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Vinod Kumar Gupta *

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Review Article

The 'Pre-Prodromal' or 'Pre-Premonitory' Phase Holds the key to the Cause-Effect Basis of Migraine Buried over 25 Centuries: Continuum of the Confusion surrounding Allodynia-Randomized Controlled Trials-Stress-Intraocular Pressure-Migraine Nexus

Vinod Kumar Gupta

(General Medicine) Medical Director – Physician Migraine-Headache Research Centre S-407, Greater Kailash-Part Two, New Delhi-110048 India.

***Corresponding Author:** Vinod Kumar Gupta, M.B.; B.S.; M.D (General Medicine) Medical Director – Physician Migraine-Headache Research Centre S-407, Greater Kailash-Part Two, New Delhi-110048 India.

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Abstract

Migraine is a protean recurrent cephalalgogenic neuro-ophthalmologic disorder caused by an 'autonomic storm' (AS) associated external-carotid arterial system linked selective / exclusive aberration of the peripheral division of ophthalmic division of the trigeminal nerve (V1) with lateralizing headache, non-homonymous visual field defects including scintillating scotoma (SS) and other forms of visual / non-visual hallucinations, and unpleasant autonomic nervous system (ANS) symptoms such as nausea / vomiting well-known over 25 centuries, since the intuitive observation of Hippocrates (c. 460-c.370 B.C.). The functional connectome of migraine that affects almost one-fifth of humankind has become an increasingly complex neuro-ophthalmological-endocrinological mystery, constituting a social stigma with exponential increase in statistical but not biologically significant data that form a series of Gordian knots of worsening proportions, both in series and in parallel. Scientific literature of migraine is frustratingly vast, increasingly diverse, and pathophysiologically and clinically disheartening. Recently, pathological (morphological and functional) principles that govern migraine and other primary headaches have been clearly evolved. Migraine is not a pan- or holo-trigeminal disorder, but selectively or exclusively involves aberration of the oculo-peripheral components of the first division of the trigeminal nerve (V1). "Trigeminovascular system" is a misleading term that obscures the overriding clinic-pathological importance of peripheral computations of the oculo-trigeminal system, including V1, oculo-sympathetico-intraocular pressure and sclero-corneal systems. Overemphasis on different symptomatic phases of migraine, absolutely without any neurophysiologic scientific basis or a pivotal systematic structuring of the scattered diversely expanding evidences into a robust, generalizable, predictable, logical, defensible, and constantly enlarging overview has worsened the cause-effect conundrum. Division of a common entity such as migraine into pathophysiologically-incomprehensible apparently distinct phases such as the prodrome / premonitory, aura, headache, and postdrome intervals does not allow for a seamless, comprehensive and gestaltic synthesis. 'Ictal' (attack) and 'interictal' (between attack) phases complete the presumed circle of migraine, with an erroneous or pseudo-link with epilepsy that extends to both theory and therapy. Lateralizing V1 headache (unilateral, bilateral, side-shifting, or side-fixed) is the most consistent phase of migraine while aura (SS / other hallucinations) is the most varied and inconsistent phenomenon, creating and sustaining the debatable entities, migraine with aura (MwA) and migraine without aura (MwoA). Non-homonymous nasal-visual field sparing digitally-displaceable and ocular movement-synchronous SS is the pathognomonic visual feature of MwA, the typical expression of which requires a normally-functional eye. The origin of migraine lies in the pathophysiologic aberrations of the asymptomatic or subclinical currently unlabeled 'pre-prodromal' or 'pre-premonitory' phase. Onset of spontaneous / experimental migraine attacks is generally insidious and linked to a threshold that may be primed by a single or multiple triggers. Psychosocial stress is the commonest precipitant of migraine, the

pathophysiological mechanism(s) of which remains completely unknown. The psychosocial stress / stressor (overt or subliminal) and other trigger-linked AS that operates in the 'pre-prodromal / pre-premonitory' phase covertly generates migraine, with the clinical consequences of the primary ANS aberration, i.e. AS flowing variably into the so-called phases. A conceptual divide between homeostatic / adaptive and pathogenetic physiologic aberrations clarifies both the cause-effect spectrum as well as the typical and hitherto unexplained but characteristically delayed onset of the migraine attack. With increasing understanding of the vasopressin-noradrenaline-serotonin nexus, the vast phenomenology of migraine (central and / or peripheral, episodic or chronic, clinical or pathological) has begun to be clearly categorized either as adaptive or pathogenetic. A hyperfocus on the 'pre-prodromal' / 'pre-premonitory' phase critically shifts the pathogenesis of spontaneous / experimental, self-limited headache (4-72 hours), and other protean manifestations of migraine attacks (aura-headache) from a pan-trigeminal disorder to V1 as well as to the eye rather than the brain. In 100 years of dedicated research including technological explosion, exponential data expansion, and foundational statistical significances, the prelude of the subliminal AS phase of migraine has not been integrated into any extant brain theory or any generally accepted other phase(s) of migraine. The 'pre-prodromal' / 'pre-premonitory' phase of AS of migraine is discussed towards a complete evolution of the disorder, including integration of episodic and chronic forms of migraine. A bluish-discoloration of the supero-lateral corneo-scleral envelope is presented as a particularly weakened or susceptible pathophysiologic and functional region of the eye that can generate spontaneous or experimental nociceptive neurologic deformation or activation of V1 to develop sui generis or idiosyncratic but ocular-tamponade self-limited migraine headache attacks (4-72 hours). The higher incidence of migraine in females and decline with age / menopause is also rationalized. The 'pre-prodromal / pre-premonitory' phase of migraine is the largest, most unpredictable, attack-initiating patho-functional AS component of migraine. The pathology of migraine and its functional components are thus brought together. A full discussion of the blue-discolouration of the corneo-scleral envelope and its mural components as related to migraine is beyond the scope of this article.

Keywords : migraine ; pathophysiology ; prodromal / premonitory phase ; 'pre-prodromal' phase / 'pre-premonitory' phase ; migraine with aura (MwA) ; migraine without aura (MwoA) ; chronic migraine (CM)

Introduction

Migraine is a common cyclic / periodic but unpredictable and protean age-linked painful neuro-ophthalmological disorder with its onset often manifesting a circadian rhythmicity or 24-hour day-night pattern, affecting 15-20% of the general population, known historically to humankind in its primal form as early as 3000 B.C. in Sumerian / Mesopotamian / Egyptian writings, or even 6000 years previously. [Amiri et al., 2022; Goadsby et al., 2017; Eadie, 2012; Silberstein, 2005; Silberstein and Young, 2004; Jones, 1999; Pearce, 1986; Friedman, 1972]

Historically, Hippocrates provided by observation and inference the clearest and most intuitive statistics-free account of severe pain in one half of the head (megrim, hemicrania) associated with disturbance of sight in only part of one eye [Pearce, 1986; Allory, 1859]. Hippocrates astutely also was the first to assess the headache-decreasing effect of nausea / vomiting whenever it was possible. The cardinal features of the visual aura with unilaterality of visual brilliance were also first understood by Hippocrates. The basis of the pathologic (morphological and functional) principles underlying these components of migraine have struggled to be generally understood 25 centuries later well-into in the Third Millennium, passing through various neurological brain-related theories in different eras. Researchers and / or therapists in migraine in the later centuries offered exhaustive descriptive writings including intricate case-histories to give some logical and scientific understanding to otherwise hopelessly misunderstood observations of Hippocrates and later scientists. [Pearce,1986]

In this article, a comprehensive synthesis is offered in an attempt to further the phenomenology, pathophysiology, and therapeutics of migraine as well as to elucidate the precise onset and site of origin of the migraine attack in the 'pre-prodromal / pre-premonitory' phase.

Last 100 years (1925-2025)

Over the last 100 years, advancing technology and methodology, principally and increasingly involving maximal-impact randomized controlled clinical trials / randomized controlled trials (RCCT / RCT), use / misuse of placebo controls and statistics, and exponentially expanding divergent, dissociative, and uncritical data accumulation have been the central thrust of migraine research. However, without a central theoretical overarching framework or logic or unifying hypothesis, and, a paucity of precisely replicating studies have led to an arbitrary rigid pseudo-understanding of migraine, almost as an exclusively brain-based neurologic disorder, that over time, has become mixed with traditional or canonical authoritarianism, mysticism, myths, assumptions, serendipity, and various forms of rationalism, empiricism, pragmatism, bias, advocacy, and irrational skepticism. [Gupta, 2024; 2023; 2019; 2010; 2009; 2006a].

Such partial comprehension of migraine, a largely functional and typically protean disorder with a prominent female predominance in adults, has encouraged purely phenotypical nosological hyper-splitting sans pathophysiologic basis, wide fragmentation of the research question itself by stimulating investigative laboratory data, and analyses / meta-analyses data at the expense of an overriding robust generalizable predictive and gestaltic synthesis. [Gupta, 2024; 2023; 2019; 2010; 2009; 2006a]. Laboratory data create artificial or misguiding individuality impeding the recreation of the whole. [Gupta; 2019; 2009; 2007; 2006a; Blau, 1992] Medical myths or assumptions can only rarely if ever be constructively corrected. In every era, the principal psychosocial functions of myths are designed: (i) to offer a vicarious resolution of the ignorance that lies between our insecurities and expectations, (ii) to blur the requirements for evolution of critical research questions, (iii) to encourage the publication of novel but paradoxical and controversial statistically-significant data, and (iv) to dissipate the value of the face-validity and pithy commonsense. [Gupta, 2024; 2019; 2010; 2009; 1997; 2006a; Feinstein, 1994; Popper, 1976; Medawar, 1967] All observation is subjective, including the RCCT / RCT. There is nothing like a purely objective observation or an apparently absolute and invaluable scientific abstract, the Popperian logic and futuristic relevance of which cannot be improved [Lancet, 1992; Popper, 1976; Watson, 1968; Medawar, 1967]. Current abstracts in published articles in migraine / primary headache are far from definitive, but are carried on the shoulders of pre-published empirical and / or experiential statistically-significant data or visions or hypotheses, huge components of hedge terms (may, might, should, likely, can, possible), hope, hype, and hokum, and inevitably end-up with

proposition of more investigations and hypotheses in the same vein. The specific philosophic approach of the investigators to the problem at hand may itself become a critical variable in the design and conduct of a given research strategy; dampening of overenthusiasm and appropriately spurring each other or the group is pivotal to scientific discovery (see below) [Gupta, 2024; 2010; Watson, 1968; Popper, 1976; Carrel, 1959].

