All About Cluster Headaches

Clinical Features, Epidemiology, Biochemical Abnormalities, Pathogenesis, Personal Burden, and More

By Jeremy Tucker

According to the International Classification of Headache Disorders (ICHD), cluster headaches are a member of the trigeminal autonomic cephalalgia (TAC) family of headaches [1]. Trigeminal refers to the network of nerves that service the jaw, cheekbone, and eye regions of the face; autonomic refers to the features of runny nose, tearing, sweating, constricted eyelid, and sagging eyelid that accompany the attack; and cephalalgia refers to head. Other TACs include paroxysmal hemicrania, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), and hemicrania continua. TACs differ from other headache classes (tension headaches and migraine) in that their durations are shorter, and they are accompanied by autonomic symptoms. As with all TACs, cluster headache is considered a primary headache disorder, meaning it is not caused by another disease or disorder. A headache that occurs in response to brain injury, tumor, or lesion would be a secondary, or "epiphenomenal" headache. Of all the TACs, cluster headache is the most common [2].

Clinical Features

The ICHD's 3rd edition describes cluster headache (CH) as "Attacks of severe, strictly unilateral pain which is orbital (eye), supraorbital (above the eye), temporal (temple), or in any combinations of these sites, lasting 15-180 minutes and occurring from once every other day to eight times a day." CH pain can also sometimes manifest in the mandibular region [3]. In all but 3% of patients [4], the pain is accompanied by autonomic symptoms: ptosis (drooping eyelid) miosis (constricted pupil) lacrimation (tearing) conjunctival injection (redness of eye), rhinorrhea (runny nose), nasal congestion, eyelid edema (swelling), and facial sweating, always ipsilateral (on the same side) as the pain. Psychomotor agitation, or restlessness and pacing, is sometimes considered an additional autonomic symptom [5]. Less frequent symptoms include photo- and phonophobia, nausea, and aura [6]. As many as 20% of American CH patients experience aura [7], with photo- and phonophobia occurring in about 50 to 65% of patients [8]. Additionally, bradycardia, (reduced pulse rate), accompanied with increased blood pressure, is sometimes found during CH attack [9]. There have also been reports of myofascial pain or "trigger points": hyperirritable spots located in the fascia in the skeletal muscle, believed to result from sensitization of muscular nociceptors (sensory receptor for painful stimuli)[10]. During an attack, the superficial temporal artery is often dilated and prominent; the artery and surrounding tissue may be tender to the touch.

The pain associated with CH, described as boring, stabbing, or lancinating, "like a knife behind the eye" [6, 11], is often considered to be the most severe known to humans [12]. It has been compared with childbirth, renal stones, limb fractures, and amputation without anesthesia [13]. The pain intensity of a CH attack is estimated to be between 100 and 1000 times worse than migraine [14]. One patient describes the pain in the following way:

> *"Imagine your eye is pushed out of its socket and your right eyelid is beginning to swell shut. You start squinting and your eye is tearing, you are convinced there was blood pouring out. A red-hot knife is crushed into your head, excruciating, horrible, horrible pain."* [4].

During an attack, approximately 90% of patients are restless, pacing, rocking, exerting pressure over the

painful area with their hand, and in some cases banging their heads against a hard surface [4, 15]. Many CH sufferers prefer to be isolated during an attack, or seek cold fresh air; some become aggressive [4]. Half of 1134 American CH patients report either hitting themselves in the head, or punching their fists against the wall [7]. There is some debate over whether pacing and restlessness are reactions to the pain, or part of the suite of autonomic symptoms--the basal ganglia, the part of the brain responsible for voluntary movement, is activated during CH [16].

Pain in CH is almost always unilateral (limited to one side of the head). The majority of both American and European patients favor a right side prevalence: 49% in US (44% left-sided); 54% in Sweden [7]. In 15% to 20% of patients, the headache changes sides during the course of their illness [6], and, in 1-2% of the CH population, occurs bilaterally [17]. In a study of 1134 Americans with CH, 8% report that pain switches side *during* an attack [7].

Cluster Headache Classifications

There are two main classifications of cluster headache: episodic and chronic. Episodic sufferers typically experience one to two "cycles" per year, averaging from one week to three months, though the IHS criteria for episodic cluster headache (ECH) includes "at least two active headache periods lasting from seven days to one year (without treatment), separated by remission periods of at least 14 days." Patients with chronic cluster headache (CCH), experience either no remission, or a remission less than 30 days per year [4], though still can experience rhythmic fluctuations throughout the year, with peaks and troughs of attack intensity. CCH can be further divided into two categories: primary chronic (unremitting from the start) or secondary chronic (evolved from ECH). In a sample group of 230 UK CH sufferers, 13% had primary CCH, 8% had secondary CCH, and 3% had ECH evolving from CCH [18]. However, other studies suggest that only around 5% of ECH patients go on to develop CCH [19]. Of CCH patients, 10 to 20% are resistant to treatment; this is known as refractory chronic cluster headache (RCCH) [4]. ECH patients make up approximately 85% of all CH cases, while CCH comprises just 15% [6].

Age of Onset, Attack Duration, and Shadows

The average age of onset for CH is 30 [6], but can occur in children as young as 2 [20]. According to a UK study, the mean age of onset of ECH was 28.4 years, and CCH was 37 years [18]. CH is a lifelong disease, but over a period of years the pain often becomes less severe and the length of attacks and periods often shortens. The severe chronic cases may change to a secondary episodic type. It is rarely seen in adults over 70, and onset declines after age 50 [21]. Attack duration is longer for CCH patients than those with ECH [22]. Between cycles and individual attacks, patients can experience mild, interictal pain known as "shadows" [23]. CCH patients are more likely to experience shadows than those with ECH. Shadows can also foreshadow or follow a cluster attack.

Daily and Annual Rhythmicity

Because of their tendency to occur at the same time per day (and per year), cluster headaches are sometimes referred to as "alarm clock headaches" [24]. More than 70% of CH patients report nocturnal attacks that wake them from sleep [25]. Nocturnal attacks account for 50 to 60% of attacks [26]. In studies involving American CH patients, attacks most commonly occurred in early evening and early morning hours. Two am was the most common time (41% of 1134 patients) followed by 1am and 3am (35%), with 8am being the least frequently time. Norwegian CH patients show a similar daily periodicity: between 4am and 10am. However, an Italian study of 180 patients indicated a peak attack time between 1pm and 3pm, perhaps reflecting that culture's "siesta". The prevalence of nocturnal attacks is possibly due to dysfunctional melatonin production: A 14-month study revealed depleted melatonin levels in ECH patients in cycle and out of cycle [21]. Many episodic sufferers experience cycles around the equinoxes, some around the solstices [21], but 40% of Americans with ECH report inconsistent annual rhythmicity. Cycle onset is most likely to occur in October, followed by September, April,

March, and November [7]. The month that is the least likely to see CH activity is June [7, 25]. However, in a study of Californian CH patients, July and January were found to be the two most significant annual peaks [27].

Daylight Levels and Cyclical Triggers

It has been suggested that changing daylight levels are responsible for the initiation of CH cycles [21]. When the periodicity of CH cycles was measured in Norway, Italy, and Argentina, onset was found to be related to daylight exposure: The higher the number of daylight hours, the lower the incidence of cluster headache periods [21]. Yet studies of Arctic CH populations, where significantly diminished daylight levels should yield earlier and longer cycles, revealed periodicity rates comparable with southern populations [25]. Because annual rhythmicities in Arctic, Danish, Italian, and American populations are divergent, they are more likely caused by cultural differences than daylight levels [22]. Another possible explanation is that, while circadian rhythms tend to conform to general, static patterns, circannual rhythms are highly individualized [4]. This would also explain the major differences in American CH population periodicity.

Epidemiological Studies

Cluster headache is a rare condition, affecting just .2% of the general population [28]. Prevalence rates, however, can vary from culture to culture; for instance in Norway .38% of the population has CH [29, 30]. Taking all epidemiological studies into consideration, CH occurs anywhere between 59 per 100,000 to 279 per 100,000, or .1% to .9% of the population [31, 15]. In the United States, there are roughly 500,000 individuals with CH [7]. Japanese patients showed a relatively low prevalence of CCH (2.9% to 3.5%) and a diminished sense of restless behavior compared to Caucasians (10 to 21%). Taiwanese patients experience a similarly low prevalence of CCH [32]. Men are three times more likely than women to have the disease, though this gap has been narrowing since 1963, when epidemiological investigations first began [4,15]. Indeed, some sources now put the male to female ratio at 2-1. Why the disease is increasingly affecting women may be related to significant changes over the decades in sex hormone regulation, and lifestyle factors including employment rate and smoking habits which show similar decreasing gender ratios [21]. This, however, may simply be due to increased awareness of the disease, or more women seeking treatment [4]. CH primarily affects Caucasians, although the disease can occur in any racial group [15].

Genetic Factors

Epidemiological investigations in recent decades have shown a slight but consistent genetic factor in CH. An American study found a 45.6-fold increased risk among first degree relatives; a Danish study showed a 14.1 increased risk; an Italian investigation showed a 39-fold increased risk; and a French study showed an 18-fold increased risk [29]. A 14-fold increased risk for first degree relatives, and a 2-fold increased risk for second-degree relatives are the rates most commonly cited by researchers and neurologists [21].

The search for specific CH-related genes and gene mutations has been hit or miss. An examination of the CACNA1A gene, previously demonstrated to cause several episodic neurological disorders, showed no genetic variations within CH patients [13]. And a recent study involving 149 patients showed no association between CH and PER3 clock gene polymorphism, one of the genes responsible for circadian rhythmicity [33]. However, an association of the ADH4 gene and an increased risk of CH was observed in Italian patients, though this was not confirmed in a large Swedish case-control cohort study [34]. Also, an analysis of the hypocretin receptor-2 (HCRTR) gene (involved in the regulation of the sleep-wake cycle) showed a significant association with CH [35]. And human leukocyte antigen (HLA) abnormalities have been reported in CH [29]. (Antigens are toxins that induce an immune response in the body; HLAs are used by the immune system to differentiate self cells and non-self cells.) Finally, a 2006 gene expression analysis of more than 54,000 gene transcripts

corresponding to 22,000 genes in 6 CH patients found upregulation (increased production) of proinflammatory proteins during the active phase of the disease, perhaps a secondary response [36].

More tellingly, a 1991 report found five pairs of monozygotic (identical) twins with CH. It is also known that different forms of CH (ECH, CCH) sometimes occur in the same family, suggesting a common pathogenesis in addition to a genetic predisposition [21].

While the specific mode of genetic inheritance is not known, researchers suspect one of three possibilities [21,34]: An autosomal gene disorder, an autosomal recessive disorder, or a multifactorial inheritance pattern. Autosomal disorders are those in which an abnormal gene is passed along through a single parent. An autosomal recessive disorder is one in which two copies of an abnormal gene must be present in order for the disease or trait to develop. And multifactorial inheritance patterns involve combinations of genetic and environmental factors. More genetic research related to CH is sorely needed.

