

MIGRAINE IS AN ALLERGIC DISEASE
ALBERT H. UNGER, M.D., AND LEON UNGER, M.D.
CHICAGO, ILL.

MIGRAINE has been a problem disease throughout the 5,000 years during which it has been recognized. Many theories have been advanced to explain the peculiar and characteristic events which constitute the syndrome known as migraine. The picture has been further confused recently by emphasis on syndromes having only some of the characteristics of true migraine; these are known as "migraine variants" and "migraine equivalents." In this review, we shall consider only true migraine, defined as follows:

Migraine is a syndrome, usually hereditary, characterized by periodic unilateral headaches, with complete freedom between attacks. Attacks are often preceded by an aura (most frequently visual) and associated with nausea, with or without vomiting. In our opinion, migraine is an allergic disease.

Migraine has been recognized since 3,000 B.C. Among early contributors were Aretaeus, Galen, Caelius Aurelianus, Tissot, and Brinton. Liveing published an entire book upon the subject in 1873.²³ In the same year, Latham²² first suggested the modern theory of mechanism. LaRoche, Riche, and St. Girons²¹ and Brown⁴ suggested allergy as a cause of migraine. Vaughan²⁹ obtained good results with elimination diets. Many others have since repeated his work. Wolff³³ and his co-workers have performed most of the monumental experimental work upon which the present-day theory of mechanism is based. Goltman¹¹ proved that cerebral edema occurred during attacks of migraine (induced by wheat).

The accepted theory of mechanism of migraine was worked out primarily by Wolff.³³ Prodromal symptoms are due to cerebral vasoconstriction. This is demonstrated by clinical experiments in which vasodilating agents such as amyl nitrite caused temporary abolition of scotomata (with no change in blood pressure).

The headache pain is due to dilatation of branches of the external carotid artery. This is based upon a series of experiments: Pool and Nason²⁵ showed that ergotamine tartrate in animals caused vasoconstriction of arteries of the dura, rather than the pia or the brain surface. Graham and Wolff¹³ then proved that diminution in pulsations of the temporal and occipital arteries closely paralleled relief of migraine pain (by ergotamine tartrate). During migraine, the superficial arteries of the affected side are more prominent than contralateral vessels. Also, ligation of these arteries leads to temporary obliteration of certain pain areas.

Pressure on the common carotid on the affected side relieves the headache; contralateral pressure may increase it. Intensity of pain is not related to changes in cerebral veins. Any measure which reduces cranial arterial pressure will

TABLE I. FAMILY HISTORY OF MIGRAINE AND OF OTHER ALLERGIC DISEASES

	NUMBER OF PATIENTS	MIGRAINE		OTHER ALLERGIES	
		POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Migraine only	23	13	10	12	11
Migraine and other allergies	32	13	19	24	8
All patients	55	26	29	36*	19
*Other allergies—Incidence:					
				22	
				17	
				7	
				4	
				3	
				3	

lower pain intensity. Goltman has shown that cerebral edema is present during migraine; it appears and subsides synchronously with the pain. This edema links migraine to other allergic diseases, in which edema is a main feature.

Continued dilatation of cerebral arteries leads to actual edema and thickening of the arterial walls; this explains the ineffectiveness of ergotamine in late stages of an attack. Associated with the headache proper is painful contraction of head and neck muscles; this ache may persist after the migraine itself has subsided.

Positive family history of migraine has been reported in over 60 per cent if migrainous patients; high family incidence of other allergic diseases has also been reported. Our figures are shown in Tables I and II. Our statistics are biased by the fact that many patients came to us for treatment of other allergic diseases; therefore, family incidence of other allergic diseases is unexpectedly high.

Allergy to foods has, in our experience, been the prime precipitating cause of true migraine. Patients who have frequent attacks (more often than every six weeks) are usually sensitive to foods eaten in some form almost daily. It has been known for centuries (and never properly explained) that, after a migraine, there is a latent period during which no ill effects follow stimuli which ordinarily cause attacks. Because of this, such everyday foods as milk or wheat may cause headaches as infrequently as once or twice a month. The following case is an example of this:

CASE 1.—Miss E. H., a 33-year-old, white, medical secretary, had sick headaches for 18 years. They now occur every 1 to 2 weeks. She develops increased appetite shortly before onset of pain. Pain is mostly over right eye, severe and throbbing. Nausea and vomiting