Migraine is believed to result from a salient central brain dopaminergic or limbic system / hypothalamic aberration. [May, 2018] Central computing of the differential trigeminal nerve is currently assumed to set apart the first division of the trigeminal nerve (V1) with particular pathogenetic value [May, 2018]. This key misguiding tenet of central computing of V1 neurologic traffic as the pivotal pathophysiologic source of genesis of migraine attacks, is an overriding traditional or canonical but completely arbitrary and speculative belief. Such a hyperpolarized theoretical landscape is not consonant with the reason or logic underlying both of the major phenotypic types of migraine [migraine with aura (MwA) or migraine without aura MwoA)], including recurrent spontaneous circadian origin, lateralized pain in parts of V1 (fronto-temporal, periocular, vertex, or nuchal regions) with typical side involvement such as unilateral, bilateral, side-shifting, or side-fixed, self-limited duration and spontaneous termination (4-72 hours), female preponderance in adults with decline in frequency with age in both sexes, including menopause, aggravation in the first trimester of pregnancy and subsidence in II and III trimesters, as well as non-homonymous digitally displaceable and ocular movement synchronous scintillating scotoma (SS) and non-homonymous visual field defects [Gupta, 2024; 2023; 2019]. These limitations also apply to the surgical hyperfocus on the great (greater) occipital nerve, that has been speculated upon as a possible source of compression, entrapment, or irritation that might lead to periodic and circadian attacks of migraine. [Huff et al. 2024; Guyron et al., 2023; Inan, et al., 2019; Allen et al., 2018; Martelletti, et al., 2016; Mosser et al., 2004; Guyron et al., 2002; Guyron et al, 2000] The cause or etiology of pathogenetic episodic self-limited compression, entrapment, or irritation of superficial scalp nerves or muscles, with a pronounced predilection for females that dies off with advancing age in both sexes, has also never been elucidated. Unexpected or serendipitous / chance findings in animals experiments or in human patients without a definitive etiological, mechanistic, and sound theoretical background have misdirected migraine research in the last 100 years, including CSD, CSD-suppressing pharmaceutical agents, positive and definitive results of prophylaxis with propranolol, nadolol, and atenolol, scalp muscle / nerve involvement with surgical resection and/or scalp muscle / nerve blocks by infiltration with lidocaine or botulinum toxin, closure of patent foramen ovale (PFO), or use of CGRP- or CGRP-receptor antagonists. [Caronna et al., 2024; Gupta, 2024; 2010, 2006a; Guyuron et al., 2023, 2002, 2000; Wang et al., 2022; Zhang et al., 2024; Zhang et al, 2022; Liu, et al., 2020; Tobias, et al., 2017; Blumenfeld et al., 2015; Mosser et al., 2004; Rabkin et al., 1966; Leáo, AAP, 1944; also see above] There is no theoretical basis for the uncommon-to-rare genesis of the pathognomonic SS by CGRP and its abolition by CGRP-antagonists or CGRP-receptor antagonists. In real life situations, outside the exuberance of evidence provided by RCCT / RCT and opinions of tertiary-care centres, the clinical prophylactic utility of botulinum toxin, closure of PFO, and CGRP- or CGRP-receptor antagonists is questionable, and to date, remains limited, empirical or experimental and mired in hope, hype, and hokum as predicted decades ago. [Gupta, 2024, 2019, 2010, 2009, 2006b]. The central brain computing regions -- so-called specific brain regions, including the insula, amygdala, thalamus, and cingulate, medial prefrontal, and anterior cingulate cortex, and cerebellum commonly activated by pain stimuli in patients with chronic migraine (CM) and animal models [Xaio et al., 2024; Tao, et al., 2022; Wang et al., 2022; Andreou and Evdinsson, 2019] versus peripheral origin of migraine attack remains a highly controversial issue, but certain principles or laws of migraine pathophysiology have provided a steady, logically defensible, and progressive elucidation in favour of a peripheral origin of migraine attacks with consistently lateralizing headache limited to V1, of spontaneous origin, and self-limited duration (4-72 hours). [Gupta, 2024; 2023; 2019; 2010; 2009] (see below) How painful migraine attacks spontaneously start and equally spontaneously stop are perhaps the most important defining and differentiating features of the illness, besides the SS (visual hallucination).

The trigeminal nerve is the largest and most complex of the cranial nerves. [Terrier, et al., 2021; Edvinsson, et al., 2020; Joo et al., 2014] The trigeminal nerve transmits general somatic afferents from the face i.e., pain, temperature, vibration, fine and crude touch and proprioception, as well as motor information to the muscles of mastication including temporalis, the pterygoids, masseter and some smaller muscles— tensor veli palatini, tensor palatini, anterior belly of the digastric and mylohyoid. [Huff, et al., 2022; Leston, 2009; Walker, 1990]. The mandibular (V2) and maxillary (V3) divisions of the trigeminal nerve do not share in the distribution of pain in migraine or other primary headache attacks, and, while not as yet fully understood, there is no microsurgical neuroanatomical evidence that fibres from V2 and V3 migrate to the caudal nucleus of the trigeminal nerve to the level of C2/C3 to generate sub-occipictal / nuchal pain [Gupta, 2024; 2009; 2006a]. Importantly, a large body of scientists have only recently evoked surprise over the logic and commonsense of the trigeminal nerve being proposed as the final common pathway for around 300 variants of primary headache, as detailed in the classification of headache disorders (ICHD-3). [Edvinsson et al., 2020]

Currently, no generally accepted fundamental principles or biological / biophysical laws govern migraine research. Nevertheless, migraine is not a pan-trigeminal or holo-trigeminal disorder – an absolute principle or law of migraine pathophysiology. [Gupta, 2024; 2019; 2009; 2006a; 2006b] The composite term "trigeminovascular system" is, however, widely regarded as a pivotal advance in migraine research. [Terrier, et al., 2021; Ashina et al., 2019; Messlinger and Russo, 2019] With reference to migraine pathophysiology, the all-encompassing and currently trending composite term "trigeminovascular system" is misleading, and needs to be disposed-off in the dust-bin of the history of science of migraine / primary headache research. CSD or SD or other theories of brain / meningitic / glymphatic involvement do not differentiate between trigeminal neurological innervation of the upper or lower face or lateralization of headache or genesis of non-homonymous digitally displaceable nasal visual field sparing and ocular movement synchronous SS. Only the region of the upper face, i.e., fronto-temporal region, the vertex, and suboccipital-nuchal region is involved in lateralizing migraine headache and is innervated by V1. Axiomatically, and by holistic inference, only fibres of V1 descend to the caudal (spinal) nucleus to the level of C2, C3 are involved in suboccipital and nuchal headache, including the greater (great) occipital nerve. The neuropeptide system(s), regarded as a pivotal pathogenetic component, diffusely involve(s) the 'trigeminovascular' system, and, cannot be construed to involve V1 innervation selectively or lateralizingly. This is a key neuroanatomical limitation of the neuropeptide system (s). The brain, in addition, is not a passive receptacle. Release of any neuropeptide will be invariably accompanied by simultaneous release of opposing neuropeptides as components of the finely balanced homeostatic or adaptive orchestra of the brain. (see below)

Migraine, and its study, was apparently less complex when the labyrinthine, nebulous, numerous, and circumlocutory cul-de-sacs of migraine with subdivisions such as episodic migraine (MwA or MwOA) or tension-type headache (TTH) or chronic migraine (CM) had not become crystallized into purely symptom-based but definitive nosologic divisions, with a massive acceleration of data and opinion as primary headache 'entities' coupled to an unrelenting hunt for (imaginary) but distinct etiologies with disparate therapies. [Olesen, 2024, 2018; Kung et al., 2023; Demarquay et al., 2021; Kincses, et al., 2019; May, 2018] These sophisticated subdivisions of nosology of primary headache, including

episodic migraine (MwA or MwoA), TTH, CM are, paradoxically, regarded as a 'living and developing' discipline of research [May, 2018] A dissociation between the absolute and invaluable tenets of pharmacotherapy of migraine and its so-called imaginary and disparate so-called entities (MwA / MwOA / CM or TTH) has displaced and virtually-eliminated in theory the critical role of the BBB with loss of commonsense and face-validity in the discipline(s) of science in migraine / primary headache, leaving researchers to grapple with an enlarging mass of data along with speculation, serendipity, and empiricism but with the cause-effect nexus remaining intact during investigations [Kincses, et al., 2019; Gupta, 2019]. Such a 'hyper-split' nosologic approach discourages the evolution of an integrative synthesis in the face of the remarkable accumulation of data that promotes controversy and contention without research inclusivity and integrity.

Select beta-blockers – propranolol, atenolol and nadolol -- are the single most important yet serendipitous absolute prophylactic pharmacotherapeutic factors common to EM (MwA or MwoA), CM, TTH, and clearly indicate that the elaborate and widely-embraced nosologic hyper-splitting is both misleading and non-conducive towards the elaboration of a unifying syntheses. [Andersson and Vinge, 1990; Johannsson et al., 1987; Sudilovsky et al., 1987; Olerud, et al., 1986; Forssman et al, 1983; Stensrud and Sjaastad, 1980] While propranolol is lipophilic and readily crosses the blood brain barrier (BBB), atenolol and nadolol are hydrophilic and do not readily cross the BBB. This unexplained aspect of migraine prevention holds the key to the pathophysiology of migraine / primary headaches, axiomatically and clearly indicating that the BBB is not central to the pathophysiology of primary headaches. [Gupta. 2024;2019; 2009]

The presumed signature of cortical hyperexcitability has consumed the critical capacities of migraine researchers and is expressed with several variations, including variable contribution(s) of parallel, competing mechanisms of maladaptive plasticity and neurodegeneration, with variable results in placebo-supported arbitrary therapies (both preventive and abortive), and increasing profound biological confusion. [Marti-Marca, et al., 2023; Gollion, 2021; Kincses, et al., 2019; Gupta, 2019; Welch, et al., 1990]. Strikingly, the nosologic exuberance shared in general by the very large cohort of tertiary-care migraine researchers is completely without a key or central unifying hypotheses or verifiable and absolute or definitive target organ / tissue involvement, including the BBB (also see above) [Gupta, 2024; 2019; 2009]. This large mass of shifting sands of concepts has held up progress in migraine research for over 25 centuries. However, an anti-canonical and antithetical but unifying, predictive, and logically-robust comprehensive hypothesis was first presented in 1989, and, has been further evolved progressively with a major synthesis of craniovascular, neuro-endocrinological, neuro-ophthalmological, neuro-pharmacological, and clinical characteristics with new therapies directly linked to the psychosocial stress-intraocular pressure (IOP)-V1 algogenic neural impulses [Gupta, 2024; 2023; 2019; 2010; 2009; 2004a; 1997] This cross-disciplinary theoretical proposition has rationalized the striking predominance of occurrence of migraine attacks in pubertal / post-pubertal adolescents, adult female patients, and a remarkable increase in incidence of headache attacks with or without cyclic vomiting in first trimester of pregnancy as well as subsidence-to-complete remission with second and third trimesters of pregnancy, menopause, and advancing age in both males and females. [Gupta, 2024; 2019; 2004a; 2004b; 1997]

Migraine is the classic example of a multi-faceted and widening Orwellian confusion, Murphy's law, Popperian logic, and speculative Yin-Yang dissociation or fractionation between neuroanatomy, neurophysiology, neuro-ophthalmology, neuroendocrinology, neuropeptides, evidences from animal experiments, advanced methodology including RCCT / RCT and misuse of the placebo (see below), nosology, neuropharmacology, various forms of empirical and experiential therapies including misuse of opioids or corticosteroids, controversial concepts of BBB, and the absence of emergence of a comprehensive, clinically-robust, generalizable, logical, and predictive and gestaltic whole. [Gupta, 2024; 2019; 2010; 2009; 2007, 2006]. Pain of migraine headache idiosyncratically, self-limitedly, and exclusively affects V1, unilaterally (most often) or bilaterally (less common) with fixation or shifting of sides or the nuchal region, a characteristic not rationalized by extant widely-accepted theories [Gupta, 2024; 2019; 2009; 2006].

Despite a protracted widely-supported thrust on a critical impairment of function or partial disruption of the BBB as an important part of pathogenesis during migraine attacks over the last 100 years, the integrity of the BBB has recently been found unimpaired [Hougaard, et al., 2017]. Neuro-pharmaceutically, atenolol as well as nadolol (hydrophilic) do not freely cross the BBB, but are first-line migraine prophylactic agents equivalent to propranolol (liophilic), with propranolol readily crossing the BBB. [see above] While no amount of evidence ever proves a hypothesis, any hypothesis may be disproved by a single piece of contradictory evidence [Lancet, 1992; Popper, 1976; 1959]. Migraine researchers have consigned -- and continue to consign -- wide gaps in pathology of migraine (both functional and morphological comprehension) as swept-under-the-carpet or cart-before-the-horse controversies to the future. Such an approach that allows researchers to continue to generate and publish new / novel data unconnected with past evidences, adding more Gordian knots in series-and-in-parallel, making future generations researchers to face a huge, increasingly complicated, serendipitous and speculative research question. [Gupta, 2024; 2019; 2010;2009].