Trigger Factors

Cluster attacks and cycles are often brought on by a broad range of stimuli and daily activity. By far, alcohol is the most well-known trigger, causing attacks in 50 to 80 percent of patients even when modestly consumed [37, 8]. ECH patients more commonly report alcohol-induced attacks (65%) compared with CCH (54%). Red wine is especially potent, eliciting attacks in 70% of patients [8], but other studies report beer as equally potent, perhaps suggesting that differences in prevailing alcoholic preferences between cultures determine which variety of alcohol causes CH attack. Such cultural differences may also account for why Asiatic CH patients report alcoholic-triggering in far fewer numbers. Mimicking capsaicin (the active ingredient in hot peppers), alcohol provokes neurogenic inflammation in the trigeminovascular system, as well as vasodilation (expansion of blood vessels) of meningeal (the brain's protective outer layer) vessels through CGRP (vasodilator) release from perivascular terminals. Since alcohol is a trigger for other primary headache disorders (migraine, tension headache, other TACs), it is believed that it acts on one of the brain's pain modulatory circuits; i.e. the hypothalamus [38].

Other trigger factors include nitroglycerin, increased body heat and exertion, exposure to cold, changes in barometric pressure, high altitudes, hay fever, cocaine, smoking, sleep apnea, and ingestion of certain foods (chocolate, eggs, dairy products, bacon, preserved meats, and other nitrite-rich foods) [37, 39, 40]. There have also been individual case reports of CH being triggered by orgasm [41] and emotional distress [39]. In a study of 1134 American CH patients, 52% reported alcohol as a trigger, 36% weather changes, 28% smells, 23% bright lights, 17% flashing lights, 12% watching television, and 8% hot showers [7]. In a Danish questionnaire of 275 CH patients, 80% reported nocturnal sleep as a trigger, followed by relaxation (38%), and napping (33%). Interestingly, CH patients who demonstrate consistent daily attack patterns are more likely to report sleep as a trigger factor [22]. Attacks tend to occur after stress and meals, rather than during mental and physical activity, suggesting a temporal relation to the activity-relaxation cycle, and perhaps providing an explanation for why Italian CH patients tend to report attacks around the early afternoon siesta [21]. Fortunately, triggers generally only effect patients who are in active cycle; during remission, exposure to the abovementioned stimuli do not result in attack [40].

Comorbidities, Increased Risk Factors, and Associative Disorders

A number of lifestyle traits, risk factors, and physiological abnormalities are associated with the disease of CH. Cigarette-smoking, alcohol and caffeine-overuse, head trauma, sleep disorders, and allodynia are all indicated in CH, as well as numerous immunological, neurovegetative, biochemical, and trigeminovascular abnormalities.

Cigarettes, alcohol, and caffeine

Of all the associations with CH, none is as strong as smoking. Indeed, researchers have often wondered

whether smoking is a prerequisite for CH, perhaps on the basis of a genetic background [4]. Approximately 65 to 77% of CH patients are, or have been, smokers [42, 43]. This correlation is stronger in CCH patients than ECH patients. In an Italian study of 374 male CH patients, smokers accounted for 78.9% of ECH patients, and 87.8% of CCH, with 12.9% of ECH patients and 19.6% of CCH patients smoking over 30 cigarettes a day. Of these 374 patients, 330 were either current or former smokers. All 20 patients with secondary CCH (CH evolved from episodic) were smokers. And only 32 of the 292 patients who were current smokers had started smoking after developing CH [44]. In a US study of 1134 patients, only 439 had never smoked prior to CH onset [7]. Those ECH patients who do smoke, tend to have a more severe form of the disorder [45]. Also, smoking is more common in affected than in non-affected family members, suggesting a possible hereditary link between CH and smoking [29].

A correlation between CH and secondhand cigarette smoke also seems to exist [29]. Of the abovementioned 439 American patients who were not smokers prior to CH onset, 269 (61%) had at least one parent who smoked while they were living with them. For the entire survey population of 1134 patients, 71% grew up in a household with at least one parent who smoked, whereas only 25% of all US children age 3 to 11 live with at least one smoking parent. This equates to a 2.5X greater risk. Also, those who were exposed to secondhand smoke (regardless of whether or not they themselves smoked) showed a marked tendency to develop CH prior to age 20, about 15 years earlier than average [7].

Because of these connections, one might assume that quitting smoking would have an ameliorative effect on cluster headache pain, but this is almost never the case [45, 29]. A causal relationship, therefore, between CH and smoking is unlikely.

In fact, there have even been reports of smoking-related improvement: 26% of 49 Swedish CH patients reported relief from smoking, while 8% of American CH patients reported reduced attack severity, with 2% claiming reduced attack frequency [7]. Recent discoveries showing activation of the orexinergic system in rats via acute nicotine administration provides a clue for smoking's mitigating influences. Orexin is a hypothalamic neuropeptide that is able to modulate nociceptive input (pain signals) to the trigeminal nucleus caudalis. By smoking, some patients may be unwittingly triggering an analgesic effect on CH pain.

Alcohol and Coffee

As mentioned above, alcohol is a potent CH trigger. It is ironic, therefore, that CH patients often drink excessively. In one study, 91% of CH patients drank, with 61% falling into the category of moderate to excessive drinkers; in another, more than 90% drank alcohol, with a significant proportion being heavy drinkers [46]. Interestingly, there are reports that in some CCH patients, alcohol consumption may ameliorate attacks, or lead to the remission for a period of time proportional to the amount consumed. 79% of ECH patients decrease alcohol consumption during headache periods [8]. Another study revealed alcohol abuse in 16.2% of ECH and 26.8% of CCH patients. Only 38 of 303 ECH patients (12.5%), and 1 of 41 CCH patients (2.4%) were either teetotalers or occasional drinkers. A total of 61 of 374 patients (16.5%) were found to be heavy drinkers [44].

CH sufferers also show a tendency for excessive coffee consumption. Heavy coffee drinkers were most prevalent among patients with primary CCH (whereas those with secondary CCH were more frequently heavy smokers) [32]. Another study reported excessive coffee consumption in eight of twenty-one of CCH sufferers (38.1%), but just 6.9% of ECH sufferers [44].

While these associations are intriguing, most researchers stress that they suggest a trend among CH patients to overindulge in certain living habits, rather than a causal relationship between alcohol- and coffee abuse, and smoking [44]. However, MRI studies during CH attack have indicated activation of the ipsilateral ventrolateral midbrain, a part of the brain that plays a role in addiction [4]. Is addictive behavior perhaps an underlying factor in CH pathogenesis?

CH and Head Trauma

Head trauma is sometimes associated with CH, though a causal connection is controversial. In the

abovementioned survey of 1134 American patients, 204 (18%) reported significant head trauma prior to CH onset, compared with 2% of the general population [7, 47]. An 1987 paper describes 4 patients with "minor" head injuries, two of whom developed typical CH immediately, the other two over a period of months to years. A study reviewing 78 CH cases from 1949 to 1988 found that 5.2% to 16.5% of patients reported head injury. A later review by the same author concluded that CH onset in relation to head trauma ranges anywhere from 21 months to 30 years [48]. History of head injury is more frequently reported by chronic (54.7% of cases) than ECH patients, and in particular by patients with secondary CCH. In over 75% of cases, head injury preceded CH onset, but the average interval between the two occurrences was as long as 10 years [44]. Another study concluded that CH onset in relation to head trauma ranges anywhere from 21 months to 30 years [48]. Such long spans make it unlikely that head injury causes CH; rather the high incidence may depend on behavioral and/or lifestyle patterns (excessive alcohol consumption) that could make CH patients more vulnerable to traumatic injuries or accidents in general [44].

However, there is a report of a 48-year-old woman who developed classic ECH mere hours after banging her head against an iron ladder; nineteen years later, she was still experiencing regular cycles [49]. Perhaps, then, head trauma merely hastens onset in those individuals who would have eventually developed the disease anyway. The same centralized dysfunction that would predispose an individual to greater or lesser vulnerability to events like head trauma, brain surgery, or a CNS disorder, might also predispose them to developing CH.

Sleep and CH

The relationship between sleep and CH is one of the most interesting and widely studied. As mentioned above, the majority of CH attacks occur during sleep [26]. Indeed, according to the International Classification of Sleep Disorders, CH is a sleep-related disease [50]. Sleep apnea, insomnia, disturbed REM sleep, and overall reduced sleep quality have all been linked with CH.

Sleep Apnea

Sleep apnea is a condition in which breathing is either shallow or interrupted during sleep, leading to depleted blood-oxygen levels. In obstructive sleep apnea (OSA), a blockage of the airway causes the depletion; in central sleep apnea, the brain fails to signal the muscles needed to breathe. A polysomnographic evaluation of 31 ECH patients revealed an 80.64% prevalence (25 patients) for obstructive sleep apnea. Of these, 10 had mild OSA, 11 moderate, and 4 severe [26]. Other studies suggest prevalence rates between 31% and 60%, though a recent study of 40 CH patients found no correlation whatsoever [51]. Compared with the general population, CH patients have an 8-fold higher risk of developing OSA [25]. In some instances, treating apnea with continuous positive airway pressure (using mild air pressure to keep airways open) prevents CH [52]. Because sleep apnea may exhibit seasonal variation with a winter and spring preponderance, it has been speculated that CH and sleep-disordered breathing exist in tandem [51]. Other researchers, however, question a causal relationship [26].

Insomnia

In an Arctic Norway study of 70 CH patients, 40% suffered from chronic insomnia, compared with just 11.7% of the general Norwegian population [25]. CH patients with insomnia experienced significantly longer cycles: an average 8.7 weeks for insomniacs vs. 5.1 weeks in non-insomniacs. The insomniac group also reported longer attacks (84 minutes) compared to those without insomnia (64.7 minutes).

Interestingly, insomniacs were more frequently employed in shift work than the CH group who did not suffer insomnia. Roughly half of 60 patients were shift workers, whereas only 24% of the general Norwegian population were. Shift workers tend to see lack of sleep as a trigger only if they did not suffer from insomnia, suggesting that it is not the accompanying insomnia that triggers the attacks, but the nocturnal activity or stress

factors that accompany shift work.

REM Sleep

A Danish polysomnographic study of 40 CH patients found that they had less REM sleep (17.3% vs 23% in healthy controls) and took longer to enter REM (2 hours vs 1.2 hours in healthy controls)[51]. CH patients also experienced fewer arousals--an average of 7.34 nightly arousals compared to 14.1 in healthy controls. Those patients who had both diurnal and nocturnal attacks had more REM sleep, (though this was statistically insignificant), as did those who experienced attacks during the night of the study. Also, contrary to earlier studies, there was no temporal relationship between CH and REM sleep: CH attack can occur in any sleep stage, not just REM. An association may remain, however, between nocturnal attacks and the neural circuits responsible for REM sleep, some of which are hypothalamic. Activity in the serotonergic (mood, digestion) and noradrenergic (alertness and arousal) systems leads to suppression of REM sleep. Involvement of "REM-off" neurons located in the periaqueductal gray (pain modulation) and lateral pontine tegmentum (arousal and sleep stage modulation) could be one key region affecting both sleep and trigeminal pain regulation. The decreased arousals experienced by CH patients could be related to dysfunctional hypocretin production, a neuropeptide associated with regulation of arousal, possibly via a mutation of the HCRT-2 gene, mentioned above. Arousal during sleep is a normal phenomenon that increases with aging. Hypoarousal has been implicated in both CH, hypnic headache, and migraine.