TABLE II. OTHER ALLERGIES IN 55 PATIENTS WITH MIGRAINE

None	22
Present	33
Hives	18
Hay fever	13
Perennial allergic rhinitis	12
Bronchial asthma	8
Gastrointestinal allergy	5
Nasal polyps	3
Atopic dermatitis	1

follow two hours later, although she does not vomit with every attack. Spells last 24 to 48 hours. No association with menses. They occur often on week ends and frequently follow aggravation. Past history noncontributory. Complete previous examinations of eyes, ears, nose, and throat were normal. Blood pressure remains normal during attacks. Sugar did not relieve the headaches. Complete physical examination, urine, blood count, and Kahn test revealed no abnormalities. Previous ineffective medications include sedatives, bromides, antihistaminics, vitamins, nicotinic acid, methyl testosterone, ergotrate maleate, Gynergen, Beller-gal, nitroglycerine, caffeine, and thiamine. Cafergot gave slight relief.

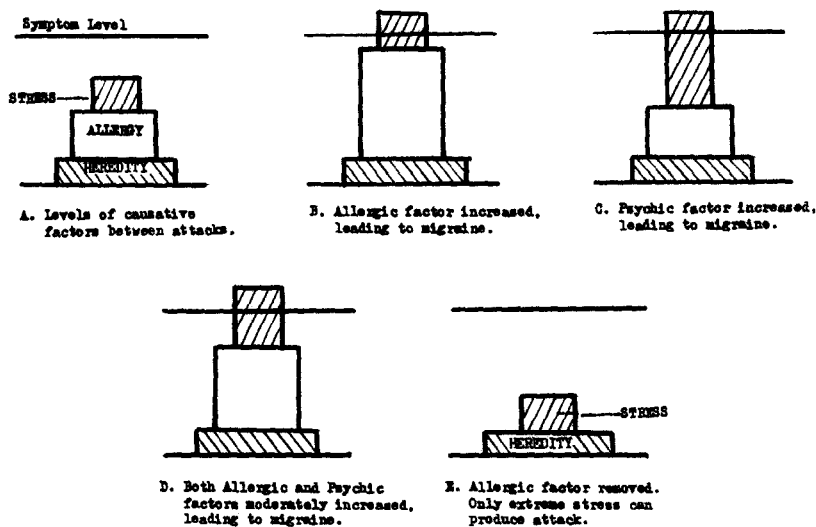


Figure 1. Relation of Allergy and Stress to Migraine attacks.

The patient rarely drank milk, because it usually gave her diarrhea. Because of this, she was placed on a milk-free diet; one week later, she was given a milk feeding test, consisting of two feedings of milk, one hour apart. A leukopenic index done at this time had equivocal results, with white cell counts (at 20 minute intervals) of 7,150, 8,750, 7,850, 6,700. Two hours after the second feeding of milk, she developed the worst migraine she has ever had, with severe pain, primarily on the left side, and vomiting which persisted for twelve hours steadily. The headache lasted over a period of 36 hours.

She was maintained on a milk-free diet during succeeding months. Her attacks of migraine have disappeared completely, although she has had mild generalized tension headaches on occasion. Pork gives her a slight headache and nausea if she eats it in large quantities. Despite the fact that she has remained at the same job and under the same stresses, she has had no migraine attacks for almost two years.

Chocolate is the most common cause of migraine, but most patients sensitive to it only find out for themselves and never consult a doctor. Patients who have attacks at long intervals usually know they are due to an obvious or exotic food. Other authors have reported cases of true migraine due to inhalant allergens; we have seen none of these. Table III lists the proved causes of migraine in our patients.

Some attacks of migraine follow unusual mental strain or psychic trauma; they occur either during the stress period or upon relaxing afterward. Attacks of any other allergic disease (i.e., hives, asthma, atopic dermatitis) may also

TABLE III. FOODS KNOWN TO CAUSE MIGRAINE (45 PATIENTS)

Milk* †	15	Fruits	7
Chocolate†	14	Apricots	
Wheat†	10	Raspberries	
Pork†	8	Watermelon	
Other meats	2	Prunes	1 each
Egg†	2	Apple	
Fish	2	Citrus fruits	
Shellfish	2	Pears	
Coffee	2	Miscellaneous	9
Vegetables	14	Chicken	
Peanuts	3	Corn	
Onions	2	Root beer	
Celery	2	Molasses	
Potato		Pistachio	1 each
Tomato		Caraway seed	
Soybeans		Sugar (beet, cane, corn)†	
Peppers	1 each	Garlic	
Asparagus		Yeast	
Endive		Liquor (?)	2
Broccoli family		Medicines (?)	2

*Patients sensitive to milk are also sensitive to the common forms of chocolate because they contain milk.