As a simple extension of Murphy's law and a twin statistical and serendipitous challenge to Popperian logic, speculation in migraine research begets speculation with ideas supported by mathematics or canonical myths, perspectives, and visions. The massive rapidly-enlarging data bank of migraine constantly dispels and worsens certitude and clarity of scientific principles. Migraine research, as is currently in vogue over the last century, is a determined collective approach to gather and publish data while dismissing any need for integration of data and absolute scientific principles, including pharmacotherapy. [Gupta, 2024; 2019; 2004] Propranolol, nadolol, and atenolol are equally effective in preventive therapy for MwA and in MwoA, the single most challenging aspect of the arbitrary and generally-accepted hyper-splitting of the classification of migraine in the last fifty years [see above]. Without resolution of extant myths in the science of migraine, no progress can be envisioned. Scientific study of migraine has become a muddled art mired in contradictions.

Error is intrinsic to human endeavor, statistical or non-statistical. [Gupta, 2024; 2019; 2010; Ioannidis, 2018; 2005; Lancet Editorial, 1995] Falsehood flies while truth comes limping much later. The credibility our research efforts depends on exclusively and meticulously following a disinterested pursuit of the truth in a non-compete fiscally-unrelated environ, a readiness to acknowledge error and to correct course of the approach, along with an overriding quest for new and replicable knowledge free from arbitrary consensus, in particular reproducibility of pharmacotherapeutics. [Gupta, 2019; Ioannidis, 2019; Kassirer, 1993] For reasons that can still not be scientifically teased apart satisfactorily, the manuscript that claimed that aspirin prolongs bleeding time was turned down [Desforges, 1993]. Additionally, therapeutic replication is intrinsically difficult in any migraine cohort because of the protean nature of the disorder, with a wide variety of triggers – single or cumulative, tangible or intangible -- and a headache phase lasting between 4-72 hours or longer while the pre-prodromal / pre-promonitory phase may last weeks, to months, to years, to decades. In the last five decades or more, much of published medical science is false, with statistical significance blurring biological / bioclinical significance while propelling 'false discoveries' [Howick, et., 2022; Ioannidis, 2019, 2005; Amrhein, et al., 2019; Mellis, 2018; Gupta, 2010]. According to the American Statistical Association, the p-value does not indicate independent or unchallengeable

clinical significance [Wasserstein and Lazar, 2016]. Continued use of the p value still appears to be a necessary drawback, even with lower values [Ioannidis, 2018]. Chance, in many forms, has become lost in data surrounding bias or prejudice, overt or covert. The quest for quantitative statistical truth has introduced and buttressed a façade of mathematical acceptability in bioscience or biomedicine that risks drawing the clinician / researcher away from clinical reality and commonsense / face-validity. [Feinstein, 1994, Horton and Kendall, 1991].

While denial of error perpetuates or aggravates confusion, acceptance of error opens the road to the hidden art in medical science providing a glimpse of the truth that can eventually lead to the elusive blue-print of pathophysiology of migraine and other primary headaches, as well as purely science-based therapies unlinked to statistics, speculation or myths. While enthusiastic authors cannot be expected to expose the flaws of their own studies, unless such flaws are detected by the editor or reviewers or by post-publication correspondence, flaws in such studies remain half-hidden and the study remains in print to mislead indefinitely or forever. [Lancet Editorial, 1993]

For over four decades, central brain computation or distribution or cross-talk of the neurons of 'trigeminovascular system' has been believed to underlie migraine attacks [Ashina, et al., 2019, May, 2018]. Therapeutic strategies using humanised monoclonal antibodies directed against calcitonin gene-related peptide (CGRP) and / or its receptor appear to support this hypothesis. Nevertheless, use of anti-CGRP therapy for preventing migraine attacks is a placebo-empowered empirical or experiential therapy with its several well-acknowledged critical limitations amounting to an over-simplification that can limit progress in the science of migraine for a long period running into several decades and even centuries [Gupta, 2020; 2019] Additionally, lateralizing headache, in particular unilateral headache characteristic of migraine, cannot be rationalized by such absolute reliance on the "trigeminovascular system" and / or the role of systemic or diffuse actions of neuropeptides. The migraine attack, as discussed above, is not a pan- or holo-trigeminal nociceptive disorder, but is typically limited to the peripheral components of V1 [Gupta, 2024; 2019; 2009; 2006a] Additionally, one of the most important features that limits deliberation of pathogenesis of migraine to central components of the V1 is the inability to rationalize the non-homonymous nasal visual-field sparing distribution of the pathognomonic SS or nasal-field sparing visual defects. (see above)

Allodynia

Mechanical allodynia (other pain) is a painful sensation caused by innocuous stimuli like light touch. [Lolignier, et al. 2015] Hyperalgesia and allodynia are frequent symptoms of disease and may be useful biologic adaptations to protect vulnerable tissues; it is far less likely that hyperalgesia / allodynia represents aetio-pathogenetic distinct disease disorders. [Sandkühler, 2009; Ashkenazi and Young, 2004] This phenomenon, also known as sensitization, is believed to more specifically involve the caudal trigeminal nucleus. [Aguggia, 2012; Ashkenazi and Young, 2005] Being an aspect of untreated migraine, allodynia is more common in patients with CM and MwA, often associated with motor and sensory symptoms sometimes present during the attacks. [Aguggia, 2021] The presence of allodynia in the course of migraine attacks is presumed to greatly increase both the disability of the patient as well as its recognition. The central sensitization underlying allodynia has, however, supplemented and / or replaced the role of CSD. Both allodynia and CSD cannot rationalize the protean, self-limited, lateralizing headache of migraine, probably its most unarguable and vital components. [Gupta, 2024; 2021; 2019] Similar critical limitations apply to the presumed pathogenetic inflammation of the meninges as well as of the brain cortex. (see above). Nevertheless, sensory innervation of the caudal trigeminal nucleus is best known to arise from the V1. [Gupta; 2019; 2009; 2004a] Just like inflammatory hyperalgesia, allodyna appears to have a protective biological role rather than any primary pathogenetic influence. Allodynia is believed to reflect central sensitization in migraine, which is, in turn, presumed to occur in second and third neurons sequentially but without support for lateralization of migraine headache. At best central sensitization in migraine reflects a secondary sensitization in brain neurons, not a primary one.

Animal experiments in migraine have largely gained strength for allodynia and / or hyperalgesia as a distinct component or mechanistic facet of migraine as well as underscored its therapeutic potential in human migraine patients. [Pijpers, et al. 2023; Polk et al., 2020; Verkest, et al., 2018; Goadsby, 2005] Scalp allodynia (more correctly than cutaneous allodynia) is an easily accessible self-perceived well-localized repetitive usually nummular nociceptive phenomenon in human migraine and less well-localized painfully elicited phenomenon in experimental animals that has, however, speculatively been believed to represent an algogenic central sensitization that is, in turn, believed to be an important mechanism in migraine chronification. Such multiple but simplistic assumptions in series and in parallel are quite frequent in migraine research. Chronic migraine (migraine chronification) is itself merely a phenomenological / symptomatic or clinical increase in a migraine headache frequency to a figure => 15 days per month with no distinct or definitive or intuitive knowledge in pathophysiology in either EM or CM simply with greater frequency of headache. It is presumed to occur in second and third order neurons sequentially, resulting in an analogous spatial distribution of cutaneous allodynia with cephalic and extracephalic symptoms. (see above)

RCCT / RCT, Informed Consent, and the Placebo in migraine / primary headache research

RCCT / RCT sits at the pinnacle of the medical evidence-based pyramid. Science and scientists as well as approving authorities – the Institutional Ethical Committees, European Agencies, and the Food and Drug Authority of United States of America (FDA of USA) – refuse to acknowledge the intrinsic limitations of the RCCT / RCT, thereby stifling the very heart of science, particular in migraine / primary headache research with its soft-end points and purely symptomatic nosology. [Gupta, 2010] The moral, ethical, and scientific compulsions of financial sponsoring of RCCT / RCT by the purely bottom-line focused Industry is not easily perceived or overcome by the scientific community. There is a mind-numbing displacement of quality and commonsense by the quantity offered by RCCT / RCT, particularly when the quasi-therapeutic comparable effect of the placebo in disease entities with purely subjective soft end-points are used, such as in migraine and other primary headaches, wherein numbers are created by grading of symptoms (see below) and given significance through statistics. [Gupta, 2010] All end-points of migraine and other primary headaches are 'soft', quite unlike myocardial pump failure, cardiac arrythmia, and death in acute myocardial infarction. [Gupta, 2010]

While the onset of headache remains nebulous or indistinct in most migraineurs, the duration, severity, localization, nausea and vomiting, and quality of life also are variables or confounders that compose an intrinsic part of the plebian nature of migraine that cannot be accounted for accurately in RCCT / RCT but can only be further blurred by large-scale statistics including the p-value, that, in turn, does not permit biological / biophysical neuro-synthetic rationalization of results from such trials. Consequently, no definitive or predictive value ensues from the results of the RCCT / RCT in migraine / primary headaches. Since no 2 cohorts of migraine are strictly comparable in terms of disease components, replication becomes impossible. Larger the cohort, greater is the intrinsic variability, and lesser is the statistical value of p. Fundamentally, the RCCT / RCT is not suitable for advancing the pathophysiology or the science of migraine / primary headaches, compelling researchers to maintain a shifting-sands empirical / experiential stance. The value of atenolol for migraine prevention was the only positive RCCT / RCT, over 40 years ago, that has advanced migraine science, pharmaceutically underscoring the negligible role of the BBB in its genesis and significantly advancing its management. [Gupta, 2024; 2019; 2004;

Hougaard, et al., 2017; Stensrud and Sjaastad, 1980; Johannsson et al., 1978]

RCCT / RCT has become a flashpoint between finance and medical science – a tribute to the human capacity to misuse every possible tool. Now, particularly in migraine / primary headache research, the RCCT / RCT determines the science, rather than the other way around. [Gupta, 2010] No cardiovascular or cerebrovascular benefit is associated consistently with PFO-closure for prevention of migraine or crypotogenic stroke (see below). The true nature or cardiovascular function of PFO (adaptive or pathogenetic) has not yet been elucidated. Migraine and embolic / cryptogenic stroke consequent to or co-morbid with PFO are assumptions that have created much confusion in cardiovascular and neurovascular medicine, both in theory and therapy, and key questions remain unanswered while tremendous controversy persists both in migraine therapeutics as well as in management of cryptogenic stroke or of any pathogenetic link between the 2 entities. [Zhang et al., 2022; Elbadawi, et al., 2018; Feldman, et al., 2018] On the basis of sound scientific principles, the prediction that PFO closure has (or would have) no definitive role in management of migraine has held true. [Gupta, 2010]

Besides publication pressure and other questionable research practices, some of which are discussed herein, the greatest appeal of the RCCT / RCT is to allow researchers to carry out new or novel scientifically quasi-credible research without having to discern the crucial clinal pathophysiological phenomenon in terms of basic sciences – a questionable scientific practice that overcomes the fundamental pillars of research propriety, inclusivity, equity, and advocacy. RCCT / RCT has encouraged researchers to suspend or even jettison clinal judgment in the hope of chance to unlock the key hidden biological process(es) underlying the entity or disorder. In the world of publication, logic, face-validity, and non-statistical commonsense are essential components of clinal judgment, that have inversely come to be regarded in RCCT / RCT as not only inconsequential, but are feared and despised as impediments to the systematic and unhindered unravelling of clinical knowledge. The Achilles heel of such clinical trials – generally sponsored by the pharmaceutical industry – is the confusing scientific premise detailed in the introduction or background and / or lost in statistical significances that complicate results. To acquire such quasi-theoretical substance, a series of assumptions are linked together in the RCCT / RCT, in series or in parallel. Acquisition of scientific data in medicine disciplines in not an end by itself. Data require a well-defined a priori matrix that is further required to be integrated into an intelligent, generalizable, predictive, and gestalt synthesis transforming scientific efforts into meaningful knowledge and wisdom. A presumptuous knowledge bridge, however, across canonical assumptions will eventually prove to be weaker than the assumptions themselves. Myths beget myths in a tortuous circle of assumptions, carrying the researcher farther away from clinical reality and commonsense. [Gupta, 2010] Quests for scientific truth demand searing personally-singeing honesty and admission of error or significant course-correction by the researchers rather than just learning the ropes of methodology and statistics to simplistically manage and publish data. [Gupta, 2024; 2019; 2010].