Other sleep-related phenomena

More sleep abnormalities were identified in CH patients suffering from left-sided attacks compared to those with right-sided attacks, according to a Moscow-based study of 18 subjects. These subjects also demonstrated a predominance of superficial sleep stages with a prolonged pre-sleep period, and a complete absence of dreams [21]. There is also the case of the 49-year old ECH sufferer who reported being awoken twice-a-night at the same time for 7 days prior to the initiation of his regular cluster cycle. The patient, who had no previous sleep complaints or other symptoms, described the events as being "suddenly fully awake", with no pain or restlessness. The awakenings were regular--3am and 5am--and his CT and MRI brain scans were normal. This further supports the hypothesis that the hypothalamus triggers CH cycles; not just attacks [53].

On the whole, CH patients demonstrate consistently impaired sleep quality which improves as the cycle abates. Yet only when remission lengths approach a year do CH patients' sleep quality match those of healthy controls. This suggests a connection between sleep and CH that transcends the direct disturbance caused by the attacks themselves, and again implicates circuits in the hypothalamus and brainstem [22].

Allodynia in CH

Allodynia, the experience of pain in response to normal, non-painful stimuli, is driven by central pain sensitization, which is when the nervous system becomes trapped in a state of high reactivity [54]. Cutaneous allodynia, most frequently associated with CH, is pain sensitization involving the skin. In a study of 10 CH patients, 4 (40%) had cutaneous allodynia (CA) in both trigeminal and cervical dermatomes (areas including the arms, neck, and shoulder). The patients with the longest CH histories were the ones most likely to have CA, suggesting that the latter is a time-dependent process of neuronal or receptor sensitization. Another report describes two ECH patients who, during an attack, developed allodynia in the ipsilateral hand and foot [55]. Pain hypersensitivity has also been reported in CH patients outside of cycle: Decreased pain threshold were reported both on the contralateral (opposite to pain side) face, as well as arms and even legs [56]. Revealingly, the pace of the development of CA seems to mirror the pace of the disease itself: migraineurs develop it more slowly; CH patients more rapidly (55). In one ECH patient experiencing an attack, CA was relieved via oxygen therapy [57]. Because allodynia effects both CH patients in cycle and out of cycle, and because the hypersensitivity extends beyond the trigeminal matrix into the neck, arms, and in one instance, the feet, it has

been suggested that CH involves a centralized impairment of the pain transmission system [56].

Lifestyle Factors

According to an Italian survey, male CH patients tended to have jobs involving greater responsibilities than the general population. CH patients were also more frequently self-employed [44], and are more likely to work full time jobs compared with their non-affected relatives [25]. These are not widely believed to be causally related to CH, but rather related to behavioral traits [44].

Shift work, mentioned above, is also associated with CH. A Norwegian study of 49 CH patients found that 51% were shift workers, and another nine (18%) had previously worked shifts, whereas only 33% of the general Norwegian population performed such work. A circadian misalignment brought on by shift work could, in theory, serve as a trigger in predisposed individuals. This raises the question of whether the pathology exists in the biological clock itself, or in the adaptation between the clock and the environment [33]. Interestingly, a study of 149 CH patients found 38 (51%) had evening type chronotype, 27 (37%) intermediate type, and 9 (12%) morning type. Chronotype refers to the propensity for an individual to sleep at a particular time during a 24-hour period. The majority of CH sufferers, therefore, can be said to be "night owls."

Associations in Female Sufferers

Estrogen seems to play a role in both CH onset and remission, though this remains controversial. A 1988 study of eight female CH patients found that six (75%) experienced remission during pregnancy [58]. However, a more comprehensive investigation involving 82 women found that CH remained unaffected by pregnancy, as well as menstruation and puerperium (the 6 week period following childbirth). Still, a study of 196 women CH sufferers found that 62% experienced their first attacks after pregnancy, as opposed to 37% before [59]. The success of kudzu, which has estrogenic properties, in treating CH suggests that estrogen may have a protective effect against the disease, perhaps explaining the decreased rates of attack during pregnancy [46]. There is also a case report of a 25 year-old women who experienced pure menstrual CH: Every 3rd or 4th day of her menstrual cycle, she would experience approximately 5 CH attacks, which she treated using melatonin and topiramate. Another patient experienced CH attack onset in tandem with ovulation, and remission with menstruation [60]. Also, CCH sufferers in a Japanese study were all postmenopausal women who experienced onset in their sixties and seventies, again lending support to estrogen's protective role against CH [32]. However, the abovementioned study of 82 patients, along with another study of 34 patients, cast doubt on any widespread correlation [60]. Finally, women with CH also demonstrate lower pain and cold thresholds compared to their male counterparts [59].

Associative Illnesses

In a study of 130 CH patients, 56.9% were found to have comorbid disorders. Thirty-one (23.8%) had chronic sinusitis, compared with 16% in the general population, perhaps caused by repeated autonomic symptoms (rhinorrhea or nasal congestion) that accompany CH attack. Diabetes, high blood pressure, depression and anxiety disorders, cervical spondylosis (wear and tear of spinal discs) and gastric and duodenal ulcers were also found [61]. Increased gastric acid secretion is also frequently reported in CH patients [62]. Turbinate hypertrophy, a condition in which the turbinates (paired structures inside the nasal cavity), become enlarged, has a high affinity for CH. In one study, 29 of 30 (96%) of ECH patients and 4 of 6 (66%) of CCH patients had the disease, though again, this is likely a manifestation of repeated autonomic outflow, rather than a CH precursor [21]. Many CH patients also suffer from migraine: Approximately 51% have a either personal or family history with migraine [15]. There is also an interesting report of two CCH patients who after onset developed cataracts (clouding of eye lens) on the same side as the pain. Neither had taken corticosteroids, a known cataract precipitator, and, amazingly, both shared the same uncommon last name, despite their not being related [63].

Even more interestingly, CH has been linked with low prevalence of cardiac disease as well as cerebrovascular disease, cardiovascular disease, heart attack, bypass surgery, stroke, emphysema, chronic obstructive pulmonary disease, and lung cancer. Might CH have some type of protective effect against artherosclerotic disease in the heart and brain [7]?

Physiological and Psychological Abnormalities

In the early years of the modern CH research period, patients were believed to exhibit clear and categorical personality types and physical appearances. Few, if any of these are still considered valid, but they are noteworthy, if only to highlight the difference between generalizations and well-crafted, controlled studies [21].

In terms of physical appearances, patients were said to have "rugged, lined, and leonized (lion-like) faces, perhaps to a degree greater than that which would be expected by chance alone." Broader skulls, and "peau d'orange" (coarse, orange skin) were also indicated.

Psychologically, CH patients were described as aggressive, masculine, possessing athletic prowess, ambitious, hard-working, and demonstrating a strong sense of upward mobility, beneath which was anger, insecurity, and guilt. Kudrow suggested that patients were generally reserved, rigid, detached, self-critical, conscientious, persistent, staid, moralistic, self-sufficient, resourceful, socially precise, compulsive, tense, and easily frustrated. Graham described the men as "often lead and represented by their wives", like a "powerful mouse pulling a red wagon in which was proudly perched Leo the Lion." He called his patients "mice living inside lions": timid individual with strong hysterical streaks and increased dependency needs. Friedman and Mikropoulos described CH patients as having a "constitutional predisposition to sustained emotional states" who were incapable of recognizing "that they were under greater stress, more emotionally upset or fatigued prior to an attack than in the preceding months or years." Lesse claimed that cycles were preceded by emotional crisis, and that tension and conflict could initiate attacks [9].

Male patients in particular had "rugged" characters, and exhibited a greater tendency towards gun ownership. In fact, a 1981 Michigan CH population study found 71% of 77 male sufferers and 24% of 24 female sufferers owned guns, compared to 60% of men and 15% of women controls. Gun ownership and aggressive behavior during CH attacks were thought to perhaps reflect deeply repressed emotions [9].

Pacing, yelling and head-banging during attacks were suggested to reflect hysterical tendencies. In one study, CH patients scored higher on the hysteria and hypochondriasis scales of the Minnesota Multiphasic Personality Inventory than nonheadache controls. Another study of 50 patients also showed higher scores than controls for hysteria and hypochondriasis, but not for depression. A 1963 study, however, found all but 3 of 53 patients to have moderate to severe depression. The presence of depression in CH patients was thought to be the result of ambivalence towards parental dominance or strained father-son relationships. OCD tendencies were also more prevalent in CH sufferers [9].

Yet as mentioned above, the majority of these studies, relying on anecdotal observations or generalizations and not supported by well-designed epidemiological investigations, are no longer considered valid. Broader skulls, leonized faces, or any other anatomical differences were not found in later, larger, more accurate studies; nor were peculiar personality types [21]. Theories citing emotional stress as a precipitator of attacks were similarly disproved, as were associations with anxiety and OCD [9].

Pathogenesis: What Causes CH?

Among CH sufferers and researchers alike, there is perhaps no question more pertinent than that of pathogenesis. What causes cluster headaches? Why do some people get the disease but not others? What underlying biochemical, neurological, vascular, hormonal, and immunological abnormalities are responsible? The following section attempts to answer some of those questions, as well as chart the progress from the beginning of the "modern" research period in the 50's, to the current state of understanding about the disease's driving factors. While a complete etiological mapping of CH remains far from finished, advances in imaging technologies have resulted in wellspring of knowledge that may some day lead to a cure for the world's most painful condition.

Early Studies and Pathogenic Theories

In the early days of the modern research movement, CH was believed to be a vascular headache, that is, precipitated by lesions or obstructions in cranial blood vessels and structures. The hallmark pain and autonomic symptoms of a cluster attack were thought to be *peripheral* in nature, as opposed centrally-precipitated, as is currently understood. The very earliest theories, tracing back to Horton in the 1930s, involved histamine, an inflammatory and immune response. Inflammation in the cavernous sinus, a large channel of venous blood in the head with proximity to the trigeminal and oculomotor nerve (the nerve that services the muscles of the eye and eyelid), were later believed to be responsible for CH's hallmark pain and autonomic symptoms [15]. The external and internal carotid arteries, the main blood supply to the neck, face, and brain, were also implicated.

Histamine

Noting that injections of histamine induced a dull headache in most people but CH attack in predisposed individuals, Horton implemented a regiment of histaminic desensitization (repeated infusions of intravenous histamine) to treat a number of intractable patients. The release of histamine, and in some species serotonin, may precede the release of kinins and prostaglandins (vasodilators) that may be responsible for the initial inflammatory response. Increased histamine levels were found in the urine of approximately one-third of patients on days of attacks, and whole blood histamine levels were found to be 20% higher in CH patients than migraineurs and control subjects [9]. Other studies found increased histamine levels in platelet-rich plasma extracted from general venous circulation, along with decreased histamine in blood taken from the ipsilateral jugular vein. Finally, skin biopsies of the pain areas of 13 CH patients had increased mast cell levels (cells responsible for releasing histamine during allergic reactions).

