

*Kaiser Permanente Medicine 50 Years Ago:*

## Migraine, Histamine, Allergic and Other Related Cephalgias

**Dannenberg TB. Migraine, Histamine, Allergic, and Other Related Cephalgias. *Permanente Foundation Medical Bulletin* 1944 Oct;2(4):183-91.**

Headache is one of the most common complaints the patient presents to his physician; it is probably overshadowed in frequency only by constipation. It has been estimated that approximately 50 percent of patients who seek medical advice have headache as one of their complaints.<sup>1</sup> Spriggs,<sup>2</sup> in a clinical study of headache, studied 4796 consecutive patients and found that 500 (10%) complained of headache as a major symptom.

The causative factors of headache are difficult to locate and evaluate, its mechanisms are obscure, but a therapeutic program that is not aimed at the causative factors is unlikely to bring results.

Headache occurs in a great variety of diseased states, for example: arterial hypertension, chronic nephritis and gastro-intestinal disease. It seems certain that the factors concerned are not the same in all instances. The headache occurring in intracranial conditions—tumor, hemorrhage, abscess, and inflammatory lesions blocking the ventricular system, is usually the result of the general rise in intracranial pressure, but may be due to the irritation of nerve endings in the immediate neighborhood of the lesion.<sup>3</sup> Elsberg<sup>4</sup> points out that sudden changes in intraventricular

pressure, whether in the nature of a rise or fall, are likely to cause headache, quite apart from any significant change in general intracranial pressure. He considers the headache that results from the withdrawal of cerebrospinal fluid by lumbar puncture to be due to the lowered pressure within the third ventricle, and upon the optic thalami, which form the ventricular walls. It is generally agreed that the brain itself is incapable of sensation, but the brain covering has sympathetic nerve fibers associated with the vascular supply and these have been shown to carry pain fibers.

Electrical stimulation, traction pressure, and heat will stimulate the dural sinuses and cause sensation of pain; stimulation of the middle meningeal artery will cause pain. Headache may originate directly from stimulation of sensory fibers in the head or reflexly from nerves elsewhere in the body. The trigeminal nerve and the sympathetic plexuses are the chief supply of the dura matter; the choroid plexuses have a rich nerve supply, and the sympathetic nerve fibers which arrive from the plexuses of the vertebral and internal carotid arteries are present in the walls of the pial blood vessels. Stimulation of the end organs in the abdominal and thoracic viscera creates impulses which are carried by the vagus to the medulla where they are brought in relation with the

### Commentary

*by Joel S Richmon, MD*

I am struck by how much the practice of medicine has changed in the half century since this article was written. In the 1940s, the medical subspecialties were sometimes practiced by general internists who had a special interest in another area of medicine and who gained knowledge in a subspecialty largely by observational experience. Dr Dannenberg was just such a practitioner, and he is to be lauded for acquiring enough experience to write an extensive review of migraine.

Another noteworthy observation is how much our knowledge about migraine has increased since those days, when Dr Dannenberg characterized migraine as a “big allergic reaction—akin to asthma or urticaria.” That characterization now seems quaint and is even considered erroneous. Dr Dannenberg’s reference to the “emotional immaturity” of the migraineur underlines a widely prevalent European view—still held today by many in both Europe and the United States—that migraine is a disease of rich, bored housewives. This characterization, of course, is also far from the truth.

Migraine affects a substantial percentage of the population, occurs in all civilizations, and has been recognized since the dawn of recorded history. The condition may indeed have been a scourge or an encouragement to the likes of Caesar, Paul, Kant, and Freud, but migraine is also a daily fact of life to anonymous millions who suffer in secrecy and silence. The forms and symptoms of migraine, as Burton, in 1621, remarked of melancholy, are “irregular, obscure, various, so infinite, Proteus himself is not so diverse.” The nature and causes of migraine puzzled Hippocrates and have been the subject of argument for two millenia.

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A reprinted  
57-year-old  
article from  
the *Permanente  
Foundation  
Medical Bulletin*  
with a current  
commentary

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trigeminal branches and the sensation of the head pain results.<sup>1</sup> It is not within the scope of this paper to enumerate the various diseased states, altered physiological factors, or emotional disorders which may give rise to headaches—they are numerous.

