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# REVIEW OF LITERATURE

## ❖ DEFINITION

Migraine headaches are recurrent headaches that are either preceded by a focal neurologic symptom (Migraine With Aura), occur independently without preceding focal neurologic symptoms (Migraine Without Aura), or have atypical presentations (Migraine Variants).[(1)]

- The migraine aura typically is characterized by visual or sensory symptoms that develop over 5 to 60 min.
- If aura includes motor weakness, the migraine is referred to as hemiplegic. In migraine with and without aura, the headache is typically unilateral, pulsatile, and associated with nausea and vomiting, photophobia, and phonophobia.
- Migraines that occur ≥15 days every month for ≥3 months are known as chronic; otherwise, they are referred to as episodic.[(1)]

## ❖ EPIDEMIOLOGY & DEMOGRAPHICS

### ➢ Incidence

Increases from infancy, peaks during the third decade of life, then decreases.[(1)]

### ➢ Prevalence

In the India, It is more common in women & when a family history is often present (60% of cases).[(2)]

Migraine is felt by almost **220-240 million** people in the population.[(3)]

Majority of the patients with migraine, 80% have migraine without aura.[2]

In USA the prevalence in Females is up to 18% while in Males it is 6%. More than 50% of persons affected by migraine headaches report reduced work or school productivity.[1]

## ➢ Age

Attacks begin in late childhood, adolescence and early twenties.[2]
Peak prevalence is between ages of 18 and 49 years[1]

## ➢ Predominant Sex

Female/male ratio of 3:1[1]

## ➢ Genetics

- Familial predisposition: more than 50% of migraine sufferers have an affected family member.
- Autosomal-Dominant transmission for some rare migraine variants (Familial Hemiplegic Migraine, Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [CADASIL]); familial hemiplegic migraines have been associated with calcium channelopathy, sodium channelopathy, and Na+/K+-ATPase dysfunction.[1]

## ❖ ETIOLOGY

The Pathophysiology of Migraines is not clearly understood. It is believed that a primary neuronal event results in a Trigeminovascular Reflex causing neurogenic inflammation. Serotonin, Substance P, Nitric Oxide, and Calcitonin Gene related Peptide also play a role, but the exact mechanism is unknown. Cortical Spreading Depression is probably responsible for the Aura.[1]

### ➢ The Hyperexcitable Brain[4]

If the migraine is inherited then one way to think about this inheritance is that migraine patients have a brain that is too excitable, a so-called "Hyperexcitable Brain." For some reason, specific neurons in the brain or nuclei discharge too easily, activating pathways that initiate the mechanism of pain and associated symptoms, and resulting in the migraine syndrome. The tendency to fire is what is inherited.

### ➢ Nitric Oxide[4]

Neurons of the brain communicate with each other by chemical and electrical signals. Neurons can fire individually or en masse. There are many hypotheses about what it is in neurons that makes them hyper excitable. One possibility is that migraine nerve cells are too sensitive to nitric oxide, a chemical messenger released by some nerve cells to activate certain others.

An interesting piece of evidence in favor of nitric oxide causing migraine is what happens when people are administered nitroglycerin. It is given to patients with chest pain (angina) caused by blockage of the coronary arteries; it also carries nitric oxide into the brain. People without migraine who take nitroglycerin for angina will get a brief, unpleasant

headache afterward. People with migraine who take nitroglycerin get the brief headache, but hours later also get migraine. The theory is that nitric oxide is a cell messenger that causes migraine, but this does not explain why the migraine occurs in bursts or what happens when nitric oxide fulfills its usual functions in the body.

### ➢ Magnesium[4]

Another theory is that some patients with migraine have too little magnesium in the brain. Low magnesium may lead to nerves becoming hyperexcitable. Low magnesium destabilizes nerves by altering the ability to control the influx and efflux of charged ions, resulting in nerve cells firing too easily.

This low Magnesium has been found in the nerves of migraine patients with aura, and in patients with migraine around their menstrual periods. Intravenous magnesium terminates some menstrual migraines. Other patients respond to daily magnesium supplements with a decreased number of migraines. Not everyone given magnesium supplementation benefits (and many patients get diarrhea from the magnesium). The lack of uniform clinical success with magnesium supplementation suggests that the causes of hyperexcitability associated with migraine vary.

