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# "Cluster" headaches: A review of the literature

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"CLUSTER" HEADACHES:  
A Review of the Literature

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# CONTENTS

	PAGES
INTRODUCTION . . . . .	1
HISTORY . . . . .	1-4
CLINICAL PICTURE . . . . .	4-17
Pain . . . . .	4-5
Nose and Eye signs . . . . .	5
Other associated signs and symptoms . . . . .	5
Cluster frequency . . . . .	5-6
Cluster duration . . . . .	6
Cluster timing . . . . .	6
Frequency of headache attacks . . . . .	6
Headache duration . . . . .	6-7
Attack timing . . . . .	7
Age . . . . .	7-8
Sex . . . . .	8
Race . . . . .	8
Incidence . . . . .	8-9
Family History . . . . .	9
Social Status . . . . .	9-10
Personality . . . . .	10-11
Precipitating factors . . . . .	11-13
Factors which relieve headaches . . . . .	13
Peptic ulcers . . . . .	13-14
Homer's syndrome . . . . .	14-15
Allergy . . . . .	15-16
Physical exam . . . . .	16
Lab findings . . . . .	16
Miscellaneous . . . . .	16
DIFFERENTIAL DIAGNOSIS . . . . .	17-20
ASSOCIATED ANATOMY AND PATHOPHYSIOLOGY . . . . .	21-23
TREATMENT . . . . .	25-31
Histamine "desensitization" . . . . .	25-26
Ergotamine tartrate and preparations . . . . .	26-27
Other vasoconstrictors . . . . .	27-28
Antihistamines . . . . .	28
Surgery . . . . .	28-29
Psychotherapy . . . . .	29
Miscellaneous . . . . .	29-30
UML 491 . . . . .	30-31
ETIOLOGY . . . . .	31-37
Histamine theory . . . . .	32
Vascular theory with noxious agent . . . . .	32-37
SUMMARY AND CONCLUSIONS . . . . .	37
BIBLIOGRAPHY . . . . .	I*V

## INTRODUCTION

Severe headaches that are frequent and recurring are problems in the lives of almost 10% of all people.<sup>1</sup> The causes of such headaches are multiple, but of recent interest in the past 20 to 30 years is a peculiar headache most often referred to as "Histaminic Cephalagia" or "Horton's Headache." Its peculiarity lies in its tendency to present clinically as unilateral headaches occurring in batches or "clusters" over weeks or months, with headache free intervals that may last months to years.<sup>2</sup> This paper attempts a review of some of the literature pertaining to the syndrome of what will be referred to as Cluster Headaches.

## HISTORY

Although Horton et al<sup>3</sup> is given credit by most for the original description of Cluster Headaches and for establishing the syndrome as a specific clinical entity in 1939, several other authors had previously published articles about the same syndrome but each author gave it a different name.

Von Mollendorf<sup>4</sup> was probably the first to describe the syndrome in Germany in 1867.

Sluder<sup>5</sup>, an American, in 1913 described the syndrome of "sphenopalatine ganglion neuralgia" and his success in relieving the headache that "...may stop and reappear cyclically as a migraine, or may stop and reappear with the stabbing sharpness as a tic.." with the application of cocaine to the sphenopalatine foramen.

Bing<sup>6</sup>, a German, writing retrospectively in 1952, states that the "new syndrome of vascular headache" described by Horton et al in 1939 is identical to the "affection" he referred to in 1913 as

"erythroprosopalgia."

Vallery-Radot and Blamoutier<sup>7</sup> in France, 1925, described a 38 year old female with recurrent, severe unilateral right sided headache and ipsilateral lacrimation and rhinorrhea. They called it "syndrome de vasodilatation hémicéphalique," thus being one of the first to recognize that vasodilation was the principal pathophysiology. They also reported that vasoconstriction gave relief.<sup>8</sup>

Harris<sup>9</sup>, an Englishman in 1926, described several cases of "ciliary (migranous) neuralgia" and used this term because he was impressed by the eye signs of ipsilateral lacrimation and redness. He suggested the cause might be due to dilatation of the meningeal vessels and reported on the beneficial effects of alcohol injections into the infra- and supra-orbital nerves and the Gasserian ganglion.

Sluder<sup>10</sup> again in 1927 described a variety of headache with "sympathetic" signs of unilateral lacrimation and nasal congestion. Glaser<sup>11</sup> in 1928, described a type of migraine with associated sympathetic phenomena.

One couldn't ask for a more classic description of Cluster Headaches than that by Dandy<sup>12</sup> in 1931. In the two cases he describes, he was so impressed with what he thought were sympathetic signs that he treated both with surgical removal of the ipsilateral sympathetic ganglia. Although he achieved immediate relief for both patients, Dandy was aware that his follow up was too short to draw any conclusions (2½ and 6 months).

Vail, in 1932, referred to the syndrome as "vidian neuralgia."<sup>13</sup>

In 1935, Brickner et al<sup>14</sup> described three cases of what he called "autonomic facio-cephalalgia." He seemed to anticipate what Horton achieved four years later when he suggested "...that

they no longer be classified as either atypical neuralgia or atypical migraine, but as typical examples of another condition." Brickner may have been the first to use ergotamine tartrate in the treatment of Cluster Headaches.

Vallery-Radot,<sup>15</sup> writing retrospectively in 1951, claimed to have reported in 1938 a "typical" case in a 26 year old male who had unilateral headache, conjunctivitis and nasal stuffiness.

In 1939, Horton's<sup>3</sup> famous article appeared in which he described 18 cases of unilateral headache so severe that several patients had to be constantly watched for fear of suicide. The following description is essentially verbatim: Patients had as many as 2 to 20 headaches a week. The pain was unilateral, constant, excruciating, burning, boring type of pain involving the eye, temples, neck and often the face. Bouts of pain would appear and disappear very quickly, but on the other hand, the headaches occurred with clock-like