

## MIGRAINE AND MAGNESIUM: ELEVEN NEGLECTED CONNECTIONS

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*... the natural sciences ... can be said to be a living organism developing by the addition of little cells, a veritable body of knowledge proving itself to be such by the very fact of this almost unconscious growth, with thousands of parts oblivious to the whole, nevertheless contributing to it.—ALLAN BLOOM. [1, p. 345–346]*

Allan Bloom's cytologic epistemology invites further analysis. A scientific article is like a cell that interacts with its neighbors to form an organ-like cluster—a set of articles or a "literature" addressed to a common set of problems and topics. These articles interact by citing one another—by conversing in print. The clusters themselves can be seen as interacting, to varying degrees, with other clusters. This essay will focus on certain failures of intercluster communication.

I shall call two literatures "logically" related if the arguments they advance about the phenomena to which they respectively refer are related in some interesting way. One can imagine that two distinct clusters or literatures might be logically related yet mutually isolated or "noninteractive"—like two clusters of cells oblivious to their relatedness, nevertheless contributing to it. The failure of two literatures to interact or communicate would suggest that any logical relationship between them may be unknown or, at least, undocumented. For any documentation acceptable to science would have to refer to or mention both literatures and so violate the assumption of noncommunication.

Undocumented connections arise neither by chance nor by design but as a result of the inherent connectedness within the physical or biological world; they are of particular interest because of their potential for being discovered by bringing together the relevant noninteractive literatures,

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like assembling pieces of a puzzle to reveal an unnoticed, unintended, but not unintelligible pattern. The fragmentation of science into specialties makes it likely that there exist innumerable pairs of logically related, mutually isolated literatures.

In earlier articles, I called attention to one such pair [2, 3]. The first literature contained evidence that dietary fish oil causes certain blood and vascular changes, and the second contained evidence that these same changes might ameliorate Raynaud's disease. The two literatures were mutually isolated but logically related by the implicit hypothesis that dietary fish oil might benefit Raynaud patients. That hypothesis apparently had not previously been published—perhaps because the two literatures had not before been considered together.

In the present article I demonstrate something similar for the pair of literatures on migraine and magnesium. The goal of this work is not simply to find unnoticed connections but to develop a systematic approach to the process of hunting for them. As in the preceding case, one begins with a disease for which neither cause nor cure is known. The problem is to find, within the literature, indirect evidence that an unknown cure might already exist. The literatures on fish oil and magnesium, respectively, were not fortuitous choices; they were the survivors of a process of elimination.

#### *A Systematic Trial-and-Error Search Strategy*

I have described in an information science article an exploratory trial-and-error process to aid in the discovery of logically related noninteractive medical literatures [4]. To illustrate that process, I showed how one could begin with the literature on Raynaud's disease and follow a search strategy that leads to a cure hypothesis without knowing the specific destination in advance. The first part of the process, aided by Medline searching, is intended to stimulate hypotheses about all plausible chains of causation and mechanisms of therapeutic action. The second part includes online searching of the SCI (Science Citation Index®) and is intended to eliminate interactive literature pairs.

In the present study, I began with an online search of the literature on migraine and followed a similar strategy. That strategy is based in part on a search for possible intermediate links in the causal chain of events that might lead from some unknown therapeutic agent to the amelioration of migraine. In the Medline file, there are about 2,500 article titles that contain the word "migraine." Scanning certain subgroups of such titles, selected in an online search, can be helpful in stimulating conjectures about words and phrases, co-occurring with migraine, that might be clues to some of the intermediate links that are sought. These words and phrases can then become the basis for further online searching to

form "intermediate" literatures that are not about migraine but that might contain clues to potential therapeutic agents.

For example, suppose one examines a list of (40 or so) titles that contain the phrase "classic migraine." One of the titles refers to the possible relation of spreading depression to the visual scotomata of classic migraine. (Spreading depression is a phenomenon experimentally induced in laboratory animals; it refers to a wave of persisting depression of neural electrical activity in the brain cortex that spreads from a point of stimulation.) The phrase "spreading depression" is next explored on its own, by examining titles in which it occurs and reading the literature itself as necessary. One can discover among other things that magnesium in the extracellular cerebral fluid can prevent or terminate spreading depression. Combining this new fact with the above connection, one is led to the conjecture that magnesium deficiency might be a causal factor in migraine.

A surmise that migraine might be a vasospastic disorder led to another connection with magnesium. By examining several hundred titles containing the word "vasospasm," one can notice a few titles indicating that a magnesium deficit can cause vasospasm. That discovery can be made more efficiently if one guesses at the outset that a deficiency of some kind might be implicated. By requiring the Medline subheading "deficiency" to appear in the descriptor field, one can narrow the several hundred titles with "vasospasm" down to four, of which three are about magnesium.

The foregoing exploratory process did not, of course, lead directly or exclusively to magnesium; it led also to many other guesses, most of which were discarded. The hypothesis that magnesium deficiency might be important in migraine was among the few survivors. The process of discarding poor guesses is based in part on weeding out hypotheses supported by interactive literatures. For example, had it been found that there were many migraine articles that referred to magnesium, or vice versa, then it is likely that any causal connection between them would already have been explored, in which case the conjectured connection would have been of no further interest here.

A Medline search can quickly provide an estimate of whether two literatures are likely to be interactive, by determining their set-intersection. In August, 1987, there were about 4,600 records that contain the word "migraine" and 38,000 that contain "magnesium" in Dialog Medline (File 155). Only six records were common to both sets. These six will be discussed at a later point, but so small a number suggests that the two literatures on migraine and magnesium are virtually noninteractive. Hence any logical connection between them is probably not well known.

Once the magnesium conjecture has been made, it becomes easy to

discover other intermediate literatures—that is, literatures that intersect both the migraine and magnesium literatures, and which therefore can be thought of as linking them. To pursue our previous example, a search for “migraine” and “spreading depression” produced 35 references, and a search for “spreading depression” and “magnesium” produced 17 references (Dialog Medline 8/1/87). Similar linkages can be found by appropriate searches based on each of the following terms, among others: vascular reactivity, depolarization, epilepsy, inflammation, prostaglandins, platelet aggregation, serotonin, brain anoxia, and calcium channel blockers. Such word linkages do not in themselves imply that there is necessarily a logical connection between the respective discussions about migraine and magnesium; they are, however, suggestive of such a connection, and so worth investigating.