### **Definition of Migraine**

The older texts describing this type of headache included under its description all types of periodic headache that contained one or all of the following characteristics: familial origin, hemicrania, preceding aura, scotomata or other visual disturbances, nausea and vomiting, constipation or diarrhea, urine retention or frequency of urination, general or one-sided chilliness, pallor or flushing—the attack lasting one hour to several days, followed by fatigue or depression, although the patient may be lively or energetic.

Attempts from time to time have been made to classify this type of headache in broad general classifications such as typical migraine or atypical migraine depending on the author's criteria, "red headache or white headache" depending on whether the patient showed pallor or flushing of the face at the time of the attack. Etiologic classifications have been proposed and are numerous, eg, allergy, endocrine, anatomical and psychic.

It remained for Horton, MacLean and Craig<sup>5</sup> in 1937 to classify one clinical entity from the group of migraine headaches. Horton stated, "The observations that have been made with reference to this specific type of headache warrant its establishment as a distinct clinical entity, classic in its symptomatology and unique in its response to histamine therapy." The entity was tentatively called "erythromelalgia of the head." Horton now refers to it as "histaminic cephalgia." Parry<sup>6</sup> first made the discovery and described it fully in 1789.

The definition of migraine headache is as variable as the manifestations of the disease itself. It is, however, generally agreed that in order to classify a case as true migraine it must have the following characteristics:

1. Periodic headache with complete freedom from pain in the interim.
2. Family history of migraine or allergy.
3. Preceding aura and usually cortical sensory disturbances.
4. Nausea or vomiting.
5. Duration of attack longer than twelve hours.

In addition to the above five characteristics one frequently sees one or more of the following: hemicrania, constipation or diarrhea, pallor, frequency of

urination or retention, tingling or numbness of arms, face or tongue, dizziness, ringing in the ears, strange odors or taste disturbances.

The age of onset is usually in the second decade of life. It is more common in females than males. It is frequently seen in women at time of menstruation, may disappear during pregnancy and following menopause. There is a tendency for remissions and exacerbations—the latter frequently associated with stresses and strains of life. Alvarez<sup>25</sup> states most patients with migraine are, "overly reactive to emotion and overly sensitive to all stimuli, highly conscientious and restless individuals who are always overworking, worrying or taking life too seriously" and above average intelligence, ability and drive.

### **Mechanism and Etiology**

The mechanism of migraine is believed to be first a vasoconstriction followed by a vasodilatation of the cerebral arteries. The former accounting for the pre-headache aura, scotomata and other cortical sensory phenomena and the latter accounting for the headache by stretching pain fibers closely associated with these arteries. That this mechanism is mediated through the sympathetic nervous system, is generally accepted; however, there is disagreement on the trigger mechanism that initiates the initial vasoconstriction and the vasodilatation that follows. In histaminic cephalgia we see only the second part of the mechanism in effect, namely that of vasodilatation. If the vasoconstriction is present it is certainly transitory for in this type of cephalgia we lack the pre-headache symptoms seen in typical migraine.

Although many theories have been proposed as to the etiology of migraine headache, none of them are wholly acceptable. The most widely accepted theory is that migraine is an allergic reaction comparable to asthma, urticaria, etc. The allergen believed to be the offender is an ingestant though inhalants have been incriminated. The allergic concept has much in its support. The age incidence is comparable, most allergies and migraine occurring in the second, third and fourth decades of life. In each there is a familial tendency. Migraine and other allergic manifestations are frequently seen in the same individual. Von Storch<sup>7</sup> reported 76 percent of 862 cases of migraine significantly allergic. Tillman<sup>8</sup> states, "The multifarious nature and distribution of migraine and allergy suggest a common physiologic morbidity." In 1927, Vaughn<sup>9</sup> proved that true migraine was allergic by (a) finding of positive skin tests, (b) relief of symptoms follow-



ing avoidance of foods reacting positively, and (c) reproduction of the headaches by feeding foods to which patients were sensitive. However, in 1939, Vaughn reported good results by management from the allergic standpoint of view in 51 percent of his patients, with complete relief in 40 percent. There remained approximately 50 percent of his series who received no benefit from allergic management, whether the offending allergen or allergens could not be discovered must of course be taken into consideration.