The second major appeal of the RCCT / RCT in migraine / primary headache research is the use of double-blind ratings. Double-blinding is presumed be bias free, even if imprecise and individually unspecified. [Feinstein, 1994] As discussed above, there is nothing like a purely objective finding; all observation is selective. [Feinstein, 1994; Medawar, 1967] Even the role of surgery or intervention as a placebo cannot be excluded as being purely objective. [Gupta, 2010; Johnson, 1994] An aura is maintained around the whole process of a clinical trial: the surroundings, the expectations, and the personalities of the both the participants and the therapists all contribute to the outcome, quite apart from the specific or non-specific effects of the procedure or placebo or both in question. Finally, the placebo effect is the effect seen in patients who have received an intervention which is believed to lack a specific action. [Gøtzsche, 1994]. Expectations, both of the patient and the therapist, are the single most important component of the placebo effect. Placebo is Latin for "I will please", implying something positive and subjective. Comparisons made in RCCT / RCT in migraine are meaningless unless the utility of the new agent is made against established treatments, such as propranolol or atenolol or nadolol. Use of placebo in primary headache research complicates the final analysis; more often than not, further trials are suggested.

The RCCT / RCT converts 'soft' endpoints in migraine patients such as frequency, severity, and duration into 'hard' numerical data through visual analogue or non-standardized rating scales, which purely symptomatic data are further subjected to mathematical logic through statistical legerdemain. [Gupta, 2010] In RCCT / RCT, the absence of scientific precision is not regarded as an important drawback. RCCT / RCT are designed to eliminate bias of various forms, but in process embrace chance with the double-blind leading the blind. Trials cloak and colour 'chance' in mathematical hues, giving respectability to much of the speculation and ambiguity in current clinical medicine, thereby giving Orwellian 'solidity' to 'pure wind'. [Gupta, 2010] Finally, the information provided as 'informed consent' in RCCT / RCT is always incomplete and to a very large extent subjective, as trials explore the vistas of incomplete and explorative knowledge in the face of limited understanding of science. [Gupta, 2010; Turney, 1996]. The provision of informed consent by the trialist has become a complex exercise that has total and unethical disregard for comprehension of informed consent by the patient / participant in a trial. Higher education of the lay patients works against their best interests and with a greater chance of inclusion in the RCCT / RCT. [Gupta, 2010] Informed consent is a an unequal but 2-way process heavily balanced in favour of the trialists and the institutional ethicists. The trialist always knows and understands the issue better than the ethicist at all levels, and misuse of ethical approval of informed consent litters the field of medical research, particularly in trials that hyperfocus on a positive result, including migraine.

"…although a modern jumbo jet comprises manifold per se sophisticated components they remain a 'heap of junk' until assembled and trimmed to perfect level of coordination that characterizes the flying wonder…" – Bjorn Folklow

RCCT / RCT gather data, but cannot assemble and trim the same into a secure neuroanatomic and neurofunctional blue-print or a progressive theory that is robust, predictive, and generalizable. Randomization is not a scientific method. However, it is an invaluable statistical strategy for the mathematical exploitation of uncertainty. [Feinstein, 1994] Medical trials generate heaps of data-related junk that cannot be assembled into a working or 'flying' hypothesis. Further discussion of the limitations of RCCT / RCT, including limitations of peer-review itself, is beyond the scope of this article.

Mathematical statistics have thrown biology out-of-the-window. [Wasserstein and Lazar, 2016; Ioannidis, 2005] For many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. There is no single, perfect way to turn data into insight. Statistical guidance provided by top-ranked journals within and between disciplines is heterogeneous and highlights a need to refine statistical practice [Hardwicke et al, 2022]. Focused on the measurable -- data and statistics – migraine researchers struggle -- but fail -- to define the term biology. [Gupta, 2010; Gupta, 2009b]

Neuropeptides, molecular structures, neuroimaging, and genetics do not constitute – and cannot supplant for -- biology of migraine. [2024; 2019; 2010; 2009]

Stress, Migraine, and other Primary Headaches

Stress and the post-stress "let-down" phase are the most common precipitants of migraine. [Stubberud et al., 2021; Marura, et al., 2019; Gonzáles-Quintanilla et al., 2015; Lipton et al., 2014; Goadsby, 2014;

Maleki, et al., 2012; Milde-Busch et al., 2011; Rains, 2009; Sauro and Beker, 2009]. Emotional exhaustion increases while personal accomplishment decreases with rise of impact on the Migraine Disability Scale (MIDAS). The Maslach Burnout Inventory (MBI) is also a potentially useful tool to study migraine impact. A fuller discussion of stress and its role in migraine is beyond the scope of this article. Suffice it is to state that no central brain theory has kept stress / stressors at the center of the hypothesis or can explain key features of migraine, including lateralization of headache, spontaneous onset and offset of headache pain, SS, and other key clinical factors as detailed elsewhere, including this article. [Gupta, 2024; 2023; 2019] Theoretical proposal for maladaptive coping mechanisms of the brain to stress [Maleki, et al., 2012] suffers similar key limitations. Neurobiological mechanisms through which stress / stressors trigger the cascade of migraine attacks remain nebulous, both the ascending as well as the final common pathway(s) involving V1. Once a migraine attack develops, it becomes a stress / stressor by itself, which stress / stressor is not relevant to its initiation or to its course. More importantly, the stress of episodic migraine is inexplicably and variably self-limited to a large spectrum of 4-72 hours, including visual and non-visual aura as well as headache. The tamponade effect of the eye has been presented as the key self-limiting factor for migraine attacks, both headache and stress itself. [Gupta, 2024; 2023]

Stress may be subliminal or subclinical (covert), obviously apparent (perceived stress), or be appreciated only retrospectively, i.e., post-stress. Currently, RCCT / RCT, in general, has no role in evolution of the link between stress and migraine. Consequently, much emphasis is laid on the assumed pathogenesis of symptoms of MwA with origin following CSD while MwoA is believed to follow “silent” or “asymptomatic” CSD [Hadjikhani and Vincent, 2019; Sauro and Becker, 2009] However, the nature or physiological role of CSD is itself debatable, as has been discussed in details over the last 2-3 decades. [Borgdorff, 2019; Gupta, 2023; 2020; 2011; 2009; 2006]. CSD is not a nociceptive phenomenon and cannot account for pain of migraine attacks, an absolute feature that eliminates the role of CSD in migraine pathophysiology [Gupta, 2024; 2009]. Much confusion prevails about the causal or pathogenetic role, if any, of CSD in migraine. A speculative and paradoxical therapeutic role for suppression of CSD has also been proposed. (Takizawa, et al., 2020) Adaptive functions of CSD, however, have been extensively elucidated over the last 3 decades, as reviewed. [Gupta, 2024; 2019; 2009; Borgdorff, 2019] A detailed review of CSD in relation to migraine is not possible in this article. Reader is referred to exhaustive reviews by Borgdorff [2018] and by Gupta [2024; 2009]. While no hypotheses is ever proven by any mass of evidences, any hypothesis can be disproved by single piece of contradictory evidence. [Popper, 1967] Female sex predomination of migraine F:M=3:1 in adults with precipitation by menstruation and I trimester of pregnancy commonly lowers the threshold of the migraine attack, while the II and III trimesters of pregnancy, menopause, ageing in both sexes ameliorate migraine or raise the threshold to develop migraine attacks. Also, first-line prophylactic effect of propranolol, nadolol, and atenolol are key characteristic features that cannot be explained by CSD or other brain-centric or brain (central) computational theories. [Gupta, 2019; 2010; 2009; 2004] Most importantly, CSD cannot explain unilateral headache or vomiting of migraine that frequently resolves the headache. [Gupta, 2024; 2019] Strikingly, CSD also cannot rationalize pain in any form as well as non-homonymous SS of MwA with sparing of the nasal field of vision of migraine or visual field defects that spare the nasal visual fields (Gupta, 2024; 2023; 2019; 2009).

Stress or sudden arousal activates the ANS, both the sympathetic nervous (SNS) and parasympathetic nervous systems (PNS). Several mechanisms proposed to underlie the link between stress and migraine do not offer clarity or certitude while the etiology of migraine remains vague. The cephalic physiological processes underlying or precipitating stress-related EM attacks (MwA or MwOA) -- classically lasting 4-72 hours or more prolonged headache attacks – have recently been defined as definitive affectation of the eye. [Gupta, 2024; 2023; 2021; 2019; 2009; 2006] Mean peripapillary retinal nerve fibre layer (RNFL) thickness for nasal and nasal inferior sectors was significantly thinner ($P \leq 0.018$) in the eyes of migraine patients than in those of the controls, as was the mean choroid thickness at the fovea and measured points ($P < 0.0001$), suggesting a link between glaucomatous barotrauma and migraine. [Kanar et al., 2021. A fuller discussion on effect of posterior pole or segment of the eye is beyond the capacity of this article. However, the chain of events leading to ocular barotrauma – both anterior and posterior -- has recently been discussed exhaustively. [Gupta, 2023] [also see below] The pathophysiological and aetiological nexus between migraine and glaucomatous affectation of the eye(s) is progressively increasing, but cannot be discussed exhaustively in this article.

This important aetio-pathological eye-versus-brain gap in our understanding of migraine has generated various divergent theories and hypotheses, with serendipity, controversies, debates, canonical myths, and empirical or experiential therapies -- including RCCT / RCT without sound support of basic sciences – thereby cluttering the research field of migraine and other primary headaches with myths and assumptions, as researchers commonly publish data without care for or availability of an overarching synthesis or answers to crucial questions. [Gupta, 2024; 2023; 2019] Consequently, confusion and disparate analyses and perspectives / viewpoints prevail as well as the need to reframe or abolish the concept of CSD / SD / spreading depolarization that is still maintained as the central pivot of genesis of migraine, notwithstanding the critical limitations of proposed primary brain aberrations [Kanar et al., 2021; Borgdorff, 2019; Gupta, 2004; 2003; 2019; 2010; 2009; 2006; Ayata and Lauritzen, 2015] (see above)

Nevertheless, it is very important to state that no biochemical or neuropeptide from serotonin to monoclonal antagonists to calcitonin gene related peptide (CGRP), and to their derivatives e.g., CGRP-receptor antibodies, can be ætiologically and definitively liked to unilateral or lateralizing self-limited headache of migraine. [Gupta, 2019] More frequent than not, migraine headache is unilateral. The role of CGRP in genesis of migraine attack, self-generated and self-limited aura, with aura lasting 15 minutes to 1 hour and with lateralizing headache lasting 4-72 hours of migraine, is unknown. CGRP- and CGRP-antagonists are large molecules that do not readily cross the BBB. [2024; 2019] Gepants, ditans, and neuromodulation are some newer management options [Puledda et al., 2023] A fuller discussion of these therapies that are diffuse or not-lateralizing in nature (i.e., cannot rationalize non-homonymous SS or lateralizing unilateral / bilateral headache) and without ætio-pathogenetic background at the level of the brain is beyond the scope of this article.