Many of these findings, however, are inconclusive or misleading. Elevated histamine levels in urine during CH cycle could simply be the byproduct of cluster pain, rather than a precipitator. Increased cutaneous mast cell prevalence in pain areas does not necessarily reflect similarly increased blood vessels levels, which would be needed to produce the behind-the-eye pain associated with CH. What's more, powerful histamine blockers (chlorpheniramine and cimetidine) had no effect on CH. And even though Horton himself claimed success using histamine desensitization, his reports contained almost no hard data on recurrence rates and follow-up duration. Histamine may yet be involved in CH pathogenesis--there may be a third, undiscovered histamine receptor left unblocked by chlorpheniramine and cimetidine--but its role is currently considered to be secondary [9].

Carotid Artery

Many factors and observations lead early researchers such as Kunkle, Ekbom, Greitz and others to suspect the carotid artery in CH pathogenesis. The carotid arteries are major blood vessels in the neck that supply blood to the brain, neck, and face. The fact that attacks were triggered by vasodilatory substances such as histamine, alcohol, and nitroglycerin; and could be aborted using vasoconstrictors such as methysergide and ergotamine provided compelling evidence in favor of strict vascular involvement. Local tenderness of the external carotid vessels were also found during CH attack, which in some cases could be relieved by raising intracranial pressure. CH-like pain could be reproduced by stimulating the carotid artery bifurcation (the place where the CA diverges into its internal and external branches). Damage to the carotid artery was thought to aggravate nerves in the parallel-running sympathetic trunk (paired nerve fibers that run from the skull to the coccyx), causing pain and autonomic outflow [9]. However, a 1969 study found only 4 of 18 CH patients with carotid ectasia (bulging or swelling), though one patient examined during attack had a slightly enlarged carotid artery, and dilated ophthalmic artery [64]. Later, Kudrow measured the velocity of blood flow through the supraorbital artery (blood vessel above eye) on both sides of the head, between and during CH cycles, and found in most patients *decreased* flow velocity on the headache side between attacks, and a further ipsilateral decrease during the headache, which was believed to indicate an obstructive disease in the sympathetic trunk. The observation of "cold spots" (areas of skin with decreased temperature) above the eye during attacks was thought to provide further proof of decreased internal carotid flow. This was further corroborated by the fact that non-CH patients with internal carotid occlusion (narrowing or blocking of carotid artery) demonstrated similar symptoms: decreased blood flow and cold spots [9]. However, later examinations of autonomic function in CH patients, including testing of pupillary response, suggested that the dysfunction was more likely located in the cavernous sinus, through which the internal carotid artery passes.

Cavernous Sinus

The cavernous sinus (CS) is a large channel of venous blood in the skull where trigeminal, parasympathetic, and sympathetic fibers converge [15, 48]. In the early days, it was proposed that a recurrent inflammatory disease within the CS and its tributary veins damaged local sympathetic fibers that service the eye, upper eyelid, forehead, and the intracranial carotid artery and its branches [65]. This single, focused disease within the CS could explain the parasympathetic symptoms of lacrimation, rhinorrhea and nasal congestion, Horner's syndrome, and facial and forehead sweating, and pain around and behind the eye [66]. Indeed, most CH patients examined during attacks have demonstrated signs of inflammation of both the superior ophthalmic vein (the blood vessel that services the eye) and the CS, particularly on the painful side; similar inflammatory signs have been found in cerebrospinal fluid and blood, which fade when the attack is over. Also, metastatic tumors located within the CS have been associated with secondary CH [48]. The efficacy of vasoconstrictive triptan drugs as well as oxygen therapy, which has a similar vasoconstrictive effect, lend further support to the CS pathogenic theory. Attacks subside when dilation in cranial arteries and veins cease, reducing the load on the CS and thus abolishing pain. How long the cycle lasts depends on the speed with which the inflammation is healed, and to what extent the damaged sympathetic nerve fibers recover. If the inflammation is particularly severe or long-lasting, CCH develops [65].

Compelling though this theory may be, it leaves many questions unanswered. First, extensive subsequent neuroimaging failed to find evidence of systemic CS inflammation. Also, while it is true that ipsilateral vasodilation of intracranial arteries accompanies CH, it has since been shown that attacks can occur *without vasodilation*. Furthermore, triggers such as nitroglycerin, capsaicin injections, or alcohol administered outside of cycle fail to provoke attacks, suggesting a central, permissive involvement [34]. Finally, CS inflammation does not explain the circannual and circadian rhythmicity of CH. The discovery of the involvement of the hypothalamus, as well as numerous immunological and biochemical abnormalities suggesting central

involvement, would provide crucial new information in unraveling the mystery of CH.

A Neurovascular Disorder

In order to fully explain CH, three major features must be addressed: trigeminal distribution of pain, ipsilateral autonomic features, and circadian pattern of attacks [67]. The rise of neuroimaging and more sophisticated means of measuring hormonal, immunological, and other biochemical changes in CH has seen a considerable advance in explaining these features. The term "neurovascular" refers to the combined involvement of nerves and blood vessels, driven by *central*, rather than peripheral, permissive processes. In this theory, the trigeminal system, cranial vasculature, and the hypothalamus all work in concert to create the phenomenon that is CH. In the following section, the trigeminal system (including the trigeminal autonomic reflex and the trigeminovascular system), the pathology of autonomic symptoms, and hypothalamic involvement are all discussed.

The Trigeminal Nerve

Known also as the fifth cranial nerve, the trigeminal nerve is responsible for sensation in the face, as well as motor functions such as biting and chewing [68]. It has three major divisions: The ophthalmic or "V1" branch that services the eye and temple; the maxillary or "V2" branch that services nose, lips, and upper teeth; and the mandibular or "V3" branch that services the jaw and lower teeth/mouth area. Most CH pain occurs via the ophthalmic branch (around and behind the eye, and the temple), though pain along the maxillary and mandibular branches (neck or jaw) is sometimes reported too. Neck and jaw pain during CH attack is sometimes considered "referred pain"; that is, pain felt in a part of the body other than its actual source. This is likely due to "cross-synapsing" of separate nerve pathways. During cluster attacks, the ophthalmic branch is activated, producing pain and autonomic symptoms. Another nerve, the 7th cranial nerve (AKA the "facial nerve") is also believed to play a role in producing autonomic symptoms.

Evidence for the involvement of the trigeminal nerve in CH attack is found in the efficacy of the drug Sumatriptan [34]. Generally, stimulation of the trigeminal nerve produces vasodilation [16]; sumatriptan acts on receptors in cranial arteries and veins to cause vasoconstriction. Also, activation of the trigeminal nerve has been shown to produce elevated levels of calcitonin gene-related peptide (CGRP), a potent vasodilator. Finally, the hypothalamus, the brain area responsible for circadian rhythms and hormone production, causes trigeminal nerve activation when stimulated [34].

Trigeminal nerve activation alone, however, is insufficient for generating CH. Patients who've undergone trigeminal section surgery, in which parts of the nerve are severed, continue to experience cluster attacks, and continue to respond to Sumatriptan, suggesting a more central involvement and a different mode of action for Sumatriptan [34]. Further, injections of capsaicin (pain-inducing chemical found in hot peppers) into the ophthalmic division produced pain, but not cluster attack [13]. (These injections, incidentally, do not trigger hypothalamic activation.) And finally, while tests involving hypothalamic stimulation did activate the trigeminal nerve, it did not lead to cluster attack. [34] Stimulation of the trigeminal nerve does not necessarily produce CH. [16]

Trigeminovascular System

The trigeminovascular system consists of the neurons that service the blood vessels within the head and portions of the brain. These neurons have cell bodies within the trigeminal ganglion, a clustering of nerve cells that serves as a relay between the trigeminal branches and sensory processing centers within the brain. Several powerful vasodilator peptides are found in the trigeminal cell bodies: CGRP, Substance P, and neurokinin A. Peptides are protein-like substances that aid in the transportation of certain substance through the cell membrane, and act as biologic catalysts that speed up metabolic reactions [70]. Findings of high CGRP levels during attacks, mentioned above, are one way the trigeminovascular system is implicated in cluster attack. If stimulated, the trigeminal ganglion provokes increased blood flow in the cerebrum, the portion of the brain that processes sensory information and controls voluntary muscle activity [13]. The trigeminovascular system and the trigeminal system differ only in that the latter is strictly neuronal, while the former involves the relationship between neurons *and* cranial blood vessels. The two terms are sometimes used interchangeably in cluster headache literature. Pain in CH attack is often attributed to trigeminal-activated dilation of the blood vessels surrounding the eye.

Trigeminal-Autonomic Reflex

The trigeminal-autonomic reflex (TAR), also known as the trigemino-parasympathetic or trigemino-facial reflex, involves the activation of the parasympathetic fibers of the trigeminal system and their functional connections [34, 21]. More specifically, it is the parasympathetic relationship between the trigeminal ganglion, the superior salivatory nucleus, (involved in facial expression formation and taste) the sphenopalatine ganglion (tear and mucus production), and the otic ganglion (salivation, swallowing, and speech) [71]. The TAR can be activated via nociceptive (pain) inputs from the ophthalmic branch of the trigeminal nerve, but not through the other two branches (maxillary and mandibular) as proven by capsaicin injection experiments. TAR activation can also trigger dilation of the internal carotid artery, providing further proof that vasodilation in CH is a secondary phenomena [13]. During attacks, the trigeminal and sphenopalatine ganglions are activated, leading to the release of CGRP and vasoactive intestinal peptide (VIP), involved in vasodilation. These and other peptides in turn lead to the majority of autonomic symptoms associated with CH: tearing, conjunctival injection, eyelid swelling, nasal congestion, and runny nose [71]. Experimental stimulation of the superior sagittal sinus, a bony cavity involved in blood drainage, has been shown to trigger CGRP and VIP release from the trigeminal, sphenopalatine, and otic ganglions [54]. The relationship of the TAR, including the trigeminal and parasympathetic nerves and ganglia, the trigeminal nucleus and the superior salivatory nucleus in the brainstem, and the hypothalamus comprise what is known as the *cluster circuit*, the specific pathway involved in CH attack [34].

Autonomic Symptoms

There are several theories as to the origins of tearing, nasal congestion, runny nose, sagging eyelid, and constricted pupil that occur in CH. These include a compromised carotid artery, vasodilation or vascular swelling due to TAR hyperactivity, and dysfunction within the hypothalamus. Another possibility is that the symptoms are not themselves primary CH phenomena, but rather the secondary result of trigeminal discharge and pain [4]. To understand the pathology of these autonomic symptoms, however, it is helpful to first understand which symptoms are driven by which of the two branches of the autonomic nervous system, the system that controls involuntary movements and bodily function. Lacrimation, conjunctival injection, nasal congestion, and rhinorrhea are thought to driven by the parasympathetic (rest and digest) nervous system by way of activation of the trigemino-parasympathetic reflex, also known as the TAR. Miosis and ptosis (constricted pupil, sagging eyelid) are the result of sympathetic (fight or flight) malfunction [54].