Rowe<sup>10</sup> reported only 17 percent failure in 247 patients by use of elimination diets. Wolf and Unger<sup>11</sup> reported a case of true migraine directly attributable to milk, which was discovered by simple feeding and elimination tests and could be produced by feeding the offending allergen.

Although the preponderance of evidence bears out the allergic theory of migraine headache there are other theories proposed.<sup>11</sup>

**Reflex**—from refractive errors leading to eyestrain.

**Central**—from local or general pressure on dura mater with increase in cerebrospinal fluid. Goltman<sup>12</sup> demonstrated edema of the brain was present at the height of an attack. The patient was operated on for supposed brain tumor. At the height of the migraine attack the scalp over the burr hole bulged, between attacks this same area was depressed. Pool<sup>13</sup> and his associates did not find the cerebrospinal fluid pressure greater in patients during the migrainous attack than in a group of normals.

**Sella Turcica Abnormalities**—Timmie<sup>3</sup> subscribes to the theory that the headache, in certain instances at any rate, is due to swelling of the pituitary body within an abnormally small pituitary recess. Other observers have been unable to demonstrate by roentgenography any significant difference in the pituitary recess of migrainous individuals than in individuals who have never had an attack of migraine headache.

**Hypoglycemic theory**<sup>3</sup>—Some point out that a low blood sugar may be a factor in causing migraine headache, citing in support of their belief, the headache of fasting and hyperinsulinism and the relief which follows the administration of glucose or of adrenaline; however, Tillman<sup>8</sup> reported two cases of headache, one of which was true or typical migraine, that were treated by hypoglycemic reactions using intravenous insulin. Both cases received marked relief from attacks of migraine in thirty to forty minutes.

**Endocrine theory**—Riley, Bricker and Kurzork<sup>11</sup> [sic] reported that in 20 out of a series of 39 female subjects of migraine, the gonadotropic principle ap-

peared in the urine preceding an attack. At the same time the female sex hormone, estrin, was either absent from the urine or present in very reduced amounts. In support of this view, that disturbance in the gonad-hypophyseal mechanism plays an important role in the production of migraine, they point out the following:<sup>3</sup> 1) "The first attack of migraine frequently coincides with puberty, 2) attacks commonly just precede menstruation, when the excretion of estrin is reduced and the gonadotropic principle may appear in the urine, 3) the subject is usually free from attacks during pregnancy when the excretion of estrogenic hormone is increased whereas the gonadotropic principle of the pituitary is reduced, 4) relief from the condition commonly follows the conclusion of the menopause."

**Emotional Immaturity**<sup>1</sup>—"In a study by Touraine and Draper of 50 patients with migraine headache they suggested that there exists a constitutional type in which the skull shows acromegaloid trends, patients show outstanding intelligence, but with a retarded emotional make-up. They observed that the headache was characteristically repeated in the same pattern for each patient and recurred in similar circumstances. Situations necessitating the individual to stand alone, such as loss of home protection, or the assumption of adult responsibilities, marked the beginning of the headaches. Headaches were observed to come through the maternal line with the factor of unconscious imitation of the mother important in the causation. They found that there was an emotional attachment to the mother which could not be resolved. This retarded the process of emotional maturity so that an arrest occurred at some point short of mature psychosexual adjustment. They concluded that the migraine attack was a syndrome comparable to any neurosis and the fact that migraine responded to such a variety of treatments spoke in favor of psychic etiology. They felt that the psychological approach offered the most in research and therapy." Wolff<sup>15</sup> believes the psychotherapy is an essential part of the treatment of migrainous patients and that all patients receive benefit from psychotherapy. Alvarez<sup>25</sup> finds that sympathetic interviews and understanding are preferable to elaborate and expensive examination. Lennox<sup>21</sup> states that, "Main reliance must be placed on the gradual education of the patient so that he will adjust his work and his methods of living to the personality and the nervous system which he has inherited."