‘Oxidative’ stress has been recently gaining traction, and, is important to mention in the context of stress and migraine. [Jiménez-Jiménez, et al., 2024; Gross et al., 2021; Borkum, 2016] ‘Oxidative’ stress covers a very wide spectrum of non-specific pathogenic mechanisms at the cellular level as an array of non-specific environmental and endogenous ætiologic possibilities that do not rationalize the wide but characteristic clinical spectrum of migraine. The key limitations of the ‘oxidative’ stress theory for precipitation of migraine are: (i) Lateralization of migraine headache, commonly unilateral (fronto-temporal or nuchal); (ii) Self-limited duration of migraine attacks with spontaneous onset and offset; (iii) Clinical characteristics of migraine, including precipitating and remitting factors, prevalence of age, pregnancy, and menstruation-linked migraine attacks, nausea and vomiting, and non-homonymous SS. [Gupta, 2024]

‘Stress’ is a term widely used in daily life, clinical practice, and research in biological sciences. [Bruce, 1992] The term stress has little specific value, applied as it to a very great width of clinical and experimental circumstances. “Stress” becomes useful in migraine pathophysiology only when it is linked to specific processes that can generate non-homonymous SS and lateralizing self-generated and self-limited

headache, explains female preponderance as well as age / pregnancy related incidence. [Gupta, 24]

Discussion

The key issue is that a generalizable, predictable, and logically-robust theory has not been evolved for migraine, both for MwA and MwoA (clinical variants of EM) and / or for CM, the specific reasons for which were a necessary prelude to discuss in this article the presentation of the invaluable role of the pre-prodromal / pre-premonitory phase as the point of origin for the migraine attack, as part of the self-generated and generally self-limited stress-related cephalic ANS storm that characterizes migraine, both with EM as well as CM. In sum, this article presents the basic framework of a single ætiology that underlies EM (both MwA and MwoA) as well as CM with clinico-physical symptomatic variations that have been misinterpreted as varied or different ætiologies for so-called or imaginary distinct entities.

Much of the evidence that supports the phasic divisions (prodrome, aura, headache with aura or headache without aura, post-headache phase) and the imaginary divisions between MwA and MwoA as well as between EM (MwA and/or MwoA) and CM arise from a markedly speculative interpretation of clinical symptoms, results of cross-species animal experiments (mice-to-men), vasomotor challenges with nitroglycerine (NTG) and allied drugs, statistical significances, placebo-effect of minor biological variations in clinical studies including RCCT / RCT, epidemiological studies of large cohorts with or without highly subjective and retrospective questionnaires, empirical or experiential / experimental challenge with presumedly or possibly therapeutic pharmacologic agents in a disorder that is typically protean (duration of headache 4-72 hours), beside the many other spontaneously variable points discussed in this article with wide aberrations of age, menstruation, and pregnancy-related incidence, comorbidities, and pain lateralization as major symptoms associated with migraine attacks, with or without any symptom of non-homonymous aura (visual or otherwise) or nausea / vomiting as well as without definitive knowledge of pathophysiology of primary headaches, including migraine [Gupta, 2024; 2023; 2019; 2010; 2009; 2006].

In the absence of an overarching hypothesis, the laboratory creates artificial individuality and misguides primary headache research and researchers. [Blau, 1994] Beginning with serotonin [Deen et al., 2017; Ferrari and Saxena, 1993] a number of other neuropeptides or neurohormones including substance P, CGRP, PACAP [Waliszewska-Prosół, et al. 2024; Cohen et al., 2022; Ashina et al., 2019] are believed to play a central role in pathogenesis of migraine.

In this article, the eye and its hemodynamics are further explored as the central model for the pathogenesis of migraine in place of the brain. [Gupta, 2004; 2019; 2009; 2006; 2003] In normal physiological conditions CGRP-induces relaxation of the rabbit ophthalmic artery with alterations of IOP. [Zschaeur, et al., 1992; Krootila, et al., 1988] While CGRP is a 37-amino acid vasodilator neuropeptide localized in the eye in the sensory nerves, anti-CGRP analogues are hypertensive. [Lentch, et al., 2022] The ocular hypertensive effect of anti-CGRP analogues was evident in the largest real-world prospective study on the use of anti-CGRP monoclonal antibodies (Mabs) in migraine, to date, showing that, across countries, only 50% patients reach a 50% or more reduction in monthly headache days with the treatment, with good tolerability. [Iannone, et al., 2022] Why does such a large fragment of migraine patients not achieve notably positive results with anti-CGRP Mabs? Is hypertension and rise of IOP due to anti-CGRP analogues central to 50% of migraine patients not achieving a >50% positive response? Hypertension or a relatively higher SBP, with particularly higher diastolic pressure is a common comorbidity of migraine, particularly in elderly patients, while most migraine patients adaptively maintain a normal or low-blood pressure. [Wang and Wang, 2021; Gupta, 2006] Intriguingly, CGRP dose-dependently produces a biphasic IOP response, with sustained ocular hypotension in rabbits, which is mediated by CGRP1 receptors. [Taniguchi, et al., 1999] While the headache 'phase' can be linked to rise of IOP by CGRP, the self-limited headache of migraine may be linked to a tamponade effect of rise of IOP. [Gupta, 2024; 2019] CGRP has been also suggested as a cardioprotective endogenous mediator released under stress to help preserve cardiovascular function. [Kee et al., 2018]. A more comprehensive analysis of CGRP, CGRP- or CGRP-R antagonists and their effects on IOP as well as cardiovascular protection by CGRP is beyond the scope of the article. Parenteral anti-CGRP monoclonocal antibodies, however, can be expected to raise both SBP as well as IOP in a large (>50%) of the cohort, thereby lowering the threshold to develop migraine attacks. [Gupta, 2024; 2019] Besides receptor affinity, the mode of administration, intravenous, intracameral, or intravitreous is also important as both SBP and IOP can be affected by CGRP and its antagonists.

To evolve a comprehensive construct of the physiologic changes that are taking place simultaneously in the early or pre-prodromal / pre-premonitory stage of a migraine attack, it is essential to maintain that no neuropeptide or neuro-hormone can be released in isolation. Additionally, it is essential to conceive that a complex homeostasis is being maintained in the pre-prodromal / pre-premonitory stage through release of several synergistic or antagonistic neuropeptides or neuro-hormones simultaneously or in concert. The 'adaptive' or 'protective' role of the vasopressin-norepinephrine-serotonin nexus forms the fundamental basis of the post-stress or delayed onset of headache that characterizes migraine, both in MwA and in MwoA as well as in CM. Migraine headache may be delayed for several hours or a few days after exposure to various forms of stimuli / triggers or psychosocial stress, including alcohol imbibition. [Gupta, 2024; 2021; 2019; 2009; 2004] Since migraine is a fronto-temporal, vertical, and/or nuchal lateralizing headache (unilateral, bilateral, side-shifting, or side-locked), it is important to consider the peripheral computations, vasomotor alterations, and the nociceptive traffic in the peripheral divisions of the first branch of the trigeminal nerve (V1) that, in turn, generates migraine headache. Migraine does not appear to be a pan- or holo-trigeminal disorder but selectively involves V1 [Gupta, 2024; 2019; 2009; 2006].

Vasopressin (AVP) appears to play a central role in the flow of stress-related events including SBP as well as intraocular hemodynamics in migraine surrounding the pre-prodromal / pre-premonitory stage. [Gupta, 2024; 2023; 2021; 2019; 2006; 1997] Additionally, nausea and / or vomiting is a key and diagnostic clinical feature of migraine. [Headache Classification of the International Headache Society, 2018] Nausea / vomiting prominently raises AVP levels and can be considered 'adaptive' in those migraineurs whose headache it ameliorates or aborts. [Gupta, 2024; 2019; 2004; 1997]. The key physiological system primarily affected in migraine is afforded a considerable, although limited and functionally exhaustible degree of pre-prodromal / pre-premonitory protection by homeostatic or adaptive defence mechanisms allowing the patient to continue to function for several hours or a few days despite exposure to the stressful migraine attack-provoking event. [Gupta, 2024; 2019; 2009; 1997] This mode of biological adaptation is essentially teleological and offers insight about primary disease mechanisms. [Gupta, 2004; 2019; 2009; 1997; 1994] Over the last three decades, a neuroendocrine 'adaptive' system that maintains vascular integrity, antinociception, and behaviour control during vasodilatory antidromic trigeminal nerve discharge in the peripheral components of V1 has been evolved, the probable components of which include a primary intrinsic ocular ANS storm [SNS and PNS] activation or hyperfunction, coupled to enhanced attack-related bioavailability of AVP, serotonin [5HT], and nor-epinephrine [NE] in the pre-prodromal / pre-premonitory phase, with the onset of the migraine attack i.e., prodrome/aura/headache/post-prodrome phases representing an overwhelming 'fatigue' of the 'adaptive physiologic system'. [Gupta, 2024; 2023; 1997] AVP is an output of hypothalamic neurons that critically influences cranial areas associated with migraine, including the eye.

The 'fatigue' of the overall 'adaptive protective system' in the covert / subclinical pre-prodromal / pre-premonitory stages of migraine initiates a primary enhancement of ocular hemodynamics including choroido-retinal blood flow along with a tamponade / self-limiting nociceptive distention of the corneoscleral envelope, that invariably results in self-limited lateralized headache (unilateral, bilateral, side-fixed or side-shifting) (MwoA or CM) but uncommonly may also result in the pathognomonic non-homonymous digitally-displaceable, ocular-movement synchronous, and nasal-visual-field sparing SS by partial stimulation of the nasal retina (MwA) based on choroido-retinal anatomic aberrations, possibly involving SD of the retina or activation of hitherto unknown cellular / tissue posterior ocular mechanisms. [Gupta, 2024; 2023; 2021] Secondarily, vascular and neuronal stimulation of various computations of the brain and its various parts (MRI / PET) has been recorded and regraded erroneously as being primary in nature or basis.

In migraine pathophysiology, CSD / SD has evolved probably into the most powerful irrational skepticism that has been maintained by selective data provided by a very large majority of neurologists including migraine researchers as a celebratory festschrift, to discover efficacy of new anti-migraine drugs, and to use suppression of CSD itself as a possible anti-migraine measure. [Tfelt, 2010; Ayata, 2010; Ayata et al., 2006; Lauritzen, 2001]. In broader neuroscience, the adaptive nature of CSD has been established in vertebrates and lower mammals, as has been exhaustive detailed in recent reviews. [Borgdorff, 2018; Gupta, 2024; 2023; 2019; 2009] The statistical limitations of animal experimental (mice-to-men) evidences as well as evidences derived from intrinsically varied migraine cohorts and subdivisons (MwA / MwoA / CM) are only rarely considered, leaving aside the much more significant assumptions of biological cross-species comparisons as well as inter-cohort variations. Untrustworthy clinical trials plague (and will continue to plague) so-called evidence-based medicine (EBM) in primary headaches. How faked or flawed clinical trial related evidences drive science and scientific practice in medicine has become a branch of science itself. [Van Noorden, 2024; Gupta. 2010]. This limitation of EBM particularly affects the discipline of primary headache, including migraine. Whose evidence is it anyway, has tragically come to haunt EBM and evidences provided by RCCT / RCT in primary headache research, including migraine. Prejudice or bias has not been overcome in migraine pathophysiology by RCCT / RCT, statistics, or hyper-splitting of nosology [Gupta, 2024; 2019; 2010]. RCCT / RCT give legitimacy to bias and prejudice, a common but rarely recognized limitation. Scientists have a moral obligation and a special responsibility to challenge and combat disinformation that may perpetuate false beliefs, and erode research integrity, scientific inclusivity, equity, and advocacy.