In the carotid artery-based theory, parasympathetic activation leads to the dilation of the internal carotid artery, resulting in compression of the fibers running along the vessel wall, giving rise to the "Horner-like syndrome" of miosis and ptosis on the pain-affected side [72]. "Horner's syndrome" is a combination of symptoms that arises when nerves in the sympathetic trunk are damaged. The sympathetic trunk, mentioned earlier, are paired nerve bundles that run from the base of the skull to the coccyx. Dilation in the carotid artery, which runs parallel to the sympathetic trunk, could cause damage there, leading to some of the autonomic reflexes described above. Autonomic symptoms in CH are sometimes referred to as a "partial Horner's syndrome," because not all of the symptoms in classic Horner's syndrome (inset eyeball and decreased sweating) are present. Further evidence for this theory can be found in the fact that during attack there is increased blood flow in the internal carotid artery ipsilateral to pain [16].

TAR hyperactivity represents another mechanism by which autonomic symptoms could be triggered. When subjected to experimental electric stimulation, the superior salivatory nucleus (SSN) has been shown to exhibit both trigeminovascular and cranial autonomic manifestations [73]. Located in the brainstem, the SSN is the "hub" for the seventh cranial nerve, also known as the facial nerve. The facial nerve, by way of the SSN, controls the muscles of facial expression, and functions in the conveyance of taste sensations [74]. The SSN is the origin of cells for the cranial parasympathetic autonomic vasodilator pathway--the matrix of nerves that are associated with pupillary regulations, as well the secretory glands in the eyes (tears) mouth (saliva), and nose (mucus) [75]. Activation of both trigeminal and parasympathetic nerves defines the TAR. And so most, if not all, of CH's suite of autonomic symptoms can be explained by way of SSN-induced TAR activation.

Another possibility is that autonomic symptoms are simply a reaction to CH pain, mediated by way of the TAR [76]. It is known that sufficient ophthalmic pain will produce cranial parasympathetic autonomic outflow [16]. Experiments involving capsaicin injections in the forehead have demonstrated dilation of the internal carotid artery on the pain-affected side. Therefore carotid dilation could result from pain in the ophthalmic (eye) division of the trigeminal nerve [16]. And as mentioned above, such dilation is one possible mechanism of autonomic expression in CH.

Either of the above theories of activation, directly or indirectly, could themselves be triggered by way of the hypothalamus. It is thought that there is descending control of the trigeminocervical complex and SSN through various brain regions associated with pain modulation: the periaqueductal gray, locus coeruleus, nucleus raphe magnus, and hypothalamus [73].

CH as a Hypothalamic Disorder

In the 1980s, as Kudrow and other researchers began to look beyond the cavernous sinus and carotid artery, the role of the hypothalamus in CH pathogenesis began to come into focus. Experiment after experiment confirmed the involvement of this most interesting brain region which sits at the crossroads of a diverse array of neuro-functions. From hormonal studies to physiological abnormalities to brain imaging, the case for central, hypothalamic involvement in CH was now beyond refute.

What is the Hypothalamus?

The hypothalamus is an almond-sized area within the brain's lower central region which is involved in metabolic processes and other autonomic activities. Synthesizing and secreting certain neurohormones, controlling body temperature, hunger, aspects of parenting, attachments behaviors, thirst, fatigue, sleep, arousal, cardiovascular control, and circadian rhythms--these are all the job of the hypothalamus [61]. It is the suprachiasmatic nucleus, a tiny cluster of nuclei within the hypothalamus, that is implicated in regulating the biological clock. This internal clock is in turn influenced by several external factors, the most important of which is light [33]. Via nerve projections of the suprachiasmatic nucleus, the hypothalamus can further influence endocrine and autonomic function, as well as other brain structures (cerebral cortex, thalamus, hippocampus, amygdala, septum, periaqueductal gray, and the spinal cord) that are involved in pain transmission, as well as other

processes integral to CH attack [76].

Hormonal Evidence of Hypothalamic Involvement

Kudrow in 1980 was the first to propose hypothalamic involvement based on findings of altered testosterone concentrations in CH patients [13]. Melatonin, cortisol, testosterone, prolactin, growth hormone, thyroid-stimulating hormone and others can all be altered during a CH cycle; some even remain abnormal during remission.

Melatonin

Melatonin, a hormone involved in sleep and circadian rhythm regulation, is produced in the pineal gland, which is modulated by the suprachiasmatic nucleus in the hypothalamus. Synthesis and secretion of melatonin is dramatically affected by light exposure to the eyes [77]. The first study of melatonin in CH reported that 24-h production was reduced in 11 in-cycle patients compared to normal subjects. Also discovered was the fact that melatonin's acrophase (the time from midnight to peak hormone level) was moved forward. It has been proposed that low melatonin may be due to reduced availability of serotonin for its synthesis, serotonin being necessary for melatonin production [34]. Thus a hypothalamic disorder involving insufficient melatonin production would not only explain the prevalence of nocturnal CH attacks, but also many of the abovementioned sleep disorders.

Cortisol

A steroid hormone, cortisol is involved in metabolism, wound-healing, electrolyte balance, memory, sleep, stress, and mood. The production and release of cortisol is stimulated by something called "adrenocorticotropic hormone", itself controlled by factors released from the hypothalamus [78]. Both CCH and ECH patients in active period demonstrate delayed peak of morning cortisol levels, as well as increased 24-hour mean and peak levels. These levels are also high during the remission phase as compared with healthy controls, indicating an hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) [79]. The HPA is a set of direct influences and feedback interactions between the three endocrine glands: the hypothalamus, the pituitary gland, and the adrenal glands; it controls reactions to stress, and regulates digestion, the immune system, moods, emotions, and sexuality. Regulation of the hypothalamic neurons that control the HPA, therefore, can be said to be defective in people with CH [78].

Gonadotropins

Gonadotropins are hormones that act on the gonads, controlling sex hormone production. Two such gonadotropins involved in CH are luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH is involved in reproduction, and FSH regulates the development, growth, pubertal maturation, and reproductive processes of the human body. Some studies have shown normal LH and FSH levels in CH patients; others have shown reduced LH levels and increased FSH levels. The LH secretion cycle in particular has been shown to be prolonged in patients with CH, and to have fewer peaks. Both are regulated via the hypothalamic pituitary axis by way of gonadotropin-releasing hormone [78, 80].

Testosterone

A series of studies in the 70s and 80s found substantially lowered concentrations of plasma testosterone in men with CH [4]. A 2006 American study found borderline low or low serum testosterone levels in seven male and two female patients [81]. Delayed morning peaks of testosterone have also been reported [78]. Testosterone production is regulated by the hypothalamic-pituitary-testicular axis via the release of gonadotrophin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The hypothalamus secretes GnRH which in turns triggers the production of LH and FSH, which then stimulate the testes [82].

Before the advent of hormonal studies, it was widely believed that male CH patients would be found to have abnormally high testosterone levels. Elevated testosterone would explain the male preponderance, and the since-debunked "hypermasculine appearance" attributed to CH patients. Further proof for this theory can be found in the rareness of CH prior to adolescence. The finding of diminished levels, however, proves only that the hypothalamus is involved, but in what way? Perhaps both the onset of CH and male preponderance coincides with the decrease in testosterone seen in men in their later years: Male testosterone levels drop in late adulthood, while estrogen and other female sex hormones tend to increase as the ovaries fail [82].

Treatment of refractory CH using testosterone replacement therapy has had mixed results. It was ineffective for a group of CCH patients [78], but for four male patients with with confirmed low testosterone levels, it resulted in remission [81]. The recent discovery of sex hormone receptors within the suprachiasmatic nucleus, the hypothalamic region implicated in biological clock-keeping, suggests that successive hormonal modulation therapy may in some manner suppress hypothalamic activation, in a sense "turning off" CH. And since women have more estrogen receptors in the hypothalamus, they may be less likely to have the disease in the first place [83].

Prolactin

Also known as luteotropic hormone, prolactin is involved in milk-production and immune system regulation, and has been found to be reduced in CH patients, both during cycle and remission [21]. Prolactin's 24-hour rhythm has been reported as altered in ECH males both in remission and active period; loss of release rhythms was found in 3 of 9 patients in one study, and 13 of 15 in another [78]. Experimental administration of metoclopramide, a drug that blocks dopamine receptors, in CH patients resulted in lower-than-normal increases in prolactin levels, suggesting defective dopaminergic control of prolactin secretion [21]. Because prolactin release immediately and rapidly follows sleep onset, and because levels are depleted in some CH patients, it is possible that it plays a role in CH's nocturnal prevalence [9]. Pituitary prolactin secretion is regulated by endocrine neurons in the hypothalamus [78].

Growth Hormone

Growth hormone (GH) is a peptide that stimulates growth, cell reproduction, and cell regeneration. Its synthesis and release are stimulated by the hypothalamic growth hormone-releasing hormone.
Interestingly, GH's secretory pattern mirrors CH: a primary peak shortly after sleep and several smaller peaks during waking hours [9]. During CH periods, the circadian rhythms of GH have been found to be altered [78]. GH is produced and released rhythmically under the control of the suprachiasmatic nucleus.

Thyroid-stimulating hormone

As its name suggests, thyroid-stimulating hormone (TSH) is a pituitary hormone that stimulates the thyroid gland [84]. TSH production and release is in turn stimulated by thyrotropin-releasing hormone, which is produced and regulated by the hypothalamus. Several investigators have reported reduced TSH response to a challenge test during cluster period compared to remission phase and and to healthy controls [78].

Interpreting Hormonal Abnormalities in CH

While these abnormalities provide compelling evidence supporting hypothalamic involvement, they shed little

light on CH pathogenesis. Changes in hormonal levels could be the result of pain, rather than the reason for it. Irregularities that persist into the remission phase (prolactin, growth hormone, and melatonin) are easier to understand, and more revealing. One possible explanation for these changes is that disturbances in hypothalamic function give periodic rise to altered hormonal "messaging", triggering lowered pain threshold in trigeminovascular system neurons. In such a scenario, a cluster cycle begins when elements within the circadian clock "misfire", and ends when hormonal levels return to normal [78].

Physiological Evidence for Hypothalamic Involvement

Hypothalamic involvement in CH has also been corroborated along physiological lines. For instance, patients who have undergone trigeminal nerve sectioning (surgical procedure involving severing parts of the trigeminal system) often either fail to experience pain relief, or only experience a brief remission followed by recurrence of pain on the previously non-symptomatic side [4]. Others who've had high cervical spinal cord stimulation procedures (electrode implanted in neck on the same side as pain), report subsequent development of attacks on the previously non-symptomatic side [85]. Another patient who had complete trigeminal root section, whose face was consequently completely anesthetized, and whose corneal and blink reflexes were abolished, still continued to experience daily CH headaches that responded to Sumatriptan [13]. These imply that there is some central brain structure, likely the hypothalamus, that is at the very least setting the stage for CH, if not outright driving it. The effectiveness of lithium treatment provides further evidence, as lithium is known to accumulate in the hypothalamus [78]. Moreover, the fact that experimental injections of capsaicin into the ophthalmic division of the trigeminal nerve trigger pain but not cluster attack suggests that it is not merely vasodilation that is creating pain, but something more fundamental [13]. Finally, it has been shown that the posterior hypothalamus is able to either decrease or increase pain responses in the trigeminal nucleus, the genetic center that projects to the three branches of the trigeminal system [4].