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### **Treatment**

The most important single concept of migraine is the realization that it is not a clinical entity and in handling this condition it must not be treated as such. It is essential to rule out any organic abnormality which might be causing the headache. If we can elicit the five cardinal points the diagnosis is true or typical migraine. If some of the various signs and symptoms of a periodic headache with complete freedom from pain in the interim are present the diagnosis of atypical migraine may be made. As will be pointed out later, histaminic cephalgia need not be confused with this group as to diagnosis.

Since the most important point of making a diagnosis is a guide to therapy and since the therapy of migraine is not specific, the diagnosis of the type of migraine in view of our present available knowledge is not too important.

The nature of the migrainous attack should be explained to the patient. Mild sedation, reeducation, encouragement and reassurance should be the initial step. This need not be time consuming and can be done at regular visits, say once a week. Interest in the patient is of importance; they have usually been seen by many other physicians and their lack of confidence is as general as their need of relief is desperate. Many have been addicted to drugs of various kinds and types in their search for relief from these severe incapacitating headaches. Narcotics should never be used, especially during attacks.

Because of the "multifarious nature and distribution of migraine," the simplest, least expensive and time consuming measures should be tried first. The belief that the actual migrainous attack is due to anaphylaxis is widely held.<sup>7-11</sup> That is, the offending allergen may be ingested with impunity between attacks, but the individual eventually becomes sensitized so that when the allergen is ingested an anaphylactoid reaction occurs. This reaction desensitizes the patient until resensitization occurs, then another headache results. Skin testing for foods is considered in many recent articles to be unreliable. Laboratory studies have proven of little value either in diagnosis or treatment.

Food elimination diets should then be tried, such as those of Rowe.<sup>10</sup> The most common food offenders are milk, wheat, egg, onion, legumes, nuts, beans, chocolate, fish, beef, pork, sea foods.<sup>16</sup> The most important point in the use of these diets is absolute elimination of foods to be eliminated.

If by adequate use of elimination diets no relief is obtained, histamine desensitization or hyposensitization

should be tried. Aside from histaminic cephalgia, in which almost 100 percent get complete relief, Horton<sup>17</sup> reports significant improvement even in those headaches not of the migrainous group.

The use of chondroitin in treatment of idiopathic headaches, including true migraine and those of the migraine group, was reported by Crandal,<sup>18</sup> et al. They reported 50 percent of 151 cases received marked relief from chondroitin therapy. Chondroitin is a mixture of chondroitin and chondroitin-sulfuric acid, containing not less than 70 percent of the mixture calculated as chondroitin-sulfuric acid.

Amniotin orally has been reported as beneficial in women with simple (typical) migraine.<sup>19</sup> Matier,<sup>20</sup> et al, reported 75 percent of patients with headache, associated with chronic constipation or colon distress, were relieved completely by colon bacillus vaccine therapy.

In women who suffer with migraine preceding or at time of menstruation, dehydration has proved to be of value.<sup>22</sup> Patients are placed on low fluid intake, salt is limited and diuretics are used such as ammonium chloride orally or mercupurin intravenously. This regime is begun one week preceding onset of menstrual period and carried through until termination of menstrual period.

Other more radical measures in the treatment of this type of headache have been employed; ligation of the middle meningeal artery, stripping the common carotid artery, or induction of artificial menopause by surgery or irradiation. None of these measures have been widely accepted or employed.

The management of the acute attack of migraine is amenable to many therapeutic measures. The most widely used and the most acceptable being ergotamine tartrate. Lennox and Storch<sup>21</sup> treated 120 carefully chosen, true migrainous patients with intravenous or subcutaneous injections from 0.5 to 1.0 milligrams of ergotamine tartrate. Ninety percent experienced prompt relief as the result of the first administration, four percent obtained slight or only temporary relief, and the headache was made worse in two percent. The dosage of ergotamine tartrate must be determined empirically. It should be great enough to produce relief from headache, but not enough to produce toxic effects such as nausea and vomiting, cortical sensory disturbances, etc. It should not exceed 1.0 milligram as initial dose. Oral ergotamine tartrate has not proved to be of value once the headache has started but may be of value in aborting the headache before it has begun. One to two milligrams placed under the



tongue or taken by mouth may abort an attack. The use of oral ergotamine tartrate as a prophylactic measure, one to three milligrams daily, has not proven of value in two cases that we have seen.