Psychophysical stress (but not oxidative stress) is one of the commonest terms used in migraine or primary headache pathophysiology but without comprehension of underlying physiologic processes. Stress (psychophysical), nonetheless, is a widely used word in clinical practice as well as in research, without having real value or meaning in biological sciences and everyday practicality. [Charlton, 1992]. Stress is both a stimulus as well as a response, as well as a combination. The last 'combination' expression or explanation for stress is a scheme that explain nothing by explaining everything. Hans Selye, in his monumental thesis "Stress in Health and Disease", has described as stress to be associated with a great variety of essentially dissimilar problems… [Kovacs, 1998] "The key phrase is 'essentially dissimilar'...while pathology is the basis of medicine." Clearly, in one sense 'stress' must be regarded as a very useful word as it can be applied so widely, but the potential for confusion is equally multiplied. Even under ideal conditions, the illogical nature of the concept of stress invariably leads to contradiction and confusion. Science as a scientifically 'respectable' concept arises from an observation of a vague correlation between inside and outside of organisms studied as a cohort. Migraine is an 'essentially dissimilar' disorder, the trans-speciality commonality or transparency of which has eluded investigators. The level of stress as a burnout inventory, emotional exhaustion, personal accomplishment, depersonalization at work, distant or indifferent towards work or negative, callous, and cynical behaviours, or interacting with colleagues or patients in an impersonal manner, and positive / negative influences are the measurable aspects of stress, that features, however, do not add up to any sensible pathophysiological component in migraine research. A thematic presentation of such a burnout is extremely complex and makes sense only with difficulty across the length and breadth of medicine.

Some famous figures including scientists, medical or otherwise, military personnel including General Ulysses Grant, and neurologists and headache-specialists, in particular female migraine therapists, are well-known to have suffered migraine [Evers et al., 2020; Yeh et al., 2018; Jarcho, 1967] Surge of emotion as with General Grant's response to news of surrender with swift-to-instantaneous stress / stressor related homeostatic / adaptive / protective neuro-endocrine activation / upgrading / relief (see below) probably can immediately relieve an ongoing migraine headache attack [Gupta, 2009]. Migraine spares no race, class, activity, profession, dietary inclination (teetotaler or tippler), or intellectual capability, indicating the involvement of a pathophysiological system that is both affected by as well as is significantly immune from all these factors and many more (see below). The relation of migraine to education and thereby in parallel participation in RCCT / RCT is truly intriguing and an a very interesting lesson in human behavior, both involving patients and their therapists. [Gupta, 2010] (see above)

People have consumed alcohol over millennia for its analgesic properties, dating as far back as ancient Egypt and Greece. As recent as the 19th and 20th centuries, it was commonplace for physicians to prescribe as well as to administer oral or intravenous alcohol prior to medical procedures due to its analgesic and anesthetic properties (Cucinello-Ragland and Edwards, 2021). Alcohol-imbibition is the commonest intoxicant used worldwide, with a rapid analgesic action. In some patients with binge alcohol consumption, migraine attacks can develop after a few hours or the next morning, 'hangover headache' [Onderwater et al., 2018]. The particular propensity of red wine to trigger migraine attacks remains unexplained, and likely reflects a behavioral and / or statistical trait. In large-scale studies, other researchers maintain that alcohol consumption and migraine have an inverse relation, possibly through a learned- or reflex-avoidance [Błaszczyk et. al., 2023]. Low-doses of alcohol consumption and a certain less-boisterous ascetic life-style also is less likely to trigger migraine [Blaszyck, et al, 2023; Vives-Mestres et al., 2022]. Weekend headache is a clinical entity that clearly needs more studies. It is not only alcohol but also oversleeping over the weekend that precipitates MwoA, a headache prevented dramatically in case reports by the topical ocular hypotensive agent ocular instillation of timolol maleate (a beta-blocker) [Gupta, 2021] Overall, delay in getting-up from nocturnal sleep the next morning with-or-without a startle, fragmentation of sleep, quantitative dependency, low consistency (# of drinks, 30 ml each) of alcohol imbibition, and low-to-high % of alcohol to precipitate migraine determines the operation of a protective yet constantly-variable homeostatic dynamic and biophysical and biophysiological adjusting mechanisms that control the idiosyncratic- or individual trigger threshold of precipitation of migraine attacks, as has been exhaustively detailed in the AVP-5-HT-NE nexus [Gupta, 2021; 2019; 2009; 1997]. Habitual alcohol use is associated with higher IOP, prevalence of ocular hypertension (OH) (IOP > 21 mmHg) with and without association with glaucoma or alcoholic liver disease or fatty liver disease. [Stuart, et al., 2022; Lee, et al., 2022; Karimi, et al.,2021; Song et al., 2020] Alcohol imbibition generally raises IOP, a key factor in the genesis of migraine attacks; the factors in the link between alcohol consumption and elevated intraocular pressure (EIOP) include the dose of alcohol, its effect on blood pressure, ANS, variance between acute and chronic alcohol consumption, and the social circumstances accompanying alcohol imbibition (binge drinking or otherwise). The delay in onset of alcohol-induced migraine / migraine-like headache the next morning indicates the operation of the important adaptive / protective AVP-5-HT-NE nexus. This clear delay in

onset of alcohol-induced migraine / migraine-like headache indicates the operation of the adaptive / protective pre-prodromal / pre-premonitory phase mediated by the AVP-5-HT-NE nexus that merges into the prodrome/headache/post-headache phases that involve, in turn, self-limited expansion and decompression of the nociceptive corneoscleral envelope / junction with self-limited genesis of ocular vasodilatory nociceptive trigeminal nerve neural traffic causing headache (over 4-72 hours) – at the anterior pole -- and much shorter SS (15 minutes to I hour) --at the posterior pole. [Gupta 2024; 2023; 2021]

Caffeine-withdrawal -- commonest stimulant used worldwide -- can trigger a migraine- or migraine-like attack over-the-weekend with inconsistent use above 200 mg daily [Magdalena, et al., 2020]. Caffeine cessation cannot be recommended for all migraine patients, while caffeine overuse may lead to migraine chronification, in itself an uncertain largely frequency related pathophysiologically-insecure or uncertain aggravation of the disorder. Tobacco / nicotine smoking, commonly co-linked with alcohol imbibition, has not been definitely or robustly linked to occurrence or worsening of migraine. Regular caffeine intake in high doses (50g/day) in 10 healthy male volunteers for 1 week failed to alter either antipyrine (quantitative test of hepatic microsomal function) or caffeine pharmacokinetics. Conversely, alcohol intake of 50 g/day significantly prolonged caffeine half-life by 72% ($p<0.005$) and diminished caffeine clearance by 36% ($p<0.0005$) but did not alter antipyrine kinetics. [George et al., 1986] These results demonstrate that alcohol, in amounts commonly consumed, is a strong inhibitor of caffeine metabolism. While alcohol, caffeine, and tobacco can alter the tendency to trigger migraine migraine attacks, no definitive principles of prevention of migraine attacks emerge. Nevertheless, a causal association between alcohol consumption and risk of hypertension, especially above an alcohol intake of 12 g/d, appears consistent with recommendations to avoid or limit alcohol intake, a link particularly effected by sex and ethnicity. [Cecchini, et al., 2024] Sex and ethnicity appear to be major effect-modifiers of such association. The association between migraine and hypertension, IOP, and ocular hemodynamics cannot be excluded. [Wang and Wang, 2021; Gupta, 2006] Insomnia and alcohol dependence also might best be thought of as co-morbid disorders, each requiring its own treatment.

The largest number of fluctuations in the IOP in the human body with pre-prodromal / pre-promonitory AS-induced choroidal-vasomotor nociceptive impulses in the aberrant corneo-scleral envelope are associated with migraine – both frequent migraine-induced headache attacks, and, intermittent-to-uncommon non-homonymous, digitally-displaceable, ocular movement-synchronous, and nasal visual field sparing changes, including SS. (see below)

A re-focus on dose-dependent alcohol imbibition, tobacco smoking, caffeine, hypertension, stress and intraocular hemodynamics in this article allows a vivid representation of the significant delay between the multiple trigger(s) and the spontaneous migraine attack, as has also been also observed with glyceryl trinitrate-induced and cilostazol experimental migraine / migraine-like headache in significant sections of the migraine cohorts. These multiple but contrary complex issues – internal and external influences, both physical and psychophysical stress and non-stress in nature -- exert a varied, diverse, and unpredictable effects on the fluctuating migraine attack threshold. A detailed discussion of migraine triggering and relieving factors of alcohol, hypertension and other factors is beyond the scope of this article but has been discussed elsewhere. [Gupta, 2023; 2021; 2008; 2006]

Suffering from different diseases, Hans Selye's patients mostly looked sick with identical signs and symptoms, possibly the first recognition of stress. [Kovacs, 1998]. Similarly, common symptoms in most patients with migraine indicate the first recognition of a central role of stress in its pathogenesis. A commonality of patients characterizes most migraineurs with variations that can be typical-to-pathognomonic. Despite the commonality as well as the variations, a creative impulse making or bringing into the being that did not exist before, a combination of previously unknown facts requiring involvement, intensity, courage, imagination, saltatory thinking, and new insights rather suddenly arising from integrative beliefs, with new concepts that rebel against well-established, generally accepted dogma, and contemporary or canonical acceptance, generate the pathology of any disorder. Pathology is the basis of medicine; it tries to understand the mechanisms of disease and to shed light on the causation of various lesions in human and animal organisms. Pathology investigates disease processes using morphologic and functional techniques. The study of abnormal physiological and structural – neuropeptide / neurochemical or neuroradiological -- features in the laboratory – pathological or neuroimaging -- is not adequate alone. Morphologic findings have to be correlated with pre-prodromal / pre-premonitory functional activities to rationalize the origin of migraine and other primary headaches. [Gupta, 2024]

True success in science requires creativity and is very important in pathology-oriented research. A certain blue-bluish discoloration of the supero-lateral corneo-scleral junction marks the structural weakness of the corneo-scleral envelope that generates sui generis or idiosyncratic – spontaneous or experimental -- and self-limited nociceptive impulses in V1 (4-72 hours) following circadian fluctuations in the IOP even within normal limits. [Gupta, 2024; 2023; 2021; fig.1, 2] It is suggested that pre-prodromal / pre-premonitory insomnia / sleep fractionation and ultimately psychosocial alarm / arousal arising from different triggers raises IOP after few hours the next morning or in any other idiosyncratic circadian pattern, and precipitates migraine or other primary headaches.

For therapists or physicians of all hues, the urge or compulsion to present or accept partial, incomplete or quasi-knowledge or even a canonical but untrue or partially-true belief / myth / assumption / serendipity / empiricism of their era as an absolute truth is incorrigible, and, as forceful a physiologic force as the need to breathe oxygen / drink water / self-narcissism / self-preservation, both egoistic and egotistic. Eminence, exaggerated self-esteem, and pseudo-prestige limit innovation to their own tight circle of comprehension, drown warnings of error in Ethical Committee-backed Institutional-Industry-Insurance-Authoritative Regulatory hunting grounds of science, including medicine / migraine, rivalry and jealousy in peer-review, and common editorial reluctance to accept unsolicited manuscripts with potential to cause massive change of status quo or an insurrection with or without data but with potential to deracinate canonical myths and assumptions and to contribute to definitive progress in the discipline. [Gupta, 2024; 2019; 2010] The prestige and eminence of established researchers of their era or any scientific theory or therapy that has captured the high-stake psyche of the Institutional herd, is far more important to Editors than the risk of logical, robust, and saltatory progress through any fresh or original cross-disciplinary gestaltic syntheses from other quarters. Even serendipity or empiricism wrapped in data and statistics is generally acceptable and quite the norm.