### ➢ Energy Metabolism[4]

The basic storage molecule of energy in the body is adenosine triphosphate, or ATP. This molecule is like a rechargeable battery. Each ATP has three phosphates in a chain on the molecule, and energy is stored in the bonds between them.

When one phosphate is pulled off the ATP, it gives off energy, and these aliquots of energy are used to run everything in the body. However,

once the ATP loses a phosphate, it becomes adenosine diphosphate, or ADP. A new phosphate has to be put back onto the ADP to make ATP and thus "recharge" the battery.

The neurons in the brains of some migraine patients have been found to have a problem recharging ADP back to ATP, and the lack of adequately phosphorylated ADP destabilizes the nerves so that they fire more easily. The patient's brain nerves therefore have a tendency to fire due to inadequate regeneration of ATP from ADP.

Certain vitamins help make the ADP into ATP. These vitamins serve as "Co-Enzymes," chemical midwives without which energy metabolism cannot move to completion. A key co-enzyme is **Vitamin $B_2$**, also called "**Riboflavin**", which helps propel a chain movement of electrons during energy reactions. Interestingly, one study showed that some migraine patients who take high-dose vitamin $B_2$ (400 mg/day for 3–4 months) can reduce their migraines.

## ➢ Calcium Channels and Familial Hemiplegic Migraine[4]

Hemiplegic migraine is associated with temporary paralysis of one side of the body, occurring during the aura and persisting for hours or even days. The genetic basis for some patients with this very rare form of migraine, Familial Hemiplegic Migraine (FHM), has been identified. One gene that causes it has been mapped to **Chromosome 19**, one to **Chromosome 4**, another to C**hromosome 1**. The genes on chromosomes **1** and **19** code for the calcium channel. (There are many gates or channels in neurons that allow ions with positive or negative charge such as sodium, potassium, or calcium into the cells. These gates open and close and allow

for establishing a certain amount of positive and negative charge in a particular cell.) The FHM gene controls the structure of one of the channels in nerve cells.

The mutant calcium channel does not open and close properly and cannot regulate the amount of calcium coming into the cell, so calcium influx and efflux regulation gets disturbed. This in turn leads to neurons firing too easily.

Ion channel abnormalities are referred to as *channelopathies* and can occur in the gates for sodium, potassium, calcium, and other ions. These channelopathies have been linked to a variety of paroxysmal neurologic conditions whose clinical manifestations occur in discrete episodes, such as epilepsy and migraine. The underlying nerve cell channels are abnormal all the time, but the discharges occur periodically, possibly due to gradual toxic buildups of charged ions. Channelopathies may underlie the co-morbidity of migraine and epilepsy.

Because abnormal calcium channels are a cause of FHM, blocking them with a calcium channel blocker specifically treats this form of migraine. Other channelopathies may cause other types of migraines.

Problems exist with all theories for the causes of migraine. One is that not all patients with migraine have low magnesium, nor do they all respond to magnesium, vitamin $B_2$, or calcium channel blockers. Another unknown is why any of these problems, which are constant, make nerve cells fire only occasionally—and why, when they do, they often fire only on one side of the brain. Migraine is polygenic. We still have a way to go in understanding what patients inherit that causes migraine, but we are a lot closer than we were a decade ago.

## ❖ MIGRAINE TRIGGERS[5]

Triggers are not the cause of migraine disease, but they can tip a susceptible brain into starting a migraine attack. Migraine triggers may be less important for many people than previously thought. Many people spend years looking for triggers when their migraine attacks are random anyway, and blame themselves for not finding them and controlling their attacks when it is impossible to do so.

Triggers for some people are important, and they can be anything like food, stress, noises, weather, etc., that set off migraine attacks for the patient. One's migraine triggers may not be the same as others' migraine triggers, and these triggers can change over time. Identifying migraine triggers may help the patient to learn how to avoid or manage those triggers.

For some patients, the migraine attack causes them to expose themselves to something they think is a trigger. Perhaps the prodrome of your migraine attack causes you to crave chocolate. Eating the chocolate does not trigger the migraine attack, but patients could be tricked by their migraine into seeing things that way.