PET Studies

The most compelling evidence for hypothalamic involvement, however, comes from brain imaging studies. In May's landmark 1998 PET scan study involving nine CH patients experiencing either nitroglycerin-provoked or spontaneous attacks, the ipsilateral hypothalamic gray matter was shown to be activated [12]. There now existed an elegant theory that explained why attacks tend to occur at the same time daily, and why cycles follow yearly patterns. Responding to decreasing or increased daylight levels, the hypothalamus initiates a cascade of neurohormonal events whose end result is TAR activation and, finally, classic CH pain and autonomic outflow, perhaps via inflammation in the cavernous sinus [78]. That the PET scans revealed activation on the same hypothalamic side as cluster attacks provided further proof. Even more compellingly, a subsequent voxel-based morphometry study of 4 ECH patients revealed increased gray matter density in the posterior hypothalamus *outside of cycle*. This suggests a permanent, underlying hypothalamic disorder in CH patients [86]. Because the posterior hypothalamus modulates the trigeminal nucleus neurons and the (TAR), it is possible that CH pain and autonomic symptoms may be due to a "disinhibition" of the TAR by the hypothalamus [34, 80].

Biochemical Abnormalities in CH

In addition to numerous hormonal abnormalities, there are a host of other physiological, neuropeptide, protein, biomolecular, and immunological alterations in CH patients. Many of these implicate the hypothalamus directly; others merely indicated central dysfunction in higher brain centers. Alterations in calcitonin gene-related peptide, Substance P, vasoactive intestinal peptide, nitric oxide, orexin, tumor-necrosis factor, brain-derived neurotrophic factor, kynurenine, have all been detected in CH patients, as well as others.

Physiological Abnormalities

Functions and vital processes of organs and body systems are referred to as *physiological*. In CH, physiological abnormalities are often present during the remission phase, revealing pertinent pathological clues about the disease. Photo- and phonophobia has been found in CH patients who are in cycle (but not during attack) compared to remission period and controls. Because these sensitivities have been found on both sides and are thus unlikely to be a mere reaction to pain, it has been suggested that they imply cyclic changes that may trigger CH cycle, and could be regarded as a marker of the predisposition to develop attacks [21].]In a study of 30 ECH patients in remission, reduced pupillary constriction velocity (pupils taking longer to react to increased light), and reduced retinal venular (tiny blood vessels within the retina) diameter were also found [72]. However, in another study of 29 patients, 16 were found to have a *supersensitivity* to pupillary and sweat gland response on the symptomatic side. [87]. CH groups also presented increased systolic blood pressure (pressure measured during contraction of the heart), while CH patients in remission had both increased systolic and diastolic (measured during expansion of heart) pressure [21]. The fact that such symptoms are present during remission implies impairment both of sympathetic (fight or flight) and parasympathetic (rest or digest) nervous systems, though in the case of the pupillary aberrations it is possible that they represent a kind of hangover effect following cluster cycle.

Neuropeptide Abnormalities

Neuropeptides are small protein-like molecules used by neurons to communicate with each other; they influence the activity of the brain and the body in specific ways. Whenever the trigeminal system is activated, neuropeptides such as calcitonin gene-related peptide (CGRP), Substance P, vasoactive intestinal peptide, (VIP), and others are released, causing vasodilation and pain. Elevated levels of CGRP, Substance P, and VIP have been found in ECH patients examined during spontaneous attacks [54, 29]. Orexin, a neuropeptide involved in trigeminal pain processing, has also been implicated. [88].

Calcitonin Gene-Related Peptide

A potent vasodilator, CGRP plays a prominent role in the transmission of pain, as well as activation and sensitization of trigeminal afferent neurons (nerves that carry information from the face to processing centers in the brain). Its presence in blood, saliva, or cerebrospinal fluid connotes trigeminal nerve activation [89]. During spontaneous CH attacks, CGRP plasma levels are increased in the external jugular vein on the pain side; ECH patients have higher jugular vein CGRP plasma concentrations during the CH period outside of the attack compared to remission period. These levels return to normal following a regiment of corticosteroids [34]. Animal studies have shown that stimulation of the trigeminal ganglion and superior sagittal sinus leads to increased in CGRP levels [21]. CGRP is also capable of enhancing Substance P, another neuropeptide involved in pain transmission [34]. Recent trials using monoclonal antibodies that target CGRP receptors have shown some promise in treating migraine, another primary headache disorder marked by high CGRP levels [90].

VIP

Vasoactive intestinal peptide (VIP) is a peptide hormone involved, among other things, in synchronizing the timing of the suprachiasmatic nucleus (the circadian pacemaker located within the hypothalamus) with the environmental light-dark cycle [91]. It is a marker of parasympathetic activation [89], and is perhaps responsible for autonomic symptoms [54]. As with CGRP, VIP release is triggered via stimulation of the trigeminal ganglion and the superior sagittal sinus [21]. Blood samples taken from the external jugular veins of 13 CH patients before and after treatment of attack, found raised VIP levels on the same side as pain [89].

Substance P

Substance P (SP) is a neurotransmitter and neuromodulator involved in vasodilation, inflammation, pain transmission, and more [92]. Because it is found in vessels in all pertinent regions involved in an attack, it has been proposed that it plays a key, if not primary, role in CH pathophysiology. Neurons associated with SP have the unique ability to convey not only pain impulses, but also motor impulses, meaning they can cause blood vessel dilation, glandular secretion, release from mast cells (cells containing histamine), and excitation of autonomic ganglion cells. When neurons containing SP are stimulated, symptoms develop that bear uncanny resemblance to CH attack, including pain and the entirety of autonomic symptoms. In addition to external stimuli such as formalin, nicotine, cigarette smoke, mustard oil, and capsaicin, SP can be released via thermal stimuli, bradykinin (a peptide that lowers blood pressure), histamine, and serotonin. Elevated levels of Substance P have been found in the saliva of CH patients during attack [89].

It has been suggested that a temporary arrest of the serotonergic system, which plays an inhibitory role in SP release, leads to elevated SP levels and, finally, CH attack. Histamine, a potent inflammatory triggered by SP, may play a further role, as CH patients have been shown to have elevated histamine-containing mast cell counts in the ipsilateral facial skin [93]. Finally, SP increases vascular permeability, increasing the ability of CGRP and VIP to affect dilation and increased blood-flow [54].

Orexin

Orexins are neuropeptides that modulate other neurotransmitter systems. The orexinergic system is wide-ranging, involved in everything from feeding to wakefulness to energy expenditure regulation to cardiovascular, neuroendocrine, visceral, and autonomic function to activation of the hypothalamic-pituitary-adrenal axis to, most recently, nociception (pain perception) [88]. Orexin-containing cells are located exclusively in the hypothalamus, with widespread projections to the entire central nervous system [79]. A mutation in HCRT2, an orexin gene, is associated with an increase risk of headache; patients with the mutation are 5-fold more likely to develop CH [88]. Recent evidence has highlighted involvement of the orexinergic system in both circadian rhythms and trigeminal nociceptive processing. Attacks of CH are most common at REM onset, when the orexinergic system is downregulated. A loss of orexinergic cells is one of the hallmarks of narcolepsy; narcoleptic patients have a greatly increased prevalence of primary headaches, with 44% to 64% of women, and 23% to 35% of men suffering from primary headaches. Thus a dysfunction in the orexinergic system, resulting from hypothalamic action or elsewhere, could be the fundamental destabilizing agent permitting trigeminal pain and autonomic symptoms [76].

Protein Abnormalities

Proteins are large biomolecules that perform a vast array of functions including catalyzing metabolic reactions,

DNA replication, responding to stimuli, and transporting molecules. They are "chief actors" within cells, carrying out duties specified by information encoded in genes [94]. Proteins implicated in CH include beta-thromboglobulin, pituitary adenylate cyclase-activating polypeptide (PACAP), and brain-derived neurotrophic factor (BDNF).

Beta-thromboglobulin

Beta-thromboglobulin (beta-TG) is a protein that is involved in cell reproduction, blood clot regulation, and glucose metabolization. It is released after platelet activation, which is caused when platelets (blood clot cells) encounter a break in the lining surrounding organs and blood vessels. A study of 17 ECH patients found higher platelet levels of beta-TG during remission, and lower levels during cycle [95]. During actual CH attack, plasma levels of beta-TG were found to be reduced by 42%; since beta-TG is released during platelet activation, it has been suggested that the latter is reduced during CH attack.

Pituitary Adenylate Cyclase-Activating Polypeptide

Similar to VIP, pituitary adenylate cyclase-activating polypeptide (PACAP) is a neurotransmitter and neuromodulator involved in stimulating enterochromaffin-like cells (cells involved in the synthesizing and secretion of digestive histamines) [96]. In a study of 9 ECH patients out of cycle, significantly lower plasma PACAP-38 levels were found compared with healthy controls. During attacks, however, PACAP-38 levels were found to be significantly *elevated.* Recently, it was discovered that PACAP-38 mediates the activation of the trigeminovascular system, and modulates the sensitization process. PACAP also has the ability to modulate circadian and circannual rhythms by way of melatonin synthesis [71]. It is therefore possible that it plays a role in CH pathogenesis.

Brain-derived neurotrophic factor (BDNF)

Another protein associated with CH, BDNF acts on the central and peripheral nervous systems, supporting the survival of existing neurons, and encouraging the growth and differentiation of new neurons and synapses [97]. It is involved with central sensitization, and has been shown to play a pivotal role in the modulation of pain signaling, by way of strengthening or weakening key synapses in the trigeminal ganglion. Inflammatory stimuli such as tumor necrosis factor (immunomodulator agent involved in cell death) and CGRP induces BDNF release within the trigeminal system. A study of 52 CH patients both in and out of cycle revealed elevated BDNF levels compared with healthy controls. That these levels remain high outside of cycle suggests continuous trigeminal activation. In theory, the release of BDNF from trigeminal neurons could underlie the interaction of inflammatory and neuronal pathways, perhaps leading to CH attack. Interestingly, BDNF has been shown capable of mediating allodynia: low doses increase pain sensitivity, while high doses lead to decreased sensitivity and numbness [98].

Biomolecular abnormalities: N-acetylaspartate and Nitric Oxide

N-acetylaspartate (NAN), the second most common molecule in the brain after glutamate, is responsible for fluid balance, myelin synthesis (fatty insulation surrounding nerve fibers), and the maintenance of creatine levels, which helps to supply energy to muscle cells. Proton magnetic resonance spectroscopy has revealed lowered NAN and creatine levels, compared with controls [86]. These levels were altered both in and out of cycle, again suggesting a persistent biochemical change in the region of the hypothalamus [80].

Nitric oxide (NO) is an important cellular signaling molecule involved in vasodilation and immune system response. Elevated NO levels have been found both in and out of cycle [21]. It has been suggested that NO could be the final promoting factor in CH, since it is involved in both central (hypothalamus) and peripheral (trigeminal nerve) activation [29]. During the active phase of CH, cyclic alterations in the hypothalamus may give rise to CH attacks via NO messaging signals. In fact, hypothalamic activation has been demonstrated in CH

attacks provoked by NO ingestion. (Exogenous NO is often used by researchers to trigger CH attack) [21]. This means that hypothalamic function can be modulated by way of NO, via activation of neural NO pathways [29]. Once activated, NO, a potent vasodilator and inflammatory agent, could trigger trigeminovascular activation, leading to CH.