As an extreme level of loss of sensibility and altruism in science, the excitement surrounding opioid use / dependence / abuse in migraine / primary headache regardless of strength of supportive evidence in well-developed countries does not promote a self-correction of chosen exploratory path / hypotheses / or the underlying fundamentals of the science of primary headache, including receptors with pain-related positive or negative (affective) features – classically seeing the trees-for-the-wood -- despite longer lengths of hospital stay and readmissions. [Shao, et. al., 2022; Vanderpluym, et al., 2021; Lipton, et al., 2020; Quinn, et. al., 2020; Dripps, et. al., 2020; Parker, et al., 2020; Masonbrink, et al., 2020] As a critical limitation of our times with claims and counter-claims to components of 'truth' or salami science, only data can be deemed original; syntheses that can create new dimensions or horizons or can integrate disciplines can never be original – a fatal flaw in conception, integration, intuition, insight, or imagination. Furthermore, data-gatherers, researchers involved in RCCT / RCT, and authors of other form

of analytic publications face no journal Editorial compulsion or ire to respond appropriately or at all to the rare constructive critiques in the Comments section of medical journals, despite a well-disseminated rule or undertaking or scientific ethos / advocacy for authors to take public responsibility for whatever is published in journal columns [Gupta, 2020; 2010] The excitement of 'new' or 'novel' via placebo-controlled RCCT / RCT has eliminated critical thinking / face-validity / commonsense as well as robust, overarching, generalizable, replicable, and predictable logic. Irrational scepticism prevails because statistically-significant data through the quantitative methodology of RCCT / RCT are never believed to be incorrect, untrue, faulty, or misguiding and have always to be justified at any cost by the trialists / proponents, leave an indelible quasi-permanent scientific statement, and have to be accepted by contemporary researchers (and later generations, occasionally endlessly) with rare exceptions, such as PFO-closure or botulinum toxin (BTX) or exogenous magnesium supplementation to prevent migraine attacks or to preserve the myocardium during acute myocardial infarction or to protect neurovascular tissue in stroke or to prevent eclampsia / pre-eclampsia. [Gupta, 2020; 2010; 2006; 2004; 1996; Saver et al., 2015] Industry-sponsored RCCTs demonstrating minimal benefit but with statistical significance are the most suspect. Medical myths never die, and such RCCTs / RCTs are designed to keep the ideas in running to allow further data accumulation in new eras and epochs. Finally, originality dies or gets lost in the data-statistics combine only to be partially or incorrectly resuscitated by replication through later generations of researchers as assumptions or speculations. The tenets of basic sciences are thus frequently lost or forgotten.

What is original has been lost in migraine / primary headache research through disparate and untrammeled data and excess of verbiage and statistical numericals in the last 100 years. In migraine / primary headache research, how to stymie science has become the most valuable art, an insurrection-in-reverse, with its own principles and methodology.

The biology of an illness does not lie solely in the laboratory, an absolute that migraine researchers and medicine, in general, refuse to accept. The biology of laboratory and clinical medicine has largely been replaced by sophisticated mathematical statistics, a very significant biological qualitative-to-quantitative retrogression since last fifty years. [Ioannidis, 2005; Feinstein 1994] The biology of migraine has been replaced by a sequential elucidation of a string of biomarkers (including CGRP), genetics, neuroimaging, animal experiments, cross-sectional epidemiologic evidences, RCCT / RCT, analyses and meta-analyses, and 'hyper-split' purely symptomatic nosology. [Gupta, 2019] The nosology as well as the laboratory are both hindering the recreation of the whole, by keeping well-apart the very many and diverse critical components of migraine / primary headache as individualistic components. The pharmacotherapeutic mechanism(s) of action of propranolol – a first-line migraine preventive agent, discovered by sheer serendipity as a side-effect of anti-anginal therapy – remains, in general, unknown well into the Third Millennium. The largest number of factors that influence migraine – aggravating / precipitating triggers or relieving psycho-physical stimuli or social circumstances / interactions -- a fuller discussion of which is beyond the scope of this article – are linked, directly or indirectly, to increase or decrease, respectively – of spontaneous / circadian / diurnal-nocturnal IOP with spontaneous genesis and subsidence of self-limited (4-72 hours) attack-generating neural impulses in the V1. The SS –that is pathognomonically non-homonymous, nasal retinal visual field sparing, digitally displaceable, and eye-movement synchronous -- probably arises from an anatomical aberration of the posterior pole responding to aggravated choroido-retinal blood flow or other currently unknown but related pathophysiologic mechanisms.

The good doctor knows how to treat, the better doctor knows when to treat, the best doctor knowns when not to treat. Whenever a researcher works diligently but without insight to make her / his theory more palatable to modern audiences of that era, truth becomes the victim that is distanced or demolished for centuries or millennia, confusion takes center-stage, the quicksand of the slippery slope of logic, as well as the 20/20 hindsight of unforgiving and unforgetting history swallows the science, the self as well as the ego. While no amount of evidence can ever prove a hypothesis, given time, imagination, intuition, evolution of sense and sensibility, acceptance of self-singeing error, overpowering of the idiosyncratic ego, acknowledgement of explosive run-away technology as more than a mere tool to gather data and secure publications without insight, ability to swim against the current, and the ultimate factor of humility, any theory can be eliminated by a single piece of contrary logic. [Gupta, 2024; Lancet 1992; Popper; 1967] The Yin-Yang superiority of logic over data finds little or no acceptance in the herd of researchers of any era. Such an approach differentiates the scientist in steadfast pursuit of the composite and invariable multi-dimensional all-encompassing robust predictable generalizable and logical truth from the researcher / trialist drowned in publications, citations, grants, patents, tenure, applause, awards, and multiple celebratory versions of the truth. Besides other uni-dimensional bench-to-bedside data or laboratory evidences or data emerging from the RCCT / RCT or animal experiments, the call for personalized treatment or artificial intelligence / machine learning is meaningless and seductive. Like other egregious medical practices that are an indelible part of human history with a shaming of the science as well as the intellect (see below), opioid use / abuse for refractory or severe migraine / primary headache has become the therapeutic norm in United States of America (USA), Canada, and Europe in the last fifty years despite a hyper-exponential increase in publications, data, and its derivatives – analyses, meta-analyses, viewpoints, reviews, opinions, editorials, and pharmacotherapeutic trials of all forms, including the much vaunted RCCT / RCT sitting at the apex of the medical evidential pyramid. Of 3,098,542 patients across 1000 community hospitals with headache inpatients in the USA between 2008 and 2014 related to migraine (55.06%), tension-type headache [TTH] (2.01%), and cluster headache [CH] (0.47%), 128,383 (2.28%) patients had abused opioids, a significant increase of opioid abuse from 2008 to 2014. [Patel, et al., 2020] Several other researchers have lamented opioid abuse in migraine. [Lipton et al., 2020; Gupta, 2020]

Advances in laboratory medicine create artificial individuality with disconnected widely-disparate neurochemical or neurotransmitter, genetic, or neuroimaging evidences – so-called biomarkers, along with the general uncritical acceptance of these principles in migraine as primary aberrations but without a unifying matrix that has generated profuse biological confusion. The human body and its organs are not empty receptacles, and significant release of any biochemical / neuropeptide / neurotransmitter will inevitably be balanced by release of a counteracting neurochemical / neurotransmitter to maintain adaptive homeostasis. Significant advances of comprehension of stress / post-stress / arousal / 'AS' linked biophysical and biophysiological principles of migraine / primary headaches have been made in the last 2 decades. [Gupta, 2004; 2023; 2021; 2019] Metoclopramide (20-60 mg, slow i.v.) has been presented as an effective opioid-alternative in the management of migraine headache, with a clear mechanism of action involving immediate substantial-to-large release (up to 1000 times) of AVP. [Gupta, 2023 -- Preprint, ResearchGate, doi:10.13140/RG.2.2.35488.76807]

Migraine, more often than not, raises or will eventually raise the question: 'Whose evidence is it, anyway?' Most schools of researchers continue to pursue data related to their own preferred hypotheses, without any alteration in course, come what may. Having learned the ropes of research, presentation (methodology, statistics, and results) migraine researchers have become slick with the cause-effect mechanisms remaining absolutely unaffected. While data and statistics remain impregnable, the rather vague idea expanded in the Introduction or Discussion or Conclusion remains vulnerable to criticism. No data arises without ideas. The idea is enveloped covertly or indiscernibly with statistical mathematics, assumptions, and hedging terms – possible,

probable, likely, may, might, should, shall, can, could…. Till yet no sentence in migraine literature is without 2-3 or more hedging terms, which literary semantics or style along with at least 4 p-values secures publication at the cost of certitude.

Shame and empathetic embarrassment or both and their absence, is perhaps the most powerful restraint for human intellect, especially for medical researchers. [Hapuarachchi et al., 2023] The protean nature of migraine, with striking variation in frequency, severity, disability, morbidity, and co-morbidity is a highly characteristic feature that complicates its scientific study by making replication of soft data difficult-to-impossible, both in theory and therapy; this variability has never been integrated into its scientific fabric. Just like atrial fibrillation, occurrence and clinical impact of migraine is highly irregularly irregular. Migraine involves recurrent episodes of an irregular short-lasting nasal-field sparing non-homonymous digitally displaceable ocular-movement synchronous visual aura (positive socotomatous visual hallucinations) and /or non-visual aura as well as cephalo-nuchal headache of varying regularity, intensity and duration (4-72 hours) with typical (and unknown) triggers as well as periods of exacerbation or remission including age, pregnancy, menstruation or menopause, with a striking predominance in adult females (F:M=3:1) but with an exclusive predilection for involvement of V1. [Gupta, 2024; 2023; 2021; 2019; 2009; 2006] There is practically no pharmacotherapeutic difference between the two main variants, MwA and MwoA. The final common afferent and antidromic efferent neural pathway for both MwA and MwoA is V1. In contrast to the general perception, migraine is not a pan-trigeminal or holo-trigeminal disorder. Far from being a precisely reproducible disorder in a sizable / large cohort or even in the same individual, the clinical / subjective variation of migraine is wide and pronounced in its components, intensity, and duration, varying from a frequently disabling disorder to an uncommon mild phenomenon.

Most researchers maintain that considerable progress has been made in elucidating the pathophysiologic mechanisms of migraine through exponential but scattered evidences from the fields of epidemiology, genetic susceptibility, neuroimaging, and neuropeptides / neurotransmitters, animal experiments, human experiments with nitroglycerine (NTG), and RCCT / RCT. [Ashina, et al., 2021; Andreou and Edvinsson, 2019] Nevertheless, the phases of migraine dynamically and variably roll into or follow each other, not necessarily in any strict order. All symptomatic phases of migraine and their components do not present identically in the same patient over time, which critically limits the value of RCCT / RCT. The search for a specific neural / neurologic mechanism for each symptom of each phase of migraine worsens the complexity of the pathophysiologic approach to the entity, besides the ineffective hyperfocus on biomarkers. Transformation of EM in some patients to a chronic form [CM] with daily or almost daily headaches (≥15 days / month) is another labyrinthine symptom-based pathophysiologic derivation that makes the emergence of an overarching robust and logically-sound synthesis for the disorder very difficult-to-impossible. 'Hyper-splitting' of entirely subjective nosology is yet another negative component of the presumed advance in science of migraine / primary headache. [Gupta, 2019; 2009; 2006]

The so-called 'evolutive' nature of migraine over a life-span is complex, with age-related ocular rigidity changing presentations and morbidities (discussed elsewhere). The term 'evolutive', however, is a semantic misconception, principally because the very basis of the genesis of migraine – unlike the atheromatous plaque -- is not pathophysiologically or generally comprehended. Migraine attacks – EM or CM -- are spontaneous in origin or self-generated as well as self-limited (4-72 hours), which ocular features have only very recently been elucidated. [Gupta, 2024; 2023] While mechanisms involving genetic and epigenetic factors, inflammatory processes, and central sensitization are proposed to play an important role, key limitations of such beliefs involve: (i) nature of anatomical structure or organ/organelle involved; (ii) nature and self-limited duration of putative inflammation, meningitis or central sensitization; (iii) adaptive nature of CSD in vertebrates, lower mammals and Drosophilia; (iv) non-homonymous nasal visual-field sparing digitally-displaceable and ocular movement-synchronous positive SS; (iv) typical lateralization of headache (unilateral, bilateral, side-shifting, or side-fixed); (v) far greater susceptibility of adult females to develop migraine (F:M=3:1); (vi) critical pathogenetic role of psychophysical stress / post-stress phase; and (vii) relation to psychophysical stress, menstruation, pregnancy, menopause, and advancing age.