†Only these foods were sole causes of migraine; all others were instances of multiple causes in individual patients.

follow periods of stress. The mechanism of this relationship between psyche and allergy is shown schematically in Fig. 1. Here we note that either psychic or allergic stimuli or a combination of both can precipitate clinical symptoms. When allergy is completely controlled, it is very difficult, although not impossible, for psychic stimuli alone to provoke symptoms. This can also be reversed to explain the good results sometimes achieved by psychotherapy. The analogy can be extended to other allergic diseases, although the psychic factor is variable in importance. Other factors can also be added, particularly the endocrine, to explain the premenstrual migraines.

Thus, we do not deny that psychic factors are important in migraine. They are not, however, the prime factor, although they may be the most obvious. Control of allergic factors will, in most patients, completely control symptoms (vide infra). Migraine should not be labeled a "psychogenic" disease, nor should the patient be considered "psychopathic."

Other contributory factors include visual defects (of minor importance) and endocrine factors. Most women have attacks with menstruation; they usually

TABLE IV. AURA WITH MIGRAINE HEADACHES
(55 Patients)

<i>Aura present:</i>	34
Visual	21
Fatigue	9
Excess energy	3
Heaviness head & neck	5
Irritability	2
Sneezing	2
Urinary frequency	1
Nausea	1
Yawning	1
<i>Aura absent:</i>	21

TABLE V. SEX AND AGE AT ONSET OF MIGRAINE
(55 Patients)

AGE	MALE	FEMALE	TOTAL
5 - 9	3	10	13
10-14	2	7	9
15-19		8	8
20-24	4	12	16
25-29	1	5	6
30-34	1	2	3
Total	11	44	55

lessen during pregnancy and after menopause. The reason for this is not known, although water retention associated with premenstrual tension may be a factor. True migraine occurs at other times and in both sexes.

SYMPTOMS

The headache is classically unilateral, throbbing, and severe. In later stages, it may become generalized. Periodicity is the most constant feature of the disease. There are no symptoms between attacks, unless the patient also has tension or other types of headaches.

An aura precedes the headache in about 50 per cent of patients (see Table IV). It is variable in type and severity. The classical prodromata are visual, including blurring of vision, scintillating scotomata, etc. Photophobia or other visual symptoms often accompany the headache. Other aura include malaise or excess energy, tinnitus, polyuria, anorexia, etc.

Nausea is a very common feature of classical migraine, leading to the old name "sick headache." The nausea usually appears at the height of the pain; if vomiting follows, the headache is frequently relieved thereafter. However, these features are not diagnostic of migraine, since nausea may follow any severe and prolonged headache.

Sensory disturbances sometimes occur, either as an aura or as part of the headache. Paresthesias are the most common. Motor disturbances such as temporary paralyses are infrequent; of these, ophthalmoplegic migraine is the best known.

Laboratory findings have shown no consistent abnormalities. Tests done included urine analyses, blood counts, blood chemical studies, gastric analyses, spinal fluid examinations, retinal and visual field examinations, blood pressures and x-rays of the spine and skull. It is essential that every migraine patient have a thorough eye examination by a competent ophthalmologist. This is one method of ruling out such conditions as brain tumors.

Women are affected about four times as frequently as men (see Table V). The onset of the disease is surprisingly early, as shown in Table V. There is also evidence that cyclic vomiting may be the infantile form of migraine.³⁴ Symptoms often lessen or disappear after the climacteric in both sexes. At this time, some patients lose their headaches, but retain the aura.

TABLE VI. DIFFERENTIAL DIA.

	INCIDENCE	AGE AT ONSET	FREQUENCY OF ATTACKS	DURATION OF ATTACKS	INTENSITY	TYPE OF PAIN
Migraine	Common	Children or young adults	2/week to one per year	Usually 12-36 hrs.	Moderate to severe	Usually pulsating
Histamine Cephalalgia	Uncommon	30-40 yrs.	Several daily or skip mos.	15 min. to few hours	Short, severe	Sharp, throbbing
Tension (Nervous)	Very common	Adults, usually	Variable; often daily	Variable	Variable, usually not severe	Dull, aching, steady may be band around head.
Sinus (Nasal)	Common	Any	May be daily	Several hrs; may be all day	Mild to moderate	Aching or drawing. Frontal in A.M. Antral in mid-aft.
Eye strain	Common	Any	May be daily	Until pt. rests eyes	Mild to moderate	Dull; follows over-use of eyes; esp. midday
Hypertension	Common	Usually 35-60	Variable, often daily	Several hours	Moderate	Dull, aching, esp. in A.M. may follow stress.
Brain tumor	Uncommon	Adults	Variable	Variable; short at first	Moderate; becomes severe	Steady dull ache; deep; worse in A.M.
Subdural Hematoma	Uncommon	Any	Becomes continuous	Steady	Becomes severe	Dull, diffuse ache; may pulsate
Temporal Arteritis	Very rare	Usually 50-70	Almost continuous	May last 1-20 months	Moderate	Throbbing at first; localized; later dull