Common Migraine Triggers include following list:[5]

- **Hormonal Changes in Women:**

  Women may get a migraine attack before or during their periods because of fluctuating levels of the hormone estrogen. Women may also experience migraine attacks while they are pregnant or going through menopause, because these are times when estrogen levels are in flux. Birth control pills (which contain hormones) or hormone replacement

therapy during menopause could trigger or worsen migraine disease too, although they may also be beneficial in managing migraine.

- **Weather Changes:**

  Barometric pressure swings, such as before a storm or when there's a shift in the weather pattern, could trigger migraine attacks.

- **Foods, Drinks, or Food Additives:**

  Salty or processed foods (which are often higher in sodium), aged cheeses, smoked or preserved foods, the artificial sweetener like aspartame, or foods with the preservative MSG (Monosodium Glutamate, a common food additive that is used to enhance flavor) can be migraine triggers for some people.

  Alcohol and caffeinated beverages are other common triggers.

  Some people find that red wine is a migraine culprit.

  One can observe that food and drink can be stronger triggers when they're combined with other migraine triggers.

  For example, a lady can have a glass of red wine without it causing a migraine attack, except during her period, when she has to avoid it.

- **Strong Odors:**

  Fresh paint, cleaners with strong chemical smells, or one's office colleague who's always doused in perfume may set off your migraine attack.

- **Sleep Disruptions:**

  If a person is traveling and get jet lag, or has to camp out in an airport overnight waiting on a flight when he would normally be sleeping, this may trigger a migraine attack.

- **Dehydration:**

Not drinking enough water after a workout or getting dehydrated because of hot weather can also bring on migraine attacks.

- **Medications:**

  In addition to birth control pills, certain drugs can trigger migraine attacks in some people.

  Vasodilators, such as nitroglycerin, which are used to treat heart conditions, open up the blood vessels, and this could set off migraine attacks in some people.

- **Stress & Anxiety**
- **Heavy Physical Exertion or Activity**
- **Bright Lights**
- **Loud Noises**

## ❖ PATHOPHYSIOLOGY

The possibility that a migraine attack may be initiated by Cortical Spreading Depression is the most favored hypothesis. This condition is a transient disruption of neuronal activity in the brain accompanied by a flux of sodium, calcium ions into the cells. This results in a brief burst of electrical activity followed by electrical silence, which progresses as an expanding concentric wave through the brain at the same rate as a developing migraine aura.[2]

Events in the Brain Leading to Migraine are as mentioned as follow:

### ➢ The Mechanism of Aura[4]

It is believed that aura was caused by blood vessels constricting, and migraine headache caused by blood vessels dilating. In that theory, aura was caused by too little blood to the brain, and throbbing migraine pain by too

much. However, it is now known that some blood vessels constrict during the headache, and that some vessels dilate during aura.

In some animals, a process called **"Cortical Spreading Depression"** has been found. In this phenomenon, abnormal nerves fire in the visual area at the back of the brain; this activation spreads forward across the brain at a rate of three millimeters per minute. In the wake of the activation, the nerves are quiescent for a period of time; this period is referred to as cortical spreading depression (even though it is in reality *Cortical Spreading Activation*). The initial firing is associated with an increase in blood flow, and the spreading depression with decreased blood flow (but not such a low flow that nerve cells are deprived of oxygen).

In search of the spreading depression of nerves as the cause of the aura, Functional MRI and other physiological studies of humans with aura suggest that this is the case. If so, aura would therefore be neurological, not vascular.

An inherited problem in the nerves of the brain causes them to act abnormally and to intermittently fire. Nerves firing in the visual portion of the brain can result in an immediate spreading depression of nerve function in the wake of the activation. This wave of activation, followed by spreading depression and decreased nerve activity, is perceived as slowly moving aura.

## ➢ The Migraine Generator[4]

The Migraine Generator was first visualized in 1995. **Dr. Hans Christoph Diener** and his associates in Essen, Germany studied men with right-sided migraine without aura. They put these patients in a Positron Emission Tomography (PET) scanner to study what happened during their migraines.

There appeared to be an area in the lower part of the brain (Brain-Stem) in which nerve cells turned on at the beginning of the migraine, remained on for the length of the migraine and clicked off at the end of the migraine. Professor H. C. Diener, of Essen, Germany, referred to this center as the **Migraine Generator** because he believed it to be the area of the brain where the migraine originates. The exact location for the generator may be the **Dorsal Raphe Nucleus of the Brainstem.**

Most functions of the nervous system are controlled by nerves that cross over to the opposite side of the brain. That is true of the migraine generator as well, and only the left brainstem dorsal raphe is turned on in patients with right-sided migraine pain.