Remarkably, one of the 35 articles on migraine and spreading depression, an article by Gardner-Medwin published in 1981, begins as follows:

In these days of library computers it is possible to search the literature for papers linking two or more keywords. If one were to pick out the following associations: *neuroglia—potassium*; *potassium—spreading depression*; *spreading depression—migraine*, one would make quite an impressive collection. Try to link neuroglia with migraine, however, and there would be little to show. The aim of this paper is to explore the three associations set out above. [5, p. 111]

The quoted passage, clearly related to the method I have been using in this series of studies, had escaped my notice for the past 6 years; not unnoticed is a certain poetic justice in this reminder of my own neglected connections, encountered while trying to remind others of theirs.

It is clear that the migraine and magnesium literatures are mutually isolated to a high degree—by and large they do not cite or refer to each other. Whether the two literatures are logically related is yet to be examined. The rest of this article will address that question.

#### VASCULAR MECHANISMS OF MIGRAINE

Until a few years ago, there seemed to be widespread agreement that the primary mechanism of “classic” migraine (migraine preceded by neurological symptoms) consisted of a chain of events initiated by cerebral arterial vasospasm and ischemia, followed by reactive vasodilation of extracranial arteries; the resulting distension of the dilated vessels was presumed to be the source of headache pain. Symptoms include periodic severe headache and often nausea and vomiting, preceded by scotomata and other visual disturbances, and paresthesias. Most therapies have consisted of vasoactive drugs [6, pp. 346–347].

New methods of measuring cerebral blood flow in humans came into use in 1981 and have led to results that are difficult to reconcile with a primarily vascular mechanism. As a result there has been renewed inter-

est in an even older, neurogenic theory of migraine. The discovery by Leão of spreading cortical depression was instrumental in rejuvenating that theory.

#### MIGRAINE AND SPREADING DEPRESSION

The literature on migraine and spreading depression for my purposes contains a story within a story. A close logical connection between two key independently developed papers, appearing in 1941 and 1944, respectively, apparently went unnoticed for 14 years. That connection, once pointed out, seemed sufficiently interesting and persuasive to generate a substantial literature of its own.

The first paper, by K. S. Lashley, described the visual disturbances that characteristically precede a migraine attack [7]. The consistency of the disturbance reported is in itself remarkable. It begins typically as a small blind spot near the center of the visual field and drifts, in a horse-shoe shape, toward the periphery. The spreading spot is fringed at the outer edge with zigzag scintillations or "fortification figures," a description that originated more than 200 years ago. In 1870, Dr. Hubert Airy had given an eloquent 15-page description, with a full-page illustration in color, of these spreading fringed scotomas and called the disorder "teichopsia," a name still in use, to suggest the wall of a fortified town [8]. Both Lashley and Airy noted that the disturbances took about 20 minutes to traverse the visual field, and that they are identical or symmetric in the two eyes. Both men concluded that the process originated in the brain. Using a figure of 67 mm for the anteroposterior length of the cortical striate area, Lashley concluded that a disturbance taking 20 minutes to travel from center to periphery of the visual field must propagate through the cortex at a rate of about 3 mm per minute, a figure that was destined to attract considerable attention many years later. Lashley characterized the scintillations as a phase of intense excitation. "They occur along the advancing margin of the area, followed by a blind region, as if a wave of strong excitation were followed by a phase of total inhibition" [7, p. 336].

Three years after Lashley's paper appeared, Aristides A. P. Leão, at the Harvard Medical School, published his classic dissertation on spreading depression of electrical activity in the cerebral cortex of the anesthetized rabbit [9]. By means of either an electrical or mechanical stimulus applied to the exposed cortex, he was able readily to induce a depression of electrical activity that started at the point of stimulus and spread in all directions over the cortex at the rate of about 3 mm per minute. A series of papers followed that confirmed and extended these results; SD (spreading depression) was no isolated curiosity—it could be evoked consistently in rabbits, cats, opossums, and pigeons. Leão

pointed out that the mechanism of spread appears similar in these animals to the slow spread of epileptiform discharge. Moreover it was accompanied by vasodilation of the pial arteries [10], a phenomenon that prompted Leão and Morison in 1945 to comment on the suggestive similarity to vasodilation in migraine and to the slow march of scotomata in the sensory sphere, in spite of the presumed association of the latter with vasoconstriction [11].

It is notable that Leão and Morison did not cite or mention the 1941 paper by Lashley, an oversight that seems to have deprived their migraine conjecture of its most suggestive evidence—the remarkable fact that Lashley had independently described a wavelike cortical depressive disturbance that propagated at the rate of 3 mm per minute. Indeed, that similarity apparently went unnoticed for the ensuing 14 years. In the meantime, Grafstein added interesting evidence based on experiments with the isolated cerebral cortex of the cat. Among other things, he discovered that the wave of SD was preceded by a brief wave of intense neuronal activity [12]. The resemblance to Lashley's description of the fortification fringe as involving intense excitation thus became even more striking, but went unnoted by Grafstein. Finally, then, in 1958, P. M. Milner, of McGill University, noticed what others had apparently overlooked and, in a one-page article, called attention to the resemblance between the processes described, respectively, by Lashley, Leão, and Grafstein [13]. In 1959, an extensive review of the literature on SD by Wade Marshall at the National Institutes of Health cited 146 references and mentioned only Milner as calling attention to the Lashley paper [14]. A check of the SCI, and its online version, since 1955 turned up 25 papers that have cited both Leão and Lashley, none earlier than Milner's and at least 16 of which mention Milner as being the first to notice the Lashley/Leão connection.

The above story represents, in miniature, the main point of this article—namely, that by bringing together logically related but noninteractive literatures (in the Milner case, two single articles) one might discover unintended and unnoticed connections of value.

The extraordinary citation history of the Milner paper itself is of interest. An "average" paper is cited most heavily in the few years after publication and would be expected to receive 80 percent of its total citations within the first 13 years [15, p. 28]. During the first 13 years following its publication (1958 through 1971) the Milner paper was cited 10 times; during the next 13 years (1972 through 1985) it was cited 37 times, in journals covered by the SCI. These data suggest that interest has been steadily increasing in the association between migraine and spreading cortical depression.

Apparently the first author to examine in depth and critically the suggestion Milner put forward was Gardner-Medwin in 1981 [5, 16],

followed a few years later by A. J. Hansen [17]. Gardner-Medwin points out that, if SD occurs at all during migraine, it probably would occur during the initial pre-headache phase when, according to the classic vascular theory of migraine, vasoconstriction is presumed to occur. The fact that a migraine attack can be aborted by inhalation of a CO<sub>2</sub>/O<sub>2</sub> mixture, a potent vasodilator, had long been taken as evidence in support of a vasoconstrictive initial phase [6, pp. 234–235]. Gardner-Medwin showed that a CO<sub>2</sub>/O<sub>2</sub> mixture inhaled by anesthetized rats was effective in terminating SD within a minute or so [18]. Although the mechanism of action was unknown, this new finding undermined any argument that migraine abortion through CO<sub>2</sub>/O<sub>2</sub> inhalation counted more strongly for the classic vascular theory than for mechanisms involving spreading depression. Gardner-Medwin and Skelton concluded that: "In our view the evidence strongly suggests that SD is responsible for the symptoms of the aura in at least some types of migraine attack" [16, p. 131].