Erythrocyte choline

Erythrocytes are red blood cells, and choline is the precursor molecule (molecules necessary for the creation of other molecules and compounds) for acetylcholine, a neurotransmitter involved in memory and muscle control. Erythrocyte choline (EC), therefore, is choline concentrations within erythrocytes. In a study of 24 CH patients, EC concentrations were reduced by 58% in cycle, and 55% out of cycle, compared with normal, healthy controls. Interestingly, the same study found cholesterol levels to be reduced by 20% for in cycle-patients, and by 23% for out of cycle-patients [99].

Immunological Abnormalities

The network of cells, tissues, and organs that work together to defend the body against microbial attack is known as the immune system. Many immunological cells have been shown to be altered during both phases of CH: natural killer lymphocytes, monocytes, T helper cells, regulatory T-cells, interleukin-1 and 2, and kynurenine [21].

Early Immunological Pathogenic Theories

Before hormonal and PET-scan studies confirmed the involvement of the hypothalamus, it was thought that an injury or infection within the cavernous sinus lead to the release of proinflammatory cytokines--signaling cells that are involved in the body's immune response. These cytokines, in particular interleukin-1 (IL-1) were thought to unleash a cascade of hormonal reactions and related biochemical imbalances which included endorphins, cortisol, melatonin, prolactin, and testosterone. In predisposed individuals, an irritative or mechanical focus could promote trigeminal nerve activation, causing an activation of positive circuits between IL-1, Substance P, and 5-HT, resulting in the release of nitric oxide and, finally, the occurrence of CH [100].

Killer Cells: Natural and Lymphokine-Activated

Natural killer (NK) cells are a subset of white blood cells that respond to tumor formation and eliminate viral-infected cells [101]. Peripheral NK activity has been shown to be diminished in ECH patients both in and out of cycle when compared with controls. In another study of 21 ECH patients during active attack, an increase was observed in NK cells in patients who were without the HLA-DR5 antigen. Antigens are foreign substances that induce an immune response; HLAs are used by the immune system to differentiate self cells and non-self cells. [102].

In another study of 10 ECH patients, an increase of lymphokine-activated killer cells was found during and after cluster period. Lymphokine-activated cells are white blood cells that have been stimulated to kill tumor cells. The above three abnormalities suggest an impairment of the bidirectional communications system existing between the immune and nervous system. It has been suggested that the HLA-DR5 antigen is the substrate on which several other etiopathogenetic factors can act [103].

Interleukin-2

The interleukins are cytokines involved in cell signaling related to immunoresponsiveness. Interleukin 2 (IL-2) is specifically involved in the body's response to microbial infection, and its presence reflects T cell activation. Eighteen in-cycle CH patients were found to have significantly increased IL-2 levels compared to healthy controls. IL-2 is known to activate the hypothalamus and stimulate corticotropin-releasing hormone, a neurotransmitter involved in stress response [79].

Kynurenine

A metabolite of tryptophan responsible for immunoresponsiveness and vasodilation, kynurenine has been shown to be significantly reduced in a study of 21 CH patients. The cause of this reduction is thought to be due to hyperactivity of the N-methly D-aspartate (NMDA) receptors. NMDAs are glutamate receptors responsible for memory and synaptic plasticity (the ability of synapses to strengthen or weaken over time). Glutamate, acting at NMDA receptors, plays a key role in facilitating nociceptive sensitization, which is when non-painful stimuli are perceived as painful. Kynurenic acid, a metabolite of kynurenine, has a known ability to restrain trigeminal system activation and neurons responsible for CGRP and nitric oxide release [104]. It is therefore possible that kynurenine plays a role in CH pathogenesis.

The Nociceptive System and CH

Recent research has shown that the nociceptive system is often significantly altered in CH patients. Nociception is the sensory nervous system's response to harmful or potentially harmful stimuli. In response to such stimuli--burning, cutting, freezing, etc--sensory nerve cells known as nociceptors produce signals that travel along the spinal cord to the brain, triggering the sensation of pain [122]. The nociceptive system is comprised of nociceptors, nociceptive neural pathways, and the brain components that process and interpret nociceptive input: the amygdala, hippocampus, hypothalamus, periaqueductal grey, insula, cingulate cortex, thalamus, and others. Nociception isn't pain per se; it is rather the signaling and processing whose end result is the *experience* of pain. Below are a series of studies and observations that demonstrate nociceptive abnormalities in CH patients, along with some possible explanations on how nociceptive derangement could influence CH pathogenesis. A faulty "pain detection system" provides one explanation why patients with complete trigeminal root section can still experience CH attack.

Warm and Cold Detection Threshold Studies

In a study of 22 CH patients, significantly increased warm detection thresholds were found on both the pain and non-pain side. Warm and cold detection thresholds are the points at which warm and cold temperatures are perceived. In another study of 8 CCH and 17 ECH patients, increased warm and cold detection thresholds were found on the pain side. However, bilateral (both sides) increased warm detection thresholds were found on the cheek, and bilateral increased warm detection and heat pain thresholds were found on the hands [86]. This may reflect biological modification of the pain conveyance system. Along with other data supporting a similar central nociceptive disorder, these studies support the hypothesis that CH patients have a lateralized derangement of the nociceptive system due to an altered mechanism of central pain regulation. Perhaps the occurrence of higher pain thresholds outside cycle is the counterpart to lowered pain thresholds found in other studies during the cluster period, implying a chronic downregulation of central pain control systems [105].

Altered Cerebral Glucose Metabolism

Increased metabolism of brain structures involved in pain control and processing (cingulate cortex, prefrontal cortex, insula, thalamus, and temporal cortex) were found in a study of 11 in-cycle ECH patients compared to the remission period. This study was carried out as a way of determining which brain structures were involved in the transition from the in-cycle to the out-of-cycle period. In the brain, "metabolism" means the conversion of glucose into cellular energy. Decreases in metabolism were found in the cerebellopontine, the area associated with the facial nerve, believed to be responsible for certain autonomic symptoms. When compared with healthy control subjects, regional brain metabolism was found to be decreased overall, providing further proof of a dysfunctional central pain modulation of antinociceptive pathways and circuits [106]. The hypothalamus, with its ability to act as a "top-down modulator" of the trigeminovascular system, may be the central brain structure in question [59].

Enkephalins, Endorphins, and the Opioidergic System

Enkephalins and endorphins are morphine-like substances produced by the body to suppress pain. Enkephalins act by blocking pain signals in the spinal cord; endorphins block pain at the brain stem [107]. Both are key components of the "opioidergic system", the combined actions of specific neuropeptides and brain structures responsible for regulating "antinociception", the action of blocking the detection of painful or injurious stimuli. A study of 5 CH patients revealed undetectable enkephalin levels in cerebrospinal fluid [9]. During CH attack, however, enkephalin and endorphin levels show consistent elevation [89]. Both studies suggest central opioid system dysfunction in CH patients. Indeed, whereas the opioidergic system of healthy individuals demonstrates circadian rhythmicity, CH patients' do not [21]. Even more tellingly, a study of 7 in-cycle CH patients revealed opioid receptor abnormalities within the pineal gland, the part of the endocrine system responsible for melatonin production. In addition to having a direct functional connection with the hypothalamus, the pineal gland is anatomically and functionally linked to the ophthalmic branch of the trigeminal nerve, the typical location of CH pain. It is therefore possible that dysfunctional opioidergic mechanisms within the pineal gland and the hypothalamus play a role in CH genesis. The fact that opioids increase the secretion of melatonin and that melatonin in turn alters endorphin levels provides another interesting clue: disordered opioidergic function may be the underlying factor in diminished melatonin levels reported in many CH patients [108].

CH and the Serotonergic System

Serotonin, AKA 5-hydroxytryptamine (5-HT), is a neurotransmitter involved in the regulation of mood, appetite, sleep, memory, and learning. It is primarily found in the gastrointestinal tract, blood platelets, and the central nervous system [109]. The serotonergic system is comprised of the 5-HT neurotransmitter itself, the brain regions where it is synthesized and released, the nerve fibers it travels along, and the numerous 5-HT receptors upon which it acts. The raphe nuclei, a cluster of nuclei found in the brain stem, is where serotonin is produced and released. These nuclei project to numerous brain structures, including the dorsal horn where they regulate the release of pain-modulating enkephalins, and to the suprachiasmatic nuclei, where they contribute to circadian rhythmicity [110]. Once serotonin reaches its target, it binds to one of over a dozen specific receptor types. Receptors are protein molecules that receive signals from outside a cell; when a neurotransmitter such as serotonin binds to a receptor, it causes a specific cellular/tissue response. 5-HT receptors are broken into 7 general classes and 14 subtypes--5-HT1 through 5HT7, etc--each with varying biological effects [111]. Serotonin receptors modulate the release of many other neurotransmitters, including glutamate, dopamine, epinephrine, norepinephrine, acetylcholine, as well as many hormones: prolactin, cortisol, substance P, and others. Given its involvement with key biochemical components of CH pathology, it is no surprise that the serotonergic system has been found to be altered in CH patients. Altered serotonin levels, the efficacy of serotonergic drugs,

irregular hypothalamic-pituitary-adrenal axis response, and reduced melatonin synthesis all implicate central serotonergic dysfunction.

Serotonin Level Studies

A 1998 study of 19 in-cycle CH sufferers (16 ECH, 3 CCH) found elevated plasma 5-HT levels and decreased platelet levels compared to healthy controls. (Plasma is the colorless fluid part of blood; platelets are colorless disk-shaped cell fragments involved in clotting.) There are two reasons for this apparent anomaly. The first is that platelets expended their available 5-HT stores into the surrounding plasma, leaving one depleted and the other saturated. The second, more likely explanation is that serotonin metabolism is increased in CH patients. Because pain thresholds are regulated by both the serotonergic and the noradrenergic systems (involved in fight or flight responses), and because the failure of one system results in a compensatory response of the other, it is suggested that elevated serotonin metabolism is the result of noradrenergic impairment. Indeed, recent studies of CH patients have found significantly decreased noradrenaline levels during cycle [82]. Normally, this compensation would restore antinociceptive function, but for whatever reason in CH patients it is insufficient [112].

However, an earlier study that looked at at serotonin outside of attack found decreased levels, suggesting dysfunction in the serotonergic system itself [113]. Still earlier studies found that CH improvement, either spontaneously or via lithium therapy, was associated with a drop of serotonin and histamine levels, while recurrence of attacks was linked with an increase of those levels. Serotonin uptake in CH patients was later shown to vary over the year, and to have a circadian rhythm in healthy individuals. Given what we know about the connections between the serotonergic system and the suprachiasmatic nucleus (which is responsible for generating circadian and circannual rhythms) it is tempting to speculate that CH periods begin when there is desynchronization between the two, and end when resynchronization occurs [21].