The migraine generator only indirectly causes head pain, because it first has to activate a head pain system. The generator connects to nerve pathways that lead to the meninges, coverings around the brain between brain and skull. These pathways lead to other nerves that encircle and serve blood vessels of the meninges. When this occurs, blood vessels in the meninges dilate and the neurons release inflammatory chemicals around the vessels. The combination of meningeal blood vessel dilation and inflammation is believed to be the cause of migraine pain. The dilating vessels could account for the throbbing quality of the pain.

## ➢ The Trigeminovascular System[4]

The primary problem in migraine, though, is from firing nerves, not from dilating blood vessels (although inflammation may be another cause of the migraine pain). The connection between the migraine generator and the nerves and blood vessels of the meninges is called the **"Trigeminovascular System".**

In short the migraine central generator clicks on the switch, the trigeminovascular system is activated, the blood vessels of the coverings of the brain dilate, and the meninges become inflamed. The central generator is in the brain and the peripheral pain mechanism in the meninges.

It is not known how an aura with spreading depression turns on the generator, or how the generator turns on in the absence of aura. Perhaps the generator is the major point at which the hyperexcitable nerve cells do their intermittent firing.

Meningitis is also an inflammation of the meninges, but it is usually due to an infection. Migraine pain is like sterile, noninfectious meningitis, because the meninges become inflamed. And like migraine, meningitis hurts.

## ➢ Serotonin[4]

Nerves communicate with each other via chemicals that diffuse across space between nerves and turn on the next nerve. These chemicals are called *neurotransmitters*. Certain nerves release specific chemicals; others receive only signals communicated by those chemicals. In effect, some nerves speak only one language, the language of that particular neurotransmitter. Neurotransmitters can excite or inhibit nerve actions. Some nerve chemicals can do both, depending on where they go in the nervous system, and which nerves they reach. These "ambidextrous neurotransmitters" are like a driver's foot in a car. The foot can work the brake, accelerator, or clutch.

Serotonin is a neurotransmitter that can both excite and inhibit and therein lays the story of how it controls migraine.

The seven known classes of serotonin nerves in the brain are denoted **Serotonin 1-7**. Serotonin is often abbreviated as 5-HT after its chemical

name, **5-hydroxytryptamine**. Thus, these are the 5-$HT_{1–7}$ nerves, and the areas on the nerves that receive the serotonin are the 5-HT receptors.

**5-$HT_1$** receptors are negative or inhibitory receptors; **5-$HT_2$** receptors are positive or excitatory receptors. It is possible that when serotonin binds to the excitatory 5-$HT_2$ receptors near the migraine central generator, it turns on the migraine. Serotonin 2 may be the switch at the generator or the route to the accelerator.

Migraine patients may have too much release of serotonin at the central generator, or there may be too many accelerators, or the accelerator is too easily depressed. Why the generator turns on only in distinct episodes and in response to particular triggers is one of the mysteries of migraine.

When the generator turns on, it activates the pathways that cause inflammation and blood vessel dilation in the meninges. 5-$HT_1$ receptors can turn off the inflammation and shrink the vessels. Therefore, to control the 5-$HT_1$ system is to control the migraine pain. It is like putting the foot on the brake.

Serotonin can act like a foot on the accelerator: if it binds to the 5-$HT_2$ receptors, it turns on migraine. But serotonin can act like a brake: if it binds to the 5-$HT_1$ receptors, it turns off the migraine pain, by deactivating the inflammation and shrinking the swollen vessels.

There are two main types of 5-$HT_1$ receptors, **5-$HT_{1B}$** and **5$HT_{1D}$**. The 5-$HT_{1B}$ receptor is on the blood vessels of the meninges; activating it shrinks blood vessels. When it occurs outside the brain, the 5-$HT_{1D}$ receptor turns off the inflammation by preventing the nerves from releasing the chemicals that are the cause. The chemical most likely to have neuroinflammatory effect in migraine is **Calcitonin Gene Related Peptide (CGRP)**, which also

dilates blood vessels. Serotonin, activating the 5-$HT_{1D}$ receptor, may help get rid of migraine pain by inhibiting CGRP release.

Therefore, when the serotonin binds to 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors, both mechanisms of migraine, blood vessel dilation and inflammation, are turned off.

Finally, the signal has to get back into the brain from the inflammation and blood vessel dilation. 5-$HT_{1D}$ receptors in the brain control the portal of entry of the signal from the meninges. If these "central" 5-$HT_{1D}$ receptors are activated, they block the entrance and inhibit the signal's reentry into the brain.

## ❖ PHYSICAL FINDINGS & CLINICAL PRESENTATION:

- Normal between episodes
- Normal for migraine without aura.
- Focal motor or sensory abnormalities possible for migraine with aura or migraine variants.
- Common aura types include scintillating scotoma, bright zigzags, homonymous visual disturbance such as paresthesia, speech disturbances, or hemiparesis (familial or sporadic hemiplegic migraine). Other visual phenomena include image distortion or "Alice in Wonderland" effect.[(1)]

**Table 1 : Symptoms of a Migraine Attack[6]**

| | |
|---|---|
| **Prodrome** | Fatigue, irritability, and food cravings. |
| **Aura** | Vision disturbance (seeing flashing lights or blind spots), numbness or weakness on one side of the body, slurred speech, and sensitivity to light and sound. |
| **Headache** | Throbbing headache (in 60 percent of cases, headache on one side of the head); lasts four to seventy-two hours. |
| **Associated symptoms** | Nausea and vomiting, diarrhea, lightheadedness, dizziness, and ringing in the ears (tinnitus). |
| **Postdrome** | Fatigue, euphoria, surge in energy, increased appetite, and confusion. |

## ➢ The Prodrome[6]

→ Some migraine sufferers experience *prodromal,* or preheadache, symptoms that may precede the headache by hours or days.

→ Prodromal symptoms are somewhat vague and may include fatigue, irritability, and food cravings, often for carbohydrates and chocolate.

## ➢ The Aura[6]

→ Almost 15 % of migraine sufferers experience auras in the form of visual, sensory, cognitive, motor, or speech disturbances twenty minutes to an hour prior to the development of head pain.

→ Visual auras may involve flashing lights, zigzag lines, bright spots of different shapes and colors, or loss of vision in one or more quadrants of the visual field.

→ Motor auras sometimes produce weakness or numbness on one side of the body.

→ People with speech auras can have slurred speech.

→ The aura phase of a migraine typically lasts ten to thirty minutes, after which the headache phase begins.

### ➢ The Head Pain[6]

→ Migraine headaches are typically severe, throbbing, sometimes disabling head pain, although some sufferers experience milder degrees of pain.

→ Approximately 60 percent of people with migraines report a pain on one side of the head, often behind or around one eye.

→ The frequency of attacks varies widely, from two or three attacks a week to two or three attacks a year.

→ The pain can last anywhere from four to seventy-two hours, feels sharp "like a knife" or "pressure like," and is "made worse with each heartbeat."

→ The headache can also worsen with exposure to noise, light, or any body movement; this explains why it is virtually impossible for some sufferers to go to work during an attack.

→ Usually, all the sufferers want to do is go to a quiet, dark room, and remain still, hoping to sleep off the head pain.

### ➢ Associated Symptoms[6]

→ Besides the head pain, most migraineurs report associated symptoms such as nausea and vomiting, dizziness, increased urination, and even diarrhea.

→ Others report pain in the hands and feet, probably caused by changes in blood circulation to the extremities.

→ Other associated symptoms include tingling or numbness in the lips, tongue, or face, or in the fingers on the same side as the headache.

→ Family and friends often report that migraine attacks change the sufferer's personality.

### ➢ The Postdrome[6]

→ After the headache pain and associated symptoms clear up, it is not uncommon for sufferers to feel fatigued and prefer to be left alone. (Unfortunately, friends and family members often make the situation worse by insisting on helping the migraineur during an attack.)

→ Some migraineurs experience a surge of energy, euphoria, and increased appetite up to twenty-four hours after an attack.

Other post headache symptoms include confusion, loss of memory, and difficulty performing common physical tasks.

## ❖ CLASSIFICATION

According to the International Classification of Headache Disorders, third edition (ICHD-3), Migraine headaches are classified as follow[7]:

**1** Migraine

- **1.1** Migraine without aura
- **1.2** Migraine with aura
  - **1.2.1** Migraine with typical aura
    - **1.2.1.1** Typical aura with headache
    - **1.2.1.2** Typical aura without headache
  - **1.2.2** Migraine with brainstem aura
  - **1.2.3** Hemiplegic migraine
    - **1.2.3.1** Familial hemiplegic migraine (FHM)
      - **1.2.3.1.1** Familial hemiplegic migraine type 1 (FHM1)
      - **1.2.3.1.2** Familial hemiplegic migraine type 2 (FHM2)
      - **1.2.3.1.3** Familial hemiplegic migraine type 3 (FHM3)
      - **1.2.3.1.4** Familial hemiplegic migraine, other loci
    - **1.2.3.2** Sporadic hemiplegic migraine (SHM)
  - **1.2.4** Retinal migraine
- **1.3** Chronic migraine
- **1.4** Complications of migraine
  - **1.4.1** Status migrainosus
  - **1.4.2** Persistent aura without infarction
  - **1.4.3** Migrainous infarction
  - **1.4.4** Migraine aura-triggered seizure
- **1.5** Probable migraine
  - **1.5.1** Probable migraine without aura
  - **1.5.2** Probable migraine with aura

**1.6** Episodic syndromes that may be associated with migraine

**1.6.1** Recurrent gastrointestinal disturbance

**1.6.1.1** Cyclical vomiting syndrome

**1.6.1.2** Abdominal migraine

**1.6.2** Benign paroxysmal vertigo

**1.6.3** Benign paroxysmal torticollis

## ❖ DIAGNOSIS

- In general, no additional investigation is needed with recurrent, typical attacks with usual age of onset, family history, and a normal physical examination.
- If there is an unusual presentation and/or unexpected findings on examination, investigation for other causes is required.[(1)]

### ➢ LABORATORY TESTS

- Lumbar puncture is required for history of abrupt-onset headaches and uncertain diagnosis of migraine.[(1)]

### ➢ IMAGING STUDIES

- Imaging should be done in patients with headaches and an unexplained abnormal finding on the neurologic examination.
- Imaging should be considered in patients with rapidly increasing headache frequency, history of dizziness or incoordination, headache causing wakening from sleep, or headaches worsening with Valsalva maneuver.[(1)]

# H E A D A C H E  B Y  J N O  C .  K I N G

- **Title:** Headache and Their Concomitant Symptoms With a Complete and Concise Repertory-Analysis

- **Author:** Jno C. King, M.D.

- **Edition:** Second Edition

- **Published by:** W. A. Chatterton(1891), Chicago

- **Current Publisher:** Forgotten books[8]

- **Outline of the book:**
  - Many times Headache itself becomes prominent symptom and the chief complaint of patient. So the author felt the desirability of collecting our knowledge of Materia Medica into a form available for immediate service.[9]
  - This book can be used in an emergency, or to refresh the memory, or as an index to remedies that should be more thoroughly studied for a given case.[9]
  - The book is divided into two parts:
    - **I.** Materia Medica
    - **II.** Repertory Analysis
  - Materia Medica has 169 remedies presented in alphabetical order.
  - The remedies are described in following headings:
    - **i.** Note

**ii.** Location, Direction, Character

**iii.** Other Head Symptoms

**iv.** Aggravation

**v.** Amelioration

**vi.** Concomitants

- Repertory analysis is given just after the Materia Medica.
- It is has following headings as a main chapter :

**i.** Type

**ii.** Causes

**iii.** Times

**iv.** Conditions

**v.** Peculiar sensations

**vi.** Location

**vii.** Direction

**viii.** Character

**ix.** Aggravations

**x.** Ameliorations

- Rubrics are arranged in alphabetical order.
- Sub rubrics are given without indentation which resembles to main rubric.
- Remedies are not graded in the rubrics.
- Repertory does not include concomitant symptoms because the author says that a complete repertory of concomitants would have been endless, an incomplete one worthless, therefore none has been made.[(9)]

## ❖ FORMATION OF BOOK

This work was originally undertaken by the Allegheny County Materia Medica Club. The club transferred the work to a committee; the committee in turn transferred it to the author, who desires to return sincere thanks for the use of manuscript prepared by members of the Club, and for the kind assistance rendered him by Drs. Caruthers and Strong, of Allegheny City, Pa.[9]

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