#### MIGRAINE AND SPREADING OLIGEMIA

Although it had long been known that migraine was accompanied by abnormalities of cerebral blood flow (CBF), thus supporting the idea that vascular disturbance was a key factor, recent more accurate measurements of CBF reported by Jes Olesen and Martin Lauritzen at the University of Copenhagen have changed the prevailing views of migraine. Using sophisticated high-resolution equipment to detect radioactive particles (xenon-133) introduced into the bloodstream through intraarterial injection or through inhalation, they performed serial measurements of regional blood flow simultaneously in 200–300 cranial areas in migraine patients before, during, and after headache attacks. They found that the onset of the prodrome of classic migraine (but not "common" migraine) was characterized by focal hyperemia in the occipital region, followed by a wave of oligemia spreading forward through the cortex at a rate of about 2–3 mm/minute (again!) that left in its wake temporarily impaired vascular and neurologic function associated with the region of hypoperfusion. The oligemia persisted for up to several hours following the prodromic phase—that is, well into the headache phase, thus throwing into doubt the association of vasodilation with the pain of headache. A delayed hyperemia was observed after about a 6-hour period but was clearly unrelated in timing to the headache phase [19–23].

A striking feature of the spreading oligemia was its failure to follow the territory of supply of any of the major cerebral arteries, thus refuting the idea that vasospasm within such arteries was an initiating event of

a migraine attack. One would infer that other mechanisms must be more important, such as arteriolar vasospasm or some abnormal neurogenic metabolic process within the cortex itself. Whether ischemia is regularly involved is open to question, since the reduced blood flow may be secondary to decreased metabolism. Both Lauritzen and Olesen conclude that blood flow change is probably secondary to neural or cortical events [24, 25].

Within the human cortex, spreading oligemia appears to be unique to migraine. Similar changes have not been found in over 1,000 patients with various other brain disorders studied with the same equipment [24].

Numerous authors during the past few years have interpreted these results on spreading oligemia as suggesting a link between migraine and spreading cortical depression. Such a link would argue for a neurogenic rather than a primarily vascular mechanism for migraine. Recent reviews by Lauritzen, Olesen, Pearce, and others have marshaled the evidence and the arguments in support of this view [24-30].

From animal experiments, SD is now known to be accompanied by depolarization of neurons and marked changes in the distribution of ions between the intra- and extracellular compartments, as well as by an initial brief wave of hyperperfusion followed by a 25-40 percent diminished blood flow that may last 70 minutes or more in the rat [19, 23, 24, 26, 30, 31]. The speed and mode of progression of spreading depression, its localization in the cortex, and its aftermath of hypoperfusion with impaired neurologic function are all consistent with observations of blood flow and visual disturbances in migraine [30]. The perfusion changes in migraine attacks have been closely replicated in SD experiments with rats [32].

#### MIGRAINE, NEURAL EXCITABILITY, AND EPILEPSY

Welch has attempted to encompass both the vascular and neurogenic aspects of migraine in a unifying description of the mechanistic pathway. He suggests that the cause of migraine must be sought among biochemical factors that alter the threshold of a neuronal circuit composed of projections to the intrinsic noradrenergic system. Once this threshold is set to a low enough value, numerous potentiators of a migraine attack can precipitate spreading neuronal depolarization. Thus, enhanced neural excitability and a susceptibility to spontaneous depolarization characterize migraine. Disordered neurogenic control of circulation is presumed to be secondary to the spreading depression of neuronal activity. As part of the evidence he cites in support of his model, Welch draws on a comparison with epileptic attacks, which he suggests are



initiated by spontaneous depolarization, the threshold for which is modulated by the noradrenergic system [33].

A connection between migraine and epilepsy has been suspected for most of the past century, but the nature of any such connection is still obscure. Basser in 1969 reviewed the evidence and suggested that spreading depression may be the basis for an intimate relationship between the two phenomena [34].

Olesen has argued that spreading depression may explain transient global amnesia, citing evidence that SD is easily elicited in the hippocampus of animals and that experimental SD causes amnesia and interferes with the ability to acquire new knowledge [35, 36]. A few reports have offered evidence for an association between migraine and transient global amnesia [35, 37]. Although there is no direct evidence that SD can be elicited in the cerebral cortex of man, it has been evoked in the hippocampus and caudate nucleus [36].

#### MIGRAINE, HEAD PAIN, INFLAMMATION, AND SUBSTANCE P

A possible mechanism of pain in headache has been illuminated by Michael Moskowitz and coauthors, who in 1979 proposed the hypothesis that the abnormal release of SP (substance P, a neuroactive peptide) from trigeminal nerve terminals mediates both the head pain and vasodilation of migraine headache [38]. The trigeminal nerve provides the principal afferent pathway for the transmission of head pain in humans. Studies of cats subsequently confirmed that the trigeminal nerve provides the major source of SP through fibers surrounding cerebral arteries [39]. Moskowitz describes trigeminal fibers as part of a defensive network that protects the brain both from the entry of noxious substances that may cross from the circulation under pathological conditions and from such substances produced locally within the brain. Vascular headaches, he suggests, may reflect a disturbance in the interaction between the trigeminal nerve and its target organ, the cerebral blood vessel. Pain is not attributed to dilating blood vessels but is the result of depolarization-induced release of vasodilators such as SP from sensory fibers [40].

Sicuteri and coauthors at the University of Florence have also noted that SP, released by trigeminal fibers, induces vasodilation, plasma extravasation, and conjunctival and nasal congestion, all of which bear some similarity to symptoms of cluster headache and migraine attack. Moreover, opiates and somatostatin inhibit the release of SP from primary sensory nerves and relieve both pain and autonomic symptoms of cluster headache attack [41].

The asymmetry of head pain in migraine has always been difficult to

explain in terms of a primarily vascular theory. Experiments reported recently provide support for a neurogenic theory. A clear relationship was demonstrated between the laterality of migraine pain and the rate of habituation for electrodermal responses to visual stimuli. During intervals when they were free of headache, patients with predominantly right-sided migraine were compared with patients prone to left-sided migraine. Right-sided cases were far more responsive than controls and left-sided cases far less responsive; there was no overlap in the rate of habituation between the left and right groups. The authors interpret these results as pointing to a deficiency in a mechanism that regulates responsiveness of the autonomic nervous system in controlling regional cerebral activation [42].

