6	3	2	11

Hence the double-placebo produced results at least as good as any of the other treatments, the difference between treatments being not statistically significant.

Factors affecting the outcome of treatment

It is interesting to compare the overall results of the controlled trial with the uncontrolled trial, and as the difference between treatments in the controlled trial is not statistically significant it would seem valid to combine them all and compare with the uncontrolled trial. These are set out in table VII.

It can be seen from this that the trials differ little in result ($P < 0.20$) although only in the uncontrolled trial did all patients receive what might have been thought the best treatment. This, together with the

fact that the controlled trial showed no significant treatment difference, implies that the cures must be explained by the process of treatment and not by any activity of the drugs. Sex did not appear to affect the outcome of treatment as far as can be seen from the uncontrolled trial. It is unfortunate that in the controlled trial there were so few males, this being the manner in which they were discovered, but the proportion of cures was virtually the same for each sex.

TABLE VII
COMBINED RESULTS OF CONTROLLED AND UNCONTROLLED TRIALS

	Cured	*Improved*	*Not improved*	*Total*
Controlled trial	19	18	7	44
Uncontrolled trial	23	13	12	48
Totals	42	31	19	92

Analysis was directed to see how far the chance of success varied according to such factors as age, blood pressure, and medical treatment. Of these only the age factor seemed to be significant.

TABLE VIII
EFFECT OF AGE ON TREATMENT

		Uncontrolled trial			*Controlled trial*		
		Cured	*Not cured*	*Total*	*Cured*	*Not cured*	*Total*
Age	Under 40	18	12	30	15	12	27
	40 and over	5	13	18	4	13	17
Totals		23	25	48	19	25	44

In both trials, a higher proportion of younger people are shown as cured, and by combining figures in the above table, the association between age and outcome is statistically significant ($0.01 < PC < 0.025$)—table VIII.

So it can be said that in the clinical trials the process of treatment is more important than the activity of the drugs, and that more younger people are cured than older people.

Discussion

The first part of this paper deals with the search for any common factor(s) which might be found in the 92 cases of migraine sufferers and which would support the theory of hereditary or personality diathesis. While no common factor has been found, there are four

aspects which might be of significance. Firstly, the average age of onset of the malady is found to be 25 years, which is comparable with Sweetnam and Child's figure of 23 years. This could have some significance because Wolff (1948) has said that the personality features and reactions dominant in individuals with migraine are feelings of insecurity with tension which expresses itself as inflexibility, conscientiousness, meticulousness, perfectionism, and resentment. This feeling of insecurity *begins early in childhood*, and the individual aims to gain approval by working hard and being very conscientious. Repeated frustration, and anxiety in trying to achieve perfection, leads to fatigue prostration, and this produces the tension and the setting in which the migraine attack occurs. So it could be, with a childhood complex of insecurity and the repeated episodes of frustration, that the first migraine attack takes place around 25 years of age.

Secondly, it has been shown that a family history of migraine in migraine sufferers is about five times commoner than in non-migraine sufferers.

And thirdly, that there is a ' migraine personality ', and it is approximately three times as common in migraine sufferers as in non-sufferers.

Lastly, ' emotional causes ' and menstruation compose the biggest group of ' causes of migraine ' as believed by the sufferers. These findings would encourage the view that there is a large psychological element in the disease which is based on hereditary and personality traits.

The second part of this paper concerns the drug trials, and this shows that the results of the uncontrolled trial and the controlled trial do not show any significant difference, and similarly when the controlled trial is examined it shows that there is no essential difference between the effectiveness of any one treatment over any other. In other words, it can be said that the cures and improvements effected have been due more to the process of treatment rather than to any activity of the drugs concerned. As stated, there was a six-month follow-up in all cases, but since the earliest cases were treated as long ago as five years it is interesting that in the uncontrolled trial 19 of the 23 cases who were treated between 1958–1961 and ' cured ', still remain cured. In the controlled trial 16 of the 19 ' cured ' cases still remain free from attacks for 2–3 years. This includes the case of a woman who had attacks every six weeks for 12 years, and who was treated with placebo. She has not had an attack for 2½ years. Another woman who had an attack with each menstruation for six years, treated with placebo, has not had an attack for three years.

The paper by Hunter and Ross, *Psychotherapy in Migraine* (1960)

is very interesting when compared with the results of the drug trials in this paper. Hunter and Ross saw their patients for psychotherapeutic interviews on average two or three times during the first month, and then follow-up visits at monthly or six-weekly intervals for the period of six to 12 months. In this trial the patients had to report for injection twice a week, then once a week, and then twice a month—a period of three months during which they had the opportunity of discussing the state of their migraine which would have conferred a psychotherapeutic benefit. It is in this way that the process of treatment was the effective agent in producing cures and not the therapeutic activity of any of the drugs, and this 'process of treatment' was more successful in the younger patients. This might mean that the condition is less psychologically 'fixed' in the younger patients. The findings in the second part of this paper would also support the theory of the large psychological element involved.

From these studies and investigations there seems to be some ground for believing that a hereditary and personality diathesis does exist, and that the treatment which would offer most hope of a cure lies in the psychotherapeutic field.

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