DIFFERENTIAL DIAGNOSIS

It is important to differentiate migraine from other headaches although it may sometimes be surprisingly difficult. Table VI differentiates the common types of chronic headaches. Missing from this table are menstrual headaches, which are characterized by their occurrence only before or with the menses. True migraine occurs also at other times and in both sexes. We admit that the headaches are at times otherwise identical.

Table VI also omits acute headache such as those due to subarachnoid hemorrhage or to infectious diseases, and those syndromes with constant and typical characteristics; these include trigeminal neuralgia and sphenopalatine ganglion syndrome ("lower half headache"). In Table VI the importance of nausea and vomiting has been minimized, since these follow any prolonged and severe head pain.

DISCOVERY OF CAUSE

The chief aim of this paper and the statistics presented is to convince physicians that every migraine patient deserves a complete allergic work-up. With cooperation and perseverance, the cause can usually be found, and the symptoms often completely relieved. Elimination diets and feeding tests can always be performed while the patient is undergoing other investigative procedures.

NOSIS OF CHRONIC HEADACHE

LOCATION OF PAIN	EYE SYMPTOMS	ASSOCIATED SIGNS AND SYMPTOMS	DIAGNOSTIC TESTS	THERAPEUTIC TESTS
Unilateral, usually	Photophobia, may have visual aura	N & V; Aura at times; G.I. symptoms with & between attacks	Induce attack by feeding Gynergen. Elimination of causative foods	
Unilateral, in face.	Conjunctivitis, tearing on affected side	Nasal blockage, rhinorrhea on affected side.	Histamine	Gynergen. Histamine treatment
Generalized, neck back or top head	None	Fatigue; occurs with or after stress	None	Removal from stress
Frontal or in cheeks; across bridge of nose	None	Nasal blockage; post-nasal drip; sinus tenderness	Nasal smear for eosinophils; sinus X-rays	Relief by local treatment, antihistamines
Behind and in eyes	Blurring, burning, itching, tearing	Follows prolonged eye strain (close work)	Refraction	Rest; proper glasses
Usually occipital may be genl.	May be blurring	Evidence of basic disease	None	Relieve hypertension
Variable; may be unilateral or localized	May be blurring, diplopia, etc.	Depends upon site and stage of tumor	Ventriculogram, spinal tap, encephalogram, neurologic exam.	Surgery
At site of trauma. Later genl.	Usually none	History & evidence trauma; Xanthochromic spinal fluid initially	Ventriculograms, spinal tap; encephalogram	Surgery
Over artery	Diplopia, photophobia; may lead to blindness	Fever, leukocytosis; pain on chewing; artery tender distended & tortuous	Novocaine infiltration biopsy	Surgical interruption of artery

We have found feeding tests and food diaries each of equal importance in determining the food to which the patient is allergic. Food diaries rank first, because they reveal most of the minor causes of attacks. The patient should write down everything he ingests (including all ingredients) for 24 hours before each migraine. These lists are then compared to see if certain foods or groups of foods are mentioned repeatedly. These are then eliminated, later tried again to see if symptoms follow. Elimination diets used alone were helpful in 11 patients in this series.

Feeding tests are the most important method of determining allergy to major foods. The technique is as follows:

1. Place the patient on a rigid and complete elimination diet for two weeks. Exclude one major food at a time (usually milk, wheat or pork). Chocolate is eliminated throughout all diet trials.
2. After resting in the office for one-half hour, with an empty stomach, give him a feeding of the food previously eliminated, e.g.;
 - A) One pint of milk, or
 - B) Serving of Cream of Wheat made with water, and cane sugar, or
 - C) Two cans of pure chopped pork (baby food cans).
3. If no symptoms develop, repeat the same meal one hour later and dismiss the patients with instructions to report any symptoms which may develop later.