Experiments with monkeys have shown that electrical stimulation of the locus ceruleus produced vasoconstriction in the cerebral circulation and vasodilation extracranially. It was postulated that similar neural activation in the locus ceruleus in humans might explain the changes in blood flow, vascular reactivity, and head pain during a migraine attack [43].

Pain is a classic sign of inflammation, and migraine has been described as a sterile inflammatory disease of cranial blood vessels. SP applied to the eye is known to evoke an inflammatory response and vasodilation. Moskowitz suggests the need for SP-receptor blocking drugs for the treatment of vascular headaches and certain inflammatory conditions [40].

#### MIGRAINE AND PROSTAGLANDINS

In 1968, Lars Carlson and co-workers reported experiments with eight healthy men who were given infusions of prostaglandin E1 (PGE1). A pulsating headache and other migraine-like symptoms were induced in all eight subjects, none of whom had a prior history of migraine [44]. Citing this and other evidence, Horrobin suggested in 1977 that a PGE1-like substance is the final common cause of all types of migraine [45]. In laboratory experiments with a rat artery preparation, he had found that low concentrations of PGE1 potentiated vasoconstriction and increased concentrations produced vasodilation, thus potentially explaining both the putative vasoconstrictive and subsequent vasodilation phase of migraine. He noted that, at that time, virtually all drugs useful in the treatment of migraine were prostaglandin inhibitors. Recent experiments demonstrating the antimigraine effectiveness of mefenamic acid and other fenamate compounds, all potent prostaglandin inhibitors, support the idea that prostaglandins are implicated in the pathogenesis of migraine [46]. However, the fact that migraine attacks

can be aborted by drugs other than prostaglandin inhibitors poses a challenge to the prostaglandin theory. Parantainen has proposed a way out of the difficulty by suggesting, and citing evidence, that PGE1 alone is without effect but acts strongly to potentiate the response to mediators of pain such as SP [47]. PGE1 acts cooperatively with SP in other respects as well; research on the eye of the rabbit has shown that nerve conduction facilitated by the release of SP or a similar substance seems to be required for the miotic effects of low-dose PGE1 [48].

#### MIGRAINE, SEROTONIN, AND PLATELET AGGREGATION

The discovery in 1971 by Hilton and Cumings of increased platelet aggregability and abnormal sensitivity to serotonin release in headache-free migraine patients, compared to healthy control subjects, has been corroborated in more recent studies and has been noted by many reviewers [49–56]. Hilton and others have suggested that platelets in migraine patients may differ characteristically from those of normal subjects. Results of cross-incubation experiments reported by Mück-Seler and coauthors appear to support such an idea. Blood plasma from migraine patients during attacks was able to trigger platelet serotonin release from other migraineurs but not from healthy subjects [57]. These results also imply that a specific serotonin releasing factor must be present in the blood of migraine patients. Free fatty acids (FFA) have been suggested for that role [58].

Hanington proposed the hypothesis that migraine is caused by a primary platelet disorder, citing evidence based on differences in platelet behavior and content between migraine patients and normal subjects [50, 51]. The plausibility of that hypothesis was disputed by Joseph, Steiner, and others on the grounds that the clinical response to a number of drugs, notably beta blockers, was found to be not correlated at all with platelet response [52, 53]. They suggest that platelet alteration during a migraine attack could be a nonspecific consequence of stress, a point not unrelated to Anthony's suggestion that stress followed by release of catecholamines, FFA, serotonin, and prostaglandins leads to the headache phase of a migraine attack [53, 58].

There is little doubt that platelets and serotonin are strongly implicated in migraine, but whether in a primary or secondary role is a matter of dispute. Serotonin is released from platelets during a migraine attack, thus causing a transient increase in plasma serotonin which, through its vasoconstrictive action, is then thought to play a role in the development of the headache phase of the attack. Plasma serotonin is rapidly metabolized, leading to a drop in blood levels of serotonin as a consequence of a migraine episode. Thus blood factors in migraine may depend on timing with respect to the migraine cycle.

#### MIGRAINE AND BRAIN HYPOXIA

In 1974, Bücking and Baumgartner suggested that both migraine and spreading depression might be initiated by focal cerebral hypoxia. They previously found that in experimentally induced hypoxia, brain tissue exhibited first a burst of electrical activity followed by silence, resembling what Grafstein had described for spreading depression [12, 59, 60]. In an extended review in 1980 of the effect of anoxia on ion distributions in the brain, Anker Hansen marshaled additional evidence showing even more striking similarities between SD and brain anoxia [61]. He suggested that the mechanisms controlling the ionic shifts in these two phenomena are similar and probably involve changes in ionic permeability of brain cells [62]. Such changes do not in general represent a point of no return in either SD or anoxia, but recently reported experiments with rat brain tissue have thrown light on probable mechanisms of irreversible change. In demonstrating a protective effect of chlorpromazine, which acts by delaying SD, Balestrino and Somjen concluded that SD can interact with oxygen deprivation, in the presence of extracellular calcium, to bring about irreversible damage [63]. Such damage apparently is caused through an influx of calcium into the cell, a point that is further explicated in two brief essays by Vanhoutte, who suggests therefore that there may be a role for calcium channel blockers in protecting the brain against adverse effects of hypoxia [64, 65].

The principal advocate of a hypoxia theory of migraine is Willem Amery, of Janssen Pharmaceutica in Belgium. Amery postulated that a short-lived episode of focal brain hypoxia initiates both classic and common migraine and is also responsible for the typical headache phase of such an attack. Based on that hypothesis, pharmacologists at Janssen investigated various drugs that might have a protective effect against brain hypoxia and selected flunarizine, a calcium channel blocker, as a potential migraine prophylactic. In 1982, Amery published an extensive analysis, citing 237 references, which provides a rationale for his hypoxia theory and so for the use of flunarizine as a therapeutic or preventive agent [66].

The initiating hypoxic episode postulated by Amery does not necessarily entail brain ischemia. Hypoxia arises essentially through an imbalance of supply and demand for oxygen and so may be precipitated by increased need for oxygen by brain tissue as well as by diminished supply. The theory does not require that all episodes of hypoxia lead to migraine but states only that people with migraine may be more susceptible to hypoxia. Thus, migraine in this view is a specific reaction pattern to an episode of focal cerebral hypoxia [67]. Although Amery's argument is impressive and his story cohesive, there is no single type of evidence that decisively implicates hypoxia in a migraine attack. The

case appears to rest most heavily on the putative link with spreading depression and the ion distribution similarities already mentioned, as well as evidence that Amery cites for excessive sympathetic tone in migraine patients. This latter factor may lead to uncoupling the regulatory mechanisms of oxygen supply and demand.