Migraine has been divided, as is generally accepted, into the following phases, with a different pathophysiologic mechanism being sought, rather incoherently, for each phase: (i) Inter-ictal phase; (ii) Prodrome / Premonitory phase; (iii) Aura phase; (iv) Headache phase; (v) Postdrome phase. Division of migraine into phases is an artificial research and therapeutic strategy that has generated much confusion.

The prodrome or premonitory phase of migraine with a wide variety of diverse neurologic symptoms is strongly and widely believed to herald the onset of migraine. [Schwedt, et al., 2025; Sebastianelli, et al., 2024] The phenomena of prodrome or premonitory phase of migraine itself forms a fairly large list of peripheral and central symptoms but with no common pathophysiologic focus. The common mechanistic hitherto unexplained neuro-endocrinological underpinning of the prodromal / premonitory phase is arousal that spills-over or continues from the pre-attack "pre-prodromal / pre-premonitory" phase component of the inter-ictal phase, and presents a varied stress / stressor-related idiosyncratic symptomatology across various regions of the human body that is pivotally secondary rather than primary in nature. Arousal is never static or predictable across individuals as well as temporally across the same individual on different occasions in time. Arousal presents itself as an evolutive highly variable neurophysiologic process with an ascendency, a plateau, and a decline of ANS and hypothalamo-hypophyseal-adrenal cortex (CRH-ACTH-Cortisol/Corticoid hormone) activation related symptoms coupled to experiential and commonly subliminal physico-psychic 'fatigue' or 'exhaustion', that is in turn determined by the stress-adaptive nexus of AVP-5-HT-NE "system" activated centrally or peripherally or both. [Gupta, 2019; 2009; 1997] The stress / stressor-related physiological and psycho-emotional vulnerability or resilience of the biological circadian function determines the occurrence or otherwise of the migraine attack. Thalamic / hypothalamic / brain stem nuclei activation is believed to be the primary source of genesis of migraine attacks. [Goadsby et al, 2017] Activation of such stress-linked brain (thalamus, hypothalamus, brain stem nuclei) is, however, secondary to stress / stressor-linked adaptive mechanisms, as detailed herein. The prime determinant of onset of the migraine attack is the highly variable exhaustion or depletion of the stress / stressor-related 'adaptive' or 'protective' system(s) that govern the IOP and oculo-sympathetic system that, in turn, govern the algogenic headache- and SS generating oculo-trigeminal system. [Gupta, 2023]

Box 1. Symptoms of Prodrome / Premonitory Phase [Schwedt, et al., 2025;

Karsan and Goadsby, 2024; Dodick, 2018; Burstein, et al., 2015; Kelman,

2004] that Follow "Pre-Prodromal / Pre-Premonitory" phase of Migraine

Variably but are Ultimately Linked to the Continuum of Asymptomatic

Inter-ictal / Pre-ictal Trigger-Related Subclinical Arousal, including

Psychosocial Stress.

- Yawning – [Askenasy, 1989; Aló e, 1994]
- Cravings – (Motivational arousal-linked appetitive and non-appetitive reward-seeking) [Bjorness and Greene, 2024; Mohammadkhani et al., 2024]
- Fluid retention -- [Light et al, 1983; Dong et al., 2022]

- Mood Changes -- [Cuciureanu, et al., 2024; Gazerani, 2021]
- Heightened perception (hypersensitivity to stimuli, e.g., perfume, noise) [Çiçekli et al., 2024; Imai, et al., 2023]
- Postural Orthostatic Tachycardia -- [Yun et al., 2013; Medow and Stewart, 2007]
- Digital vasoconstriction – [Raynaud's phenomenon [Manickam et al., et al, 2021; Pillar, et al., 2002]
- Sudden onset of headache or headache on awakening or post-alcohol imbibition -- [Taylor, et al., 2016; Rains et. al., 2008; Siedel et al., 2010; Göder et al., 2003]
- Fatigue with or without obstructive sleep apnea -- [Yue, et al., 2009]
- Gastrointestinal Symptoms [commonly including nausea / vomiting, and rarely constipation] -- [Murali and Hayek, 2021; Thapar et al., 2020]
- Orthostatic hypotension – [Iser and Arca, 2022; Khurana, 2018]
- Syncope / Vasovagal Syncope -- [Cutsforth-Gregory, 2020; Donadio, et al., 2007]
- Tachycardia – [Mueller and Robinson, 2022; Blishteyn, 2023; Wig and Oakley, 2019]

The dubious nosologic and phasic differences between MwA and MwoA continues to generate enormous quanta of data thereby creating an enlarging conceptual schism. Division of migraine into 'ictal' (attack) and 'inter-ictal' (between attacks) phases is also fundamentally incorrect, and an approximation to epilepsy. First-line migraine preventive agents such as propranolol, nadolol, and atenolol do not have any anti-epileptic activity. [Gupta. 2019; 2009; 2005]

Serendipity has played a major role in the diversionary or labyrinthine-like understanding of migraine over the last 100 years. Several decades of technologic explosion with recent and ongoing laboratory discoveries has created artificial individualities, breaking the whole into parts that are difficult if not impossible to re-synthesize back into a gestalt overview. The discovery of every neurochemical (neuropeptide / neurotransmitter) beginning with 5-HT has generated incomparable excitement in migraine theory and therapy. Besides, a purely symptom-based and exhaustive "hyper-split" next-generation (4th Edition) nosology that is likely to be completed in a few (4-5) years will probably further add to the extant confusion.

The unexplained causative or pathogenetic role of stress / post-stress-related migraine attacks, preventive mechanism(s) action of propranolol, nadolol, or atenolol but not of other ß-blockers, preponderance of post-pubertal / post-adolescent adult females as migraine sufferers, decline in general of migraine attacks in later trimesters of pregnancy despite fluid overload and hyponatremia, decline in migraine attacks in post-menopausal years and with advancing age pose apparently insurmountable obstructions to the current widely-accepted theory-and-therapy of migraine, promote canonical and authoritative or reiterative and eminence-based myths and assumptions that buttress and perpetuate empiricism, experiential, experimental, direct extrapolation of evidences from animal experiment-based (mice-to-men) translational therapies, and a deceptive bench-to-bedside approach and confusion derived from RCCT / RCT. The phases of migraine, as currently accepted, have no relevance to these large gaps or limitations of comprehension of migraine. The last 100 years of Institution- and Industry-sponsored research with prestige and fiscal considerations have firmly pushed ethical and scientific propriety to a much lower level. Additionally, proliferation of neuroscience medical periodicals with hyperfocus on rapid online and open-access publication has led to a completely uncontrolled scientific environment with a wide- and widening-scatter of diverse untrammeled evidences and with rapidly enlarging quantum of confusion to the research field of migraine.

Besides the personal or collective rush to print for stature, eminence, grants, tenure, or patents, there is no central agency to advocate the proper approach to research in migraine, to prevent the creation or sustenance of myths, as well as to the sweeping-under-the-carpet of mysteries that arise with serendipity, incomplete knowledge, incomprehension, and pseudo-intellectual or statistical bias, such as the closure of PFO [Gupta, 2010] or the use of botulinum toxin [Gupta, 2006] or the use of CGRP-receptor antagonists [Gupta, 2020] for prevention of migraine. Key questions arise from use of each of these high-profile therapies for migraine; such questions, however, remain unanswered. [Gupta, 2019; 2009; 2006].

Figure 1

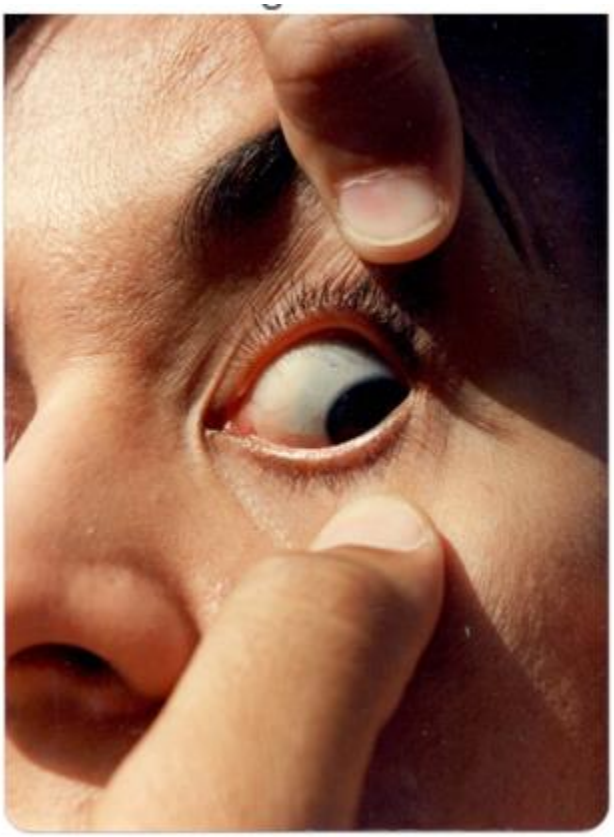

Figure 2

Figure. 1 & 2: Legend: Blue-bluish discolouration of the the supero-lateral aspect of the corneo-scleral aspect of the corneoscleral envelope, indicating a limbal barotraumatic thinning of the corneoscleral envelope and visibility of the underlying uvea due to recurrent ocular barotrauma at the anterior pole of the eye in migraine. With Permission.

Besides the personal or collective rush to print for stature, eminence, grants, tenure, or patents, there is no central agency to advocate the proper approach to research in migraine, to prevent the creation or sustenance of myths, as well as to the sweeping-under-the-carpet of mysteries that arise with serendipity, incomplete knowledge, incomprehension, and pseudo-intellectual or statistical bias, such as the closure of PFO [Gupta, 2010] or the use of botulinum toxin [Gupta, 2006] or the use of CGRP-receptor antagonists [Gupta, 2020] for prevention of migraine. Key questions arise from use of each of these high-profile therapies for migraine; such questions, however, remain unanswered. [Gupta, 2019; 2009; 2006].

Conclusion

The pre-prodromal / pre-premonitory 'phase' precedes the prodromal / premonitory phase and heralds the onset of the stress / stressor as well as the eventual onset of fatigue or exhaustion of the AVP-5-HT-NE adaptive nexus with the beginning of the migraine attack. No organisms, including humans, can survive without adaptive function. Our organs always improvise adaptive means of meeting every new situation. Physiologic processes, always incline towards the longest survival of the individual and are endowed with the property of being adaptive – a watchful automatism. Adaptive functions are the indispensable basis of our existential duration. The peripheral / antidromic computations of the V1, both afferent and efferent, constitute the neurogenic reflex of migraine. The eye and its constituents rather than the brain form the primary organ that manifests migraine and its clinical variants. A constitutive weakness of the corneoscleral envelope and choroidal hyper-circulation following exhaustion of AS generates migraine attacks. While combined congenital and migraine-related choroidal-flushing barotraumatic and nociceptive thinning of the corneosclera can manifest a bluish discolouration of the superolateral region of the anterior pole of the eye, choroidal flushing can manifest nasal-field sparing non-homonymous digitally-displaceable and ocular movement synchronous SS at the posterior pole. Migraine is a typical clinical state of threatened homeostasis with a well-defined adaptive system, the primary components of which lie in the pre-prodromal / pre-promonitory pre-clinical phase. The true onset of the migraine attacks lies in in the 'pre-prodrome / pre-premonitory' phase of migraine.

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