TABLE VII. RESULTS WITH LEUKOPENIC INDEX

	MIGRAINE AFTER FEEDING	NO MIGRAINE AFTER FEEDING
WBC drop (over 1,000 cells in one hour)	8	3
WBC rise	7	8
Equivocal (drop less than 1,000)	11	10

4. If no symptoms develop, repeat with different foods, at intervals of two weeks.

If a true migraine develops following such a feeding test, it becomes obvious to the patient that this food is one major cause of his headaches. He will almost always be cooperative in eliminating that food in all forms. If he persists in having occasional attacks, less frequently than before, the offending foods can usually be tracked down by food diaries.

Skin tests were helpful in determining food allergies in only 5 cases. Because of these occasional patients, however, we regard them as an essential part of the allergic work-up. No patient should ever be dismissed as nonallergic merely because of negative skin tests. Every positive reaction to foods must be confirmed clinically, each negative regarded as merely noninformative.

Eosinophilia in the blood is a completely unreliable index of allergy in migraine patients; nor has the leukopenic index proved reliable in our hands (see Table VII). These figures are based on a drop of 1,000 cells in the white count one hour after ingestion of the suspected food. In other words, there is no reliable laboratory test for the diagnosis of food allergy. Clinical elimination and trial feedings are the only true tests for food allergy.

MANAGEMENT AND PREVENTION

The most important way to treat migraine is to prevent the attacks. No amount of medication, however effective, can replace the wonderful sense of security which a patient obtains by finding and eliminating the cause of his attacks. Table VIII shows the results we have obtained in our patients. These statistics are based upon a survey of all our private patients who fulfilled two criteria: all had classical migraine and all have cooperated with us for a period of three months or longer. This latter stipulation is based upon the two following requirements: There is a minimum period of two weeks between feeding tests, this much time being necessary to allow an adequate number of tests, if necessary. Secondly, we have no follow-up on patients who have disappeared before that time, so that we cannot judge whether or not they were really failures.

TABLE VIII. RESULTS OF ALLERGIC MANAGEMENT IN 55 PATIENTS WITH MIGRAINE

Complete Relief	35 (64%)
Marked Improvement (75% or better)	9 (16%)
Moderate Improvement (50-60% better)	2 (4%)
No relief	9 (16%)

TABLE IX. RESULTS OF TREATMENT WITH DIHYDROERGOTAMINE

AUTHOR	NUMBER OF PATIENTS	GOOD TO EXCELLENT (RESULTS IN PER CENT)
von Storch ³⁰	150	70-90
Friedman and Wilson ⁹	36	89
Caldwell ⁵	42	76
Blumenthal and Fakler ³	51	88
Hartman ¹⁵	20	85
Horton, Peters, and Blumenthal ¹⁷	79	75
Pollock ²⁴	17	88
Charles ⁶	25	88
Bercel ²	40	87
Total	465	83

Table VIII shows that over 60 per cent of these patients found complete relief by eliminating causative foods. Another 20 per cent have been partially relieved. Altogether, over 84 per cent have found some measure of relief and almost all of these are 75 to 100 per cent better. Figures on results with psychotherapy are not easily available for comparison, but Friedman, Karron, and de Sola Pool⁸ recently estimated results from psychotherapy at 66 per cent.

Of the 9 failures in this series, we feel that several could have been helped by more complete work-ups. Until recently, we did not appreciate the importance of pork as a cause of migraine. Few of these failures were ever placed on a pork-free diet. On the other hand, we far overestimated the importance of eggs; as the table shows, only two of our patients were sensitive to egg.

Contributory factors are also important and must be treated as indicated in individual cases. Formal psychotherapy is a great aid in some patients, although most will respond to the informal type easily directed by family doctors. General good health should be maintained and existing physical disabilities corrected (especially visual and endocrine).