Migraine is usually regarded as a disease that runs a benign course, but if hypoxia is always present, one might expect migraineurs to be more prone to the eventual development of hypoxic brain damage. Amery marshals evidence in support of such an expectation [68].

The main significance of Amery's theory is that it provides a systematic account of hypoxic mechanisms in migraine without requiring a primary ischemic episode in the initiation of a migraine attack.

#### MIGRAINE AND CALCIUM CHANNEL BLOCKERS

An astonishing variety of drugs is used in the treatment of migraine, and each drug has numerous pharmacologic effects. While many of these treatments are clinically useful, none is satisfactory, and none can be considered a cure. Because of such variety, instances of successful clinical experience are of little help in identifying the pathogenetic basis for migraine or even the specific site of therapeutic action [69].

Nevertheless, the relatively recent discovery that calcium channel blockers (CCB) are effective in migraine prophylaxis raises interesting theoretical as well as practical questions. The important question of whether migraine is primarily a vascular or neuronal disorder is not, however, immediately resolved by the effectiveness of CCB, for there are apparently drug-sensitive calcium channels in neurons as well as in vascular smooth muscle [69]. Flunarizine has been among the more successful of these CCB, as evidenced by at least six placebo-controlled trials, several controlled trials comparing flunarizine with other drugs, and a large number of open trials; most of these studies have been reviewed [69–76]. Perhaps the most notable aspects of these tests has been the consistent finding that a relatively long period (2–5 months) is required to achieve optimal prophylactic effects. One reviewer notes that such a finding is difficult to understand since direct vascular effects are more or less immediate [70]. Although the superiority of flunarizine for migraine prevention is far from settled, it is worth examining some of the reasons why it might be different from other CCB.

All drugs that block the entry of calcium ions into the cell are not chemically similar. Van Zwieten has suggested that, from a pharmacological point of view, a distinction should be made between calcium channel blockers and calcium overload blockers. Calcium channel blockers inhibit the slow transmembrane current carried by calcium ions under normal physiological conditions. Calcium overload blockers, on

the other hand, inhibit only the overload of the cell with calcium ions that occurs under pathological, ischemic conditions [77]. Van Zwieten places flunarizine in this latter category and cites evidence that it is effective in protecting brain tissue against ischemia-induced calcium overload [77]. Other researchers have noted that intracellular calcium overload may be a common pathway to failure of cell functioning and eventually to cell death [78].

Researchers at Janssen have offered evidence that flunarizine treatment improves the survivability of rats placed in a nitrogen environment, and, in contrast to other CCB, protects laboratory animals against hypoxic-induced memory deficits. Moreover, they reported that flunarizine has a direct neuronal protective effect in improving post-hypoxic recovery of synaptic function *in vitro* and other studies indicating that it was effective in raising the threshold for spreading depression [79–81]. Laboratories other than Janssen have reported similar protective effects of flunarizine—against hypoxic-ischemic brain injury in rats, anoxic-induced failure of brain electrical activity in rats, hypoxic effects of cyanide in rat brain tissue, and hypoxia-anoxia in mice and rats [82–87].

The mechanism of action of flunarizine is yet to be clarified; one study *in vitro* found an antioxidant or free-radical scavenging activity that may play a role in brain protective action [88]. One report, from the Mayo Clinic, indicated a failure of flunarizine to improve either cerebral blood flow or neurologic recovery from ischemia in dogs [89]. Flunarizine has been claimed to be effective in experimental models of epilepsy and in therapeutic trials in epilepsy patients [90].

#### MIGRAINE AND TYPE A PERSONALITY

Descriptions of migraine-associated personality in the older literature bear a close resemblance to descriptions of what is now called the type A personality. Impressed by this similarity, two independent teams of behavioral scientists recently administered the Jenkins Activity Survey, which is designed to measure type A behavior, and a questionnaire about headache frequency to several hundred college students. Both teams reported a statistically significant positive correlation between type A score and headache frequency [91, 92].

#### *Magnesium-Deficiency Hypothesis*

I next examine magnesium literature in the light of the hypothesis that a disturbance of magnesium function may play a key role in classic migraine. I leave open the question of whether classic migraine is itself a single disorder, and whether other types of headache are similar enough

to classic migraine to be encompassed by the hypothesis. Headaches are not often included among the symptoms of magnesium deficiency but they are mentioned by Durlach, who also mentions paresthesias and other symptoms that may accompany migraine [93]. Anorexia, nausea, and vomiting are part of the migraine syndrome and were mentioned by Shils as being among the many consequences of experimentally induced magnesium deficiency in humans [6, 94, 95]. The first systematic identification of a magnesium-deficiency syndrome is apparently that of Hanna and coauthors, who note, among other things, that the electroencephalographic symptoms are suggestive of a focal cerebral lesion [96], a particularly interesting comment in the light of similar hypotheses about migraine [7, 8, 19, 24, 29, 33, 66].

In an article focused almost entirely on the vascular effects of magnesium, Altura and Altura mention that clinical neurological symptoms are conspicuous in states of magnesium deficiency—notably, muscle fasciculation, cramps, paresthesias, tetanoid attacks, and predisposition to epileptiform convulsions [97]. Similar symptoms have been associated with migraine prodromata or accompaniments.

Dietary surveys and metabolic balance studies have provided evidence that magnesium intake is less than optimal in the American diet and has been declining during most of the present century [97]. At the same time, there has been increasing intake of nutrients that increase the requirement for magnesium, especially vitamin D and phosphorus [98]. In a recent review of the magnesium content of food, Marier cites a U.S. Department of Agriculture survey of 37,000 individuals which showed that only 25 percent of the respondents had a dietary magnesium intake equal to or greater than the RDA (recommended dietary allowance); 39% of those surveyed had an intake less than 70 percent of the RDA [99].

Thus, neither the known symptoms of magnesium deficiency nor evidence based on average dietary intake provides grounds for dismissing, a priori, the idea that migraine may be a magnesium-deficiency disorder.

Each of the following sections will identify factors that are related to both migraine and magnesium, the same factors that were discussed in the preceding sections on migraine.