Other measures which have been employed include 100 percent oxygen inhalation (Alvarez), and hypoglycemic reactions by insulin (Tillman<sup>8</sup>). Dihydroergotamine tartrate has been used; its value has not yet been established.

Horton,<sup>24</sup> et al, used this new preparation in the treatment of migraine headaches and reported results comparable to the use of ergotamine tartrate. Nausea and vomiting was four times more frequent with ergotamine tartrate than with dihydroergotamine tartrate. They report the drug equally as effective in treatment of the acute attack. Dosage of 1-3 cc subcutaneously was employed. We have used dihydroergotamine tartrate\* on several patients with varying results: we have not found it to be as valuable a drug as ergotamine tartrate, once the headache is firmly established; the best results have been with its use early in the migraine attack.

The use of cutaneous anesthesia for relief of pleuritic pain associated with pneumonia has been reported by Dybdahl.<sup>23</sup> Similar application of ethyl chloride spray over the back of the neck and the carotid artery on the side of the headache may prove of value in the treatment of migraine. This procedure has been used on five cases here, two of which received dramatic relief and were able to leave the clinic in thirty minutes. In previous attacks, with use of ergotamine tartrate, oxygen inhalations, morphine, and codeine, these patients remained in the clinic two to four hours. The other patients on which ethyl chloride was similarly employed, experienced no relief whatsoever. In the patients who were relieved the attack had just begun; in the latter group the headache was of one to two days duration and associated with marked nausea and vomiting.

The patient in a migrainous attack should be kept in a quiet, cool, dark room and the treatment initiated early. Once the attack is well established with nausea and vomiting, the efficacy of any measure is markedly decreased.

### Histaminic Cephalgia

Horton,<sup>5</sup> et al, noticed in the group of patients with the chief complaint of headache, that certain definite signs and symptoms tended to predominate. To this group they applied the descriptive term erythromelalgia of the head, later histaminic

cephalgia because the same syndrome could be reproduced by injections of histamine. This type of headache has the following characteristics:

1. It is unilateral and always on the same side.
2. There is a lack of familial history of migraine or allergy.
3. Onset is common in the fourth and fifth decades of life.
4. It is of sudden onset and short duration, frequently less than one hour.
5. It usually occurs at night, one to two hours after the patient has gone to sleep.
6. Pain is of suicidal intensity, constant, excruciating, burning and boring; it involves the eye, temple, neck and often the face.
7. The pain is not confined to the distribution of any cranial nerve but has a tendency to conform to the ramifications of the external carotid artery.
8. Pain is eased by sitting up or standing erect.
9. Compression of the common carotid and sometimes the temporal artery, early in an attack, sometimes gives prompt relief.
10. There is occasional nausea, but no vomiting.
11. There is no preceding aura or other cortical sensory phenomena.
12. There is no relationship to menstrual period.
13. Alcoholic beverages frequently precipitate an attack.
14. Histamine 1.0 to 1.2 milligrams subcutaneously, precipitates an attack identical with that of spontaneous origin.
15. Hyposensitization to histamine usually cures the patient.

Seventy-two (40%) of 184 patients in Horton's series with a primary complaint of headache were of this type. Sixty-three were desensitized with histamine. Of 51 of these whose symptoms were typical, 48 had complete relief for varying periods of time after desensitization. In Lieder's<sup>16</sup> group of 71 patients, four of whom had histaminic cephalgia, all four got complete relief from histamine hyposensitization.

The method of hyposensitization used by both Horton and Lieder was an initial dose of 0.05 centimeter of a solution containing 0.1 milligram per cubic centimeter of the histamine base. The dose was increased 0.05 cubic centimeters at each injection until 1.0 cubic centimeter of 0.1 milligram of the base was reached. Two injections subcutaneously were given daily for a period of from 20 to 30 days. Some patients required a maintenance dose one to three times

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weekly for varying periods of time. The frequency of incidence in Lieder's group was six percent and in Horton's group was 40 percent. It is generally believed that this type of cephalgia is quite infrequent as compared to other types of cephalgia.