Serotonergic Drugs and Pain Modulation

Drugs that mimic serotonin are generally regarded as among the most effective in treating CH. These include ergotamine, DHE, triptans, Pizotifen, lithium, methysergide, LSD, psilocybin, and others. Initially, their action was thought to be due solely to vasoconstriction of cerebral blood vessels. The theory was that after binding to specific 5-HT receptors, serotonergic drugs (triptans in particular) would reverse vasodilation in the trigeminovascular system, eliminating the primary, final engine of CH pain. Later, it was revealed that triptans act not only at the trigeminal level, but also at higher central modulatory sites, such as the periaqueductal gray, the primary control center for modulating pain [114]. Further evidence of this is found in patients who've undergone trigeminal section surgery (in which the trigeminal nerve is severed) and yet continue to experience CH and respond to triptans--in order to be effective, the drugs must be acting elsewhere [34]. The effects of serotonin on pain regulation are mediated through the activation of the 5-HT1 and 5-HT2 receptor types, but the most recently discovered serotonin receptor type, 5-HT7, has been indicated in in the circadian pacemaker functions of the suprachiasmatic nucleus [111]. What this means is that the action of serotonergic drugs, especially those that have long-lasting prophylactic effects such as LSD and psilocybin, likely transcends mere vasoconstriction, perhaps even "resetting" fundamental biochemical imbalances in CH patients.

5-HT2a Receptors and Tumor Necrosis Factor

In a study of a rat, activation of the 5-HT2a receptor was shown to suppress tumor necrosis factor-induced

inflammation. 5-HT2a is neurotransmitter involved in cognition, mood, aggression, mating, feeding, and sleep. Tumor necrosis factor (TNF) is a cytokine that, when activated, induces fever, cell death, and inflammation. By activating the 5-HT2a receptor, researchers were able to not only inhibit TNF production, but also a variety of pro-inflammatory markers; i.e. interleukins and nitric oxide. TNF-mediated inflammatory pathways have been implicated in a number of diseases: atherosclerosis, rheumatoid arthritis, psoriasis, type II diabetes, Irritable bowl syndrome, Crohn's disease, depression, schizophrenia, Alzheimer's, Parkinson's, and stroke [115]. Some researchers and citizen scientists believe it could be implicated in CH as well.

M-chlorophenylpiperazine, 5-HT, and the Hypothalamic-Pituitary-Adrenal Axis

M-chlorophenylpiperazine (mCPP) is a 5-HT agonist that is known to exert effects on the cerebral serotonergic system, and has been used to probe neuroendocrine responsiveness. Agonists are neurotransmitters that encourage, rather than suppress, biological responses. In normal, healthy individuals, the administration of mCPP leads to a striking increase in cortisol and prolactin plasma levels via stimulation of the 5-HT1a/2c receptors [21]. In CH patients, however, mCPP administration leads to reduced cortisol and increased prolactin levels [116]. Cortisol, a steroid hormone, is modulated by the hypothalamic-pituitary-adrenal (HPA) axis, a set of influences and feedback interactions involved in the regulation of metabolism, immune-response, reproduction, and others. The HPA is in turn modulated by the serotonergic transmitter system, among others. Abnormal cortisol response in CH patients, therefore, implies serotonergic impairment at the level of the hypothalamus [21].

Melatonin

As mentioned earlier, melatonin, a hormone involved in the regulation of sleep and wakefulness, is synthesized by serotonin. Numerous studies have shown decreased melatonin production in CH patients, along with a delayed acrophase (the time from midnight to peak hormone levels) [117, 78]. These decreases could be the result of diminished serotonin production, lending further support for serotonergic impairment in CH.

Beyond the Hypothalamus

Recent research has challenged the theory that the hypothalamus is involved in initiating CH cycles and attacks [34]. FMRI imaging conducted in 2010 found that activation during CH attack lies not in the hypothalamus, but in the nearby midbrain tegmentum, which is involved in the control of movement and sensory systems, and is the seat of the 7th cranial nerve (the nerve responsible for autonomic outflow) [80].]It is also known that hypothalamic stimulation, AKA deep brain stimulation (DBS), does not initiate attacks or cycles; nor is it an effective abortive of acute attacks. Also, the fact that DBS's ameliorative effects can take months to appear suggests that its action is involved with modulating the antinociceptive system as opposed to curtailing the permissive process, hypothalamic or otherwise, that initiates or ends cycles. This is further evidenced by the increased ipsilateral cold pain thresholds that are found in CH patients with DBS implants: Hypothalamic stimulation raises the level at which they experience pain, but does not generally eliminate it. DBS's effectiveness, therefore, is likely due to restoring normal function and metabolism in those areas associated with pain modulation (thalamus, somatosensory cortex, and anterior cingulate cortex), thereby restoring top-down control of trigeminal pain circuits. And so it has been proposed that in CH the hypothalamus serves a modulatory rather than a triggering role, and that this brain area terminate rather than trigger attacks.

Amygdala: The Cluster Generator?

The amygdala are two almond-shaped groups of nuclei located within the temporal lobes of the brain. Part of

the limbic system, they play a pivotal role in aggressive behavior, emotions, pain, and autonomic activity. During active cluster period, increased metabolism in the amygdala has been reported, perhaps leading to disrupted "cross talk" between this brain area and the hypothalamus, thus triggering the permissive state needed to activate the cluster circuit. Hyperactive or dysfunctional amygdala activity could also be responsible for the aggressive behavior associated with CH attacks [34, 21].

CH Pathogenesis: The Search Continues

Notwithstanding CH's relative obscurity, the amount of information accrued to the disease over the last eighty years is staggering. A search of "cluster headache" on Pubmed, an online biomedical database, yields over 3500 results. And yet these data are often disparate, inconclusive, and perplexing. How do the myriad biochemical and physiological abnormalities mentioned above conspire to create the disease that is cluster headache? Which elements are fundamental, and which are merely epiphenomenal? That CH is a neurovascular headache with hypothalamic implications is by now beyond refute, but why does the disease arise in the first place? Why are more men affected? How do cycles begin? How do they end? Why are some people chronic and others episodic? How and why do the current treatments work? These and other questions remain unanswered.

One of CH's enduring mysteries is why it is so painful, or even why it is painful at all. According to the International Association for the Study of Pain, there are two possible types of pain associated with CH: Neuropathic and nociceptive. [34]. Neuropathic pain is caused "by a lesion or disease of the somatosensory nervous system"; nociceptive pain "arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors". (The somatosensory nervous system is the part of the sensory system concerned with the conscious perception of touch, pressure, pain, temperature, position, movement, and vibration, which arise from the muscles, joints, skin, and fascia) [118]. But in CH, there is no known observable anatomical or functional damage to the pain-related structures of the nervous system, the trigeminal pathways, or the somatosensory system. If you stub your toe on a chair leg, your pain has a known, quantifiable source: the unyielding chair leg. With CH, there is no chair leg. The intense pain and autonomic symptoms that accompany attacks cannot be explained solely by vasodilation in the ophthalmic branch of the trigeminal nerve, because pain can occur without vasodilation [34]. Nor by way of a recurrent infection within the cavernous sinus, as the early researchers thought. Pain in CH seems to arise due to a series of derangements, likely genetically-influenced, between the interoperations of the hypothalamus, the amygdala, and any number of neuroendocrine and neuroimmunological systems.

Dr. Peter Goadsby, one of the world's preeminent authorities on trigeminal autonomic cephalalgias, describes CH pain as: "Poor central filtering of low-level sensory signals, a normal sensory input being pathologically amplified." He suggests that the pain is a hybrid of two things: "a peripheral and especially a central sensory dysfunction." And further: "Perhaps in cluster headache the brain mechanisms are preeminent, and normal afferent traffic is perceived as painful, from time to time, rather than the primary driver being a peripheral nociceptive input." [21]. This would suggest that what CH is, at bottom, is a disease of the *experience* of pain as it relates to the trigeminal system. A disease of proportion, of sensation, of perception.

Another enduring CH mystery is the high placebo rates associated with abortive medications. In a study measuring Sumatriptan efficacy, more than a quarter of 39 patients who were administered placebo reported *complete freedom* from pain after 15 minutes [21]. The fact that the attack was totally abolished, as opposed to merely attenuated, reveals much about the disease's pathology. How can it be that such intense pain be eliminated solely by placebo effect? Even more questions are raised when you consider the wide-ranging array of medications and treatment protocols to which CH responds: Steroids, triptans, anti-seizure medications, psychedelics, oxygen, calcium channel blockers, Ritalin, Vitamin D, and more. Indeed, it sometimes seems as though CH will respond to any medication at all, if only for a while.

For now, such mysteries remain. Meanwhile, the search for CH pathogenesis continues. And with it, the

hope that one day, perhaps soon, a cure for this most horrendous disease will finally be found.

Personal Burden

Few diseases inflict such extraordinary suffering upon their hosts as CH. As mentioned above, the pain associated with cluster attacks is widely recognized as the most severe known to humans, similar to childbirth, renal stones, limb fractures, and amputation without anesthesia [12, 13]. In Rozen's study of 1134 American CH patients, 20% indicated that they lost a job because of CH, while another 8% were out of work or on disability thanks to the disease [7]. About 50% stated that CH rendered them homebound at least once per year, with 11% reporting that these homebound intervals lasted more than 30 days per year. Even though CH attack is often severe enough to prompt a visit to the ER, 63% have never gone, and 95% have gone 2 times or less, perhaps because, as noted by 70% of respondents, the physicians were unfamiliar with CH as a distinct headache condition. A Denmark study of 85 CH patients echoed these findings: The disease of cluster headache is insufficiently understood by doctors and practitioners [7].

For women with CH, there is another layer of burden: pregnancy. Females who develop the disease before having children have fewer children than those develop it after [119]. A full one third of female CH patients who do not have children cite CH as their reason for not doing so. One explanation is that the severity and all-encompassing nature of the disease renders child-rearing impossible. Another, more likely explanation, is that many prophylactic therapies (lithium, corticosteroids, etc) are contraindicated with pregnancy, and the pain is simply too severe to forgo them for any length of time.

But the most salient of burdens imparted by CH are the suicidal thoughts and tendencies that visit its sufferers. In the abovementioned study of 1134 American CH patients, 55% reported suicidal thoughts consequent of the disease. As many as two percent (approximately 23 patients) have actually attempted suicide [7]. According to another study, twenty-five percent of CH patients reported suicidal intentions at some point during the course of their disease [6]. In fact, the disease is often referred to as "suicide headaches", a moniker tracing back to US neurologist Horton, whose patients' "...pain was so severe that several of them had to be constantly watched for fear of suicide." [120].

With a prevalence rate of around .15%, CH is a common as multiple sclerosis [6], and according to neurology professor Robert Shapiro, just as debilitating [121]. Yet while $1.872 billion was spent on MS research in one decade, less than two million was spent on CH in 25 years. It bears repeating that the pain associated with CH is *either the most severe, or among the most severe that a human being can experience*. Notwithstanding this, notwithstanding the prevalence of suicidal tendencies among sufferers, notwithstanding the rich and vast literature available to all in the medical community, the disease remains underfunded, undertreated, and frequently misdiagnosed. Hence the need for great urgency, not only in raising CH awareness, but also in promoting treatments, regardless of their legal status, that show even the slightest potential for providing relief from this most awful condition. If ever there was a time to speak up, that time is now.

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