#### MAGNESIUM AND TYPE A PERSONALITY

Some subgroups of the population may be especially at risk for magnesium deficiency. Bella Altura has suggested that, because stress causes an increase in blood levels of free fatty acids, which in turn induces loss of blood magnesium, type A behavior in effect entails, at least intermittently, a virtual deficiency of magnesium [100]. There is some evidence

for such a connection [93, 98, 101, 102]. Durlach discusses stress-induced urinary hyperexcretion of magnesium [93]. Henrotte has reported experimental data that he interprets as supporting Altura's hypothesis. He identified 20 type A students by means of the Jenkins Activity Survey and measured various biological parameters before and after a stressful mental task [101, 102]. Red blood cell magnesium levels decreased significantly after the test; such a change did not occur in a control group of non-type A students. Concomitant with the red cell magnesium drop, plasma levels increased. Citing data on stress-induced urinary loss of magnesium, Henrotte interpreted the plasma magnesium increase as transient and concluded that type A behavior in the long run would be associated with magnesium deficiency. He found also that plasma magnesium levels were lower in the type A group than in the control group prior to the stress test. The difference was not statistically significant but was worth mentioning because another group had reported a similar nonsignificant difference [103]. Taken together, the two results might well reach significance, but neither author provides enough data to permit a combined statistical analysis.

#### EFFECT OF MAGNESIUM ON BLOOD VESSELS

That magnesium has a profound effect in reducing vascular tone, contractility and reactivity to a variety of vasoactive substances is well established and has been noted in numerous reviews [97, 104–106]. Hypermagnesemia induces rapid vasodilation and suppresses contractions elicited by potassium, angiotensin, catecholamines, and other neurohumoral substances. Besides modulating the effect of other substances, magnesium has a direct effect on vascular tone and may have an important role in regulating cell membrane permeability to calcium ions. Cerebral arterial smooth muscle appears to be more sensitive to magnesium manipulation than most peripheral vessels [97]. Observation of pial arterioles in cats with implanted cranial windows has shown that large (eightfold) increases and decreases of magnesium in the surrounding artificial CSF (cerebrospinal fluid) produced modest vasodilation and vasoconstriction, respectively [107]. In vitro experiments with cerebral arteries from dogs showed that withdrawal of magnesium from the surrounding medium caused vasospasm, while elevated magnesium produced relaxation [108].

Magnesium administered orally at 450 mg/day for 3 months normalized initially low levels of serum magnesium and was found to relax vasospasm in retinal vessels of patients with high-renin essential hypertension [109]. A similar effect was observed in a placebo-controlled test of tetanic patients, using rheoencephalography, a method of measuring



volume and tonus oscillations of cerebral blood vessels. A dosage of 360 mg/day of magnesium for 4 weeks significantly reduced hyperventilation-induced vasoconstriction in these patients [110].

#### MAGNESIUM AS A CALCIUM CHANNEL BLOCKER

In a 1984 editorial in the *American Heart Journal*, Iseri and French reviewed a large amount of evidence that magnesium acts as a natural calcium channel blocker. They concluded, as had Altura and Altura earlier, that membrane and extracellular magnesium can act physiologically to control and regulate the entry of calcium into smooth muscle cells; excess magnesium will block, and deficiency of magnesium will potentiate, the action of calcium [97, 105, 111].

Calcium directly affects muscle tension and neuromuscular activity. Through controlling calcium, magnesium influences the contractility, tone, and reactivity of vascular smooth muscle. Magnesium appears to compete with calcium over nonspecific binding sites. A deficiency of magnesium, leading to influx of calcium, may be responsible also for the loss of intracellular potassium. A comparison of magnesium with the calcium entry blockers nifedipine and verapamil has shown a similar profile of action in feline cerebral and coronary arteries [112]. Altura and coauthors argued that magnesium is a weak but unusual kind of calcium channel blocker. Unlike other CCB which are more specialized, magnesium can act on potential-operated, receptor-operated, and leak-operated channels [113, 114].

A mathematical model of muscle tension as a function of calcium binding, and of relaxation attributed to competition between magnesium and calcium for the same binding site, was tested on aortic smooth muscle tissue from rats and corroborated [115].

#### MAGNESIUM AND SPREADING DEPRESSION

It has been known since 1960 that magnesium ions introduced into the cerebral cortex can block spreading depression [116]. In 1978, van Harreveld discovered and more recently confirmed that two different types of SD could be elicited in the isolated chick retina. One type was based on the release of glutamate and the other on the release of potassium. The latter mechanism was originally suggested by Grafstein [12]. Van Harreveld found that the glutamate-mediated SD, but not the potassium SD, was inhibited by magnesium ions [117, 118]. The fact that magnesium was widely used to inhibit SD meant therefore that the mechanism of SD in such cases was probably based on glutamate release.

Recent experiments with isolated rat hippocampal slices showed that low magnesium in the perfusate induced epileptiform activity and

spreading depression. The authors attribute the effect primarily to the release of glutamate receptors from the inhibitory action of magnesium ions [119–121].

#### MAGNESIUM, NEURAL EXCITABILITY, AND EPILEPSY

In 1967, Durlach described successful oral magnesium therapy in a patient with spasmophilia and an "epileptic form" of latent tetany [122]. He suggested that there may be magnesium loss in epileptic neurons and that such a neuronal magnesium deficit may lower the epileptogenic threshold [122, 123]. He also reviewed earlier literature indicating abnormal levels of blood and CSF magnesium in epileptic patients and concluded, among other things, that there is a leakage of magnesium from the epileptic neuron prior to and during a seizure [123]. In 1965, Canelas found, in a study of 83 epileptics during seizure-free periods, that CSF levels of magnesium were high and blood levels were low, although these two variables were significantly and positively correlated [124]. Heipertz also found that CSF magnesium, but not serum magnesium, was abnormally high in epileptics during the period from 3 days to 1 month following a seizure, a period during which a downward drift in CSF magnesium was also observed [125]. Jain et al., on the other hand, found low values of both serum and CSF magnesium in a study of 68 patients with idiopathic epilepsy [126]. The timing of the measurements with respect to seizures was not specified.

Parenteral magnesium sulfate has long been well known as an anticonvulsant, but the site of the therapeutic action has not been clear. In 1978, experiments at The Johns Hopkins on dogs, cats, and monkeys showed that intravenously infused magnesium sulfate suppressed epileptic neural activity induced by topical application of penicillin G to the motor cortex. Normally one would not expect intravenous magnesium to penetrate an intact BBB (blood brain barrier). However, the integrity of the BBB may be at issue; the authors point to evidence that acute convulsions can increase BBB permeability in the cortex and/or thalamus [127].

Rats fed a magnesium-deficient diet become highly susceptible to epileptic seizures and have been proposed as a model for the study of epilepsy and the effectiveness of antiepileptic treatments. Seizure susceptibility depends on low CSF magnesium and not on low blood levels of magnesium, thus indicating that the relevant site of action for magnesium is in the central nervous system [128].