### Summary

A review of migraine headache has been presented, with a discussion of the types which may be seen, the mechanism and various etiological factors involved, the criteria for diagnosis, and the numerous modes of therapy.

Special attention has been paid to the allergic aspects of migraine, and to histaminic cephalgia. ♦  
*\*Dihydroergotamine tartrate was supplied by Sandoz Chemical Works, Inc.*

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### Commentary

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For many years, a vascular hypothesis<sup>1</sup> held that migraine was primarily a disease of the cranial vasculature. This theory proposed that headache pain occurred as a result of sensory nerve activation by inappropriate vasodilation or opening of arterial venous anastomosis in the cranial circulation.<sup>1</sup> Subsequently, a neurogenic hypothesis proposed that neurogenic inflammation (vasodilation and plasma protein extravasation) in the meninges may be responsible for trigeminal sensory nerve activation and generation of headache pain.<sup>1</sup> More recently, brain-imaging studies conducted during spontaneous migraine episodes have shown activation of brain stem regions that participate in central modulation of head pain and craniovascular functions.<sup>2</sup> This observation has given rise to an integrated hypothesis, ie, that migraine has a central neural basis that leads to dysfunction in various sensory, nociceptive, and vascular control pathways.<sup>3</sup>

The first observation to support the integrated hypothesis was that patients with no history of migraine developed migrainelike episodes after having surgery to implant electrodes leading to the periaqueductal gray matter and raphae nuclei within the brain stem. This finding suggested that these regions of the brain may be the loci of an endogenous "migraine generator."<sup>4</sup> Participation of brain stem regions in migraine pathogenesis is now further supported by positron-emission tomography (PET) studies showing regionally specific increases in cerebral blood flow and an index of neuronal activity within the reticular formation during spontaneous migraine attacks.<sup>2</sup> The nuclei thought to be activated most were the raphae nuclei (which have a high density of serotonergic neurons) and locus ceruleus (which has a high density of catecholaminergic

*Commentary continued on page 39.*

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## Commentary

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[eg, norepinephrine-activated] neurons). Continued activation observed in this brain stem region after successful drug therapy suggests that ongoing activity within such a “migraine generator” could be responsible for recurrence of migraine headache. This hypothesis, however, requires further investigation.

For many years, pharmacologic interest in the mechanisms of migraine focused on serotonin (5-hydroxytryptamine, or 5-HT). Current theories suggest that parasympathetic projections (containing acetylcholine and vasoactive intestinal peptide) from brain stem regions innervate intracranial meningeal blood vessels. Activation of these pathways could trigger a headache by releasing nitric oxide, which is a potent vasodilator and activator of perivascular sensory nerves.<sup>5,6</sup> Indeed, serotonin-antagonist agents used prophylactically against migraine but which are ineffective after a migraine attack has started may act by preventing this initial vasodilator stimulus. These hypotheses reflect current thinking and may provide an integrating link between the vascular and neural theories of migraine.

Dr Dannenberg’s comments on histaminic cephalgia (or “cluster headache,” as we would say today) bring to mind an interesting chapter in my life as a medical resident on the private service at Johns Hopkins in the late 1960s. A well-known and highly self-aggrandizing Baltimore internist continued to flood us with patients whom the internist deemed suitable for histamine desensitization. The hospitalizations were lengthy and, I’m sure, very expensive for the patients. The results were variable at best, and it was not unusual to see the same patients return for repeat treatments. One hundred percent oxygen inhalation (mentioned in Dr Dannenberg’s review) is often highly effective for treating cluster headache and is still very widely used.

The sheer complexity of migraine, the variety of its forms, its prevalence in our species, and the suffering it causes all continue to tantalize and challenge clinicians and researchers all over the world, and migraine research has never been as active as it is today. In contrast to the “dirty” drugs of the past, we are beginning to develop highly specific and often highly effective serotonin agonists, which seem to act both centrally (in the brain stem) and directly (in the meningeal vessels); these agents are the triptans.<sup>7</sup> But we still have pieced together only fragments of the complete puzzle—we continue to seek a synthesis which brings all the pieces together.

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