TREATMENT OF ATTACKS

During the period while finding the cause of attacks, it is essential that the patient receive the maximum possible relief. This applies also to sporadic at-

TABLE X. RESULTS OF TREATMENT WITH CAFERGOT

AUTHOR	NUMBER OF PATIENTS	EXCELLENT	GOOD	NO RELIEF	PER CENT EXCELLENT AND GOOD
Charles, C. M. ⁶	34	6	12	16	53
Cohen, S. G. & Crip, H. L. ⁷	44	13	22	9	80
Friedman, L. L. ¹⁰	28	21	2	5	82
Gotz, A. ¹²	25	15	7	3	88
Hilsinger, R. L. ¹⁸	3	0	1	2	33
Hansel, F. K. ¹⁴	6	3	2	1	84
Horton, B. T., Ryan, R. & Reynolds, J. L. ¹⁹	25	16	6	3	88
Kadish, A. H. ²⁰	30	19	7	4	87
Reeves, J. E. ²⁶	15	8	2	5	67
Ryan, R. E. ²⁷	110	81	18	11	88
Whitelaw, M. J. ³¹	76	49	18	9	88
Total	396	231	97	68	83

tacks which occur later. There are two general rules for all medicines for treatment of migraine attacks:

1. Medication must be given early and in adequate doses. When the arterial walls are thickened, no medication will relax them.
2. No oral medication can be given when the patient reaches the stage of nausea as he will usually vomit them.

There is only one specific drug for migraine—ergotamine. Only two forms of ergotamine have proved consistently effective; ergotamine tartrate is the drug of choice, with Dihydroergotamine, a close second. Peculiarly, there are practically no published statistics on the efficacy of Gynergen (pure ergotamine tartrate), which is generally recognized as the most effective of all medicines for migraine when given intravenously or intramuscularly. Patients seen in attacks should be given Gynergen or Dihydroergotamine promptly, either intravenously or intramuscularly. Results of treatment with the latter as reported in the literature are shown in Table IX.

To treat future attacks, the drug of choice is Cafergot because of its ease of administration. Results reported are shown in Table X. It must be given in full doses promptly: two tablets at first sign of a headache, followed, if necessary, by two more in one hour and two more the following hour. No more than six tablets should be given for any attack, nor should this course be repeated more than twice a week. Ergot should not be used as a preventive measure (taken daily). The manufacturers have recommended that patients who have frequent migraine attacks restrict their usual coffee intake to about two cups daily in order to assure full action of the caffeine in Cafergot.

Two other methods of administering ergotamine tartrate are undergoing investigation and appear promising. These are the rectal suppositories and sublingual tablets. The tablets and suppositories used thus far have compositions similar to Cafergot. These forms deserve further investigation because they circumvent the problem of nausea.

Ergotamine has always been used cautiously, although it is used a great deal. It is to the credit of physicians and manufacturers (particularly the Sandoz Company) that there have been reported only three cases of ergotism following use of these preparations in treatment of migraine.

Because ergotamine is so specific, other measures have been largely discarded. Of the many vasoconstrictors tried, the simplest and most effective is an icebag to the head. Others used include epinephrine, pitressin, benzedrine, caffeine, pressure on carotid or temporal arteries and inhalation of 100 per cent oxygen. Results with a new preparation, Methyloctenylamine (Octin) are encouraging, but do not compare with those for Cafergot. Nicotinic acid and testosterone have also been used recently; the latter may prove helpful in preventing premenstrual headaches.

Histamine has been used, particularly by Horton.¹⁶ Some of our patients had received histamine previously; most of them felt worse after receiving it.

Analgesics have, of course, been used. A few patients can obtain relief from the aspirin group of drugs. In our experience, sublingual aspirin (Theryl) seems more effective than other forms.²⁸ Codeine is helpful in a few patients and may be used safely. The use of such narcotics as Demerol and morphine is to be condemned. Migraine is a recurring syndrome which can easily lead to addiction. Sedatives are usually disappointing as specific treatment, but mild sedation is an aid to other forms of therapy.

One important recent addition to therapy of migraine attacks is the use of intravenous calcium. Calcium gluconate seems to have a beneficial effect upon the residual headache, apparently due to muscle spasm, which accompanies migraine and other types of long-standing headaches. We have recently used a 20 per cent solution of calcium gluconate intravenously in these cases, with rather striking results. It is given slowly and followed by a small amount of intravenous ergotamine tartrate.

Surgical measures of various types have been used, but the results are not commensurate with the discomfort and risk involved.

SUMMARY

1. In a group of 55 patients with classical migraine who have been followed for a minimum of three months, 80 per cent have been either completely or almost completely relieved of attacks by detection and elimination of the causative foods.

2. Allergy to foods is the prime precipitating cause of attacks. Statistics are presented to show the relative frequency of various foods. Chocolate is the most important cause, followed by milk, wheat, and pork.

3. A discussion is presented of the diagnosis, differential diagnosis, mechanism, and treatment of attacks of migraine.

4. It is concluded that migraine is basically an allergic disease, although psychic stimuli may provoke individual attacks in allergic individuals.

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