#### MAGNESIUM, INFLAMMATION, SUBSTANCE P, PROSTAGLANDINS, SEROTONIN, AND PLATELET AGGREGATION

Hairless magnesium-deficient rats have been proposed as a model for the study of skin inflammation [129]. Several strains of rats on a

magnesium-deficient diet developed a temporary allergy-like crisis, with a progressive redness of skin and dermatosis. Nonsteroidal antiinflammatory drugs were not active in this model, thus indicating, according to the authors, that prostaglandins are probably not directly involved [130].

Prostaglandins are involved, however, in the vascular actions of magnesium. A recent clinical study of the effect of infused magnesium sulfate on blood pressure in 10 healthy subjects showed that the expectable drop in blood pressure was accompanied by an increase in prostacyclin formation, as revealed by increased urinary excretion of prostacyclin metabolites. The authors concluded that prostacyclin release plays a key role in systemic and renal vasodilator effects of magnesium [131]. One *in vitro* study showed that magnesium sulfate increased the release of prostacyclin from human umbilical arteries and at the same time enhanced the inhibitory effect of prostacyclin on platelet aggregation [132]. The authors inferred that magnesium must act directly on the aggregation process independently of prostacyclin.

Additional evidence that magnesium inhibits platelet aggregation has been reviewed by Seelig [98]. More recently, experiments have shown that magnesium-deficient rats developed increased susceptibility of blood platelets to thrombin-induced aggregation [133, 134] and serotonin release [135, 136]. Magnesium can also abolish adenosine diphosphate (ADP)-induced platelet aggregation in whole human blood *in vitro* [137], as well as in platelet-rich plasma [138]. High levels of dietary magnesium (or calcium) fed to rabbits on a high-fat atherogenic diet caused a decrease in thrombin-induced platelet aggregation. The authors attribute the beneficial effects of magnesium and calcium to their ability to form insoluble salts with fatty acids [139]. Magnesium has also been shown to inhibit serotonin-induced contractions of vascular smooth muscle, thus mitigating one of the possibly adverse consequences of platelet aggregation [140, 141].

There is little literature indicating any interaction between magnesium and SP, but there is at least one report of an antagonistic effect of magnesium. It was found that magnesium chloride suppressed the enhancement by SP of the twitch response elicited in an isolated guinea pig *vas deferens* by stimulation of postganglionic sympathetic neurons [142].

#### MAGNESIUM AND CEREBRAL ANOXIA

There is considerable evidence that magnesium can protect the brain against damage from anoxia. Cultured hippocampal neurons from rats normally die when exposed to an oxygen-free atmosphere, and so such cultures have served as a model for the study of anoxic damage. Cell death can be prevented by adding magnesium chloride (at high, non-

physiological levels) to the culture. This protective effect might depend directly on blocking synaptic transmission, indirectly by blocking release of harmful substances, or by elevating the threshold for spontaneous activity [143]. Several investigators have shown that calcium entry into the cell is probably a key event in the mechanism of anoxic damage [143-145]. It may be worth noting, in view of the theory of migraine advanced by Lance, that this protective effect of magnesium has been observed in neurons of the locus ceruleus [43, 145].

Intravenous infusion of magnesium sulfate has been shown by White and coauthors to prevent reactive decrease in cerebral blood flow (the "no reflow" phenomenon) during reperfusion following experimental cardiac arrest in dogs [146]. Brain damage from anoxia is attributed to calcium influx and is thought to occur during reperfusion rather than during a preceding period of total ischemia. Initial hyperfusion is normally followed within 15-30 minutes by reduced blood flow consequent to a large increase in cortical cerebrovascular resistance. White et al. showed that this increase is also prevented by the magnesium infusion. These authors hypothesized that calcium influx into the neuron leads to release of arachidonic acid which passes through the BBB to enter the blood circulation and cause platelet activation and release of thromboxane, the consequence of which is a further increase of cerebrovascular resistance, reduced blood flow and further anoxia. Several calcium channel blockers, including magnesium sulfate, were tested in this model and found to be effective [146-150]. It was mentioned earlier that flunarizine protected rats against postischemic brain damage, but in that case the mechanism did not appear to be associated with altered blood flow [86].

Magnesium sulfate injections have also been shown to prolong the survival of neonate rabbits deprived of oxygen [151]. Other literature on the beneficial effects of magnesium in hypoxia has been reviewed by Seelig [98]. There is a substantial literature on studies of brain resuscitation following cardiac arrest, of particular interest here in suggesting a mechanism such as White proposed that might connect neuronal activity with cerebral blood flow phenomena in the pathogenesis of migraine. Paulson and Newman have recently argued, on the basis of a theoretical analysis of potassium dynamics in the brain, that the transport of potassium via astrocytic glial cells may be an important mechanism for the control of cerebral blood flow [152].

#### *Summing Up—Migraine-Magnesium: Eleven Linkages*

The foregoing literature analysis has identified the following 11 factors as relevant to both migraine physiopathology and to the physiological effects of magnesium: type A personality, vascular tone and reactiv-

ity, calcium channel blockers, spreading cortical depression, epilepsy, serotonin, platelet activity, inflammation, prostaglandins, substance P, and brain hypoxia. These factors are more than just relevant; the nature of the relationship in each case is consistent with the hypothesis that a magnesium deficiency of some kind may be a causal factor in migraine.

Stress and type A personality, factors associated with migraine, tend to cause magnesium wastage. Magnesium can ameliorate excessive vascular tone and reactivity, factors that may aggravate or predispose to migraine. Flunarizine and other calcium channel blockers have been used successfully in the long-term prophylaxis of migraine; magnesium acts as a weak but versatile calcium channel blocker. Spreading cortical depression elicited in laboratory animals and conjectured to be a key event in the prodromic phase of migraine is inhibited by sufficiently high levels of magnesium in the extracellular cerebral fluid. There is evidence that magnesium deficiency may increase susceptibility to epilepsy, and evidence for a connection between epilepsy and migraine. Magnesium deficits can lead to high levels of serotonin release, platelet aggregation, inflammation, and SP activity, as well as to low levels of prostacyclin release. All such effects tend to aggravate vascular effects of migraine or are thought to be implicated in its pathogenesis. Finally, magnesium may have a protective effect against brain damage from hypoxia and there is evidence and argument to suggest that cerebral hypoxia plays a role in the mechanism of migraine.

Magnesium seems to be implicated in every step of a complex cascade of events that constitutes a migraine episode and bears an implicit but unnoted relationship to every theory that has been advanced to explain the mechanism of migraine. Especially striking is the fact that migraine clearly entails both neural and vascular processes, and that magnesium plays an important role in both neural and vascular reactivity.

#### PREVIOUS LITERATURE ON A POSSIBLE CONNECTION BETWEEN MIGRAINE AND MAGNESIUM

I have already mentioned that there are very few articles about both migraine and magnesium, but my suggestion of a possible connection is not the first. In 1967, Klaus Simon included a brief paragraph on migraine in a book on the pharmacology of magnesium. He claimed to have frequently used magnesium glutamate injections to abort acute attacks of migraine combined with abdominal disturbance, but did not report a controlled study, nor did he provide data, literature references, or any discussion of therapeutic mechanism [153, p. 59]. Vosgerau in 1973 reported similar successful experience with 10 or so migraine patients, using the same treatment as Simon. He included some discussion

of the vascular theory of migraine and the presumed therapeutic action of magnesium, but his reference to the magnesium literature was limited essentially to Simon's book [154]. A more recent attempt to abort acute migraine attacks with infusions of magnesium sulfate in five angina patients was reported as unsuccessful [155]. In connection with this latter failure, it should be noted that the successful use of calcium channel blockers for migraine prophylaxis required 2–5 months of therapy. The reported successes of Simon and Vosgerau in aborting acute migraine attacks apparently have not been repeated or explained. So far as I have been able to determine through literature searching, there have been no clinical trials of migraine prophylaxis with either oral or parenteral magnesium.

The only substantial recent discussion of a migraine/magnesium hypothesis appears to be that of Burton Altura [156]. Altura observed that all drugs recommended for treatment or prevention of migraine attacks act on cerebral blood vessels. He went on to call attention to most of the links with the vascular theories of migraine that I have mentioned in this article. He did not, however, point to connections with neurogenic theories. It is notable that Altura's paper has not yet been cited by other authors. One other group has made a unique contribution. In 1985, A. C. Jain and coauthors reported finding significantly low levels of CSF magnesium in migraine patients, during both headache and nonheadache phases, compared to controls. Serum magnesium was not found to differ [157].

The principal objective of my research is to bring to light unintended and unnoticed connections in the medical literature. A second purpose is to call attention to similar discoveries by others whose work may not be appreciated as being unusual in standing almost alone as a bridge between two otherwise noninteractive literatures, as does Altura's for migraine and magnesium.

#### A CO-CITATION ANALYSIS

A search was conducted for all articles in the Dialog Scisearch® database that cited any of the 65 migraine articles or any of the 63 magnesium articles in the references listed for this article. By appropriately sorting the search output one can readily locate all articles that co-cite any two or more articles among those searched.

The outcome was as follows: 179 articles cited two or more migraine articles among the 65 that were searched, 115 articles cited two or more magnesium articles among the 63 that were searched, but only 10 articles cited at least one magnesium article and at least one migraine article together. None of these 10 articles discussed a migraine/magnesium

hypothesis or cited the migraine and magnesium literatures together to any significant degree. In short, this co-citation analysis turned up nothing substantial or new on the migraine-magnesium connection, but it did confirm that the migraine and magnesium literatures were communicative clusters within themselves but were in effect mutually noninteractive.

#### FITTING THE PIECES INTO A COHESIVE STORY

Almost all existing theories of migraine have focused on mechanism rather than on underlying cause. The idea of magnesium deficiency as a cause therefore has the advantage of filling a vacuum as well as unifying an impressive number of indirect connections. Whether such deficiency is purely a matter of diet, and perhaps stress, or whether disorders of metabolism or regulation intervene to produce magnesium deficits in red blood cells, neurons, glial cells, cell membranes, blood serum, or CSF are still open questions.

The periodicity of migraine headache is a feature not well explained so far by any proposed theory or mechanism; there seems to be little doubt that a refractory period follows a migraine attack, and the same may be true of epilepsy. Such periodicity is suggestive of a self-limiting, or homeostatic process. Perhaps in this direction lies a more complete and cohesive story.

Magnesium within the CSF is normally regulated and maintained within fairly narrow limits, at a consistently and substantially higher level than blood magnesium but almost independently of fluctuation or manipulation of the latter [158]. Little seems to be known about the mechanism of that regulatory process. We might suppose that epilepsy and migraine are different manifestations of a similar disorder of homeostatic regulation, a response to a magnesium deficit that entails, among other things, excessive excursions of both neural activity and CSF and blood electrolytes. If that is so, then individuals with epilepsy or migraine would be expected to show cyclic variation of serum and CSF levels of magnesium correlated with attacks and remissions; there is some evidence that this is so. Any sample of such individuals taken at random times with respect to migraine attacks or epileptic seizures would be expected therefore to have much higher inter-individual variability of blood and CSF magnesium than would healthy controls. That surmise appears to be supported by three separate series of magnesium measurements in epileptics; the reported standard deviations are from two to four times higher in epileptics than in normal controls [124–126]. The timing of magnesium fluctuations with respect to the cycle of either epileptic seizures or migraine attacks requires further investigation.

#### SIGNIFICANCE OF THIS RESEARCH

The significance of this analysis lies in the form of its argument and the citation structure of the literature on which that argument is based. To understand that form and structure is to gain insight into how, through a process of online searching and literature exploration, new knowledge might be extracted from the body of knowledge already published. The process of exploration and extraction depends on identifying mutually isolated, logically related literatures and piecing together their respective arguments to yield new conclusions and connections not apparent in the separate literatures.

This paper, and the earlier example [2], show how such new connections might be discovered; whether the physiological hypothesis advanced in each case turns out to be correct or mistaken is incidental to the more general purpose of illuminating form, structure, and process. I hope these examples will encourage others to engage in similar adventures of literature exploration in a quest for connections that cut across the boundaries of insular specialties. The opportunity for discovery is limitless, for the information explosion is, above all, a connection explosion.

Expertise in all specialties is not a prerequisite for seeing new connections. My own ignorance underscores this point, for better or worse. Being neither physician nor physiologist, I do not bring to this review any medical knowledge that goes beyond what is obvious in the literature I cite; my purpose has been to assemble the ideas of others, like putting together a puzzle—albeit a puzzle with some unknown number of missing pieces. This analogy can perhaps best be appreciated by noticing that the titles of the appended references almost by themselves suggest a good part of the story told in this review. Rearranging the references into certain migraine-magnesium pairs is even more suggestive. Notice, for example, the titles of the following seven pairs: [16, 119], [34, 128], [41, 142], [56, 139], [57, 140], [71, 111], and [91, 100], bearing in mind that the respective members of each pair are cells from mutually oblivious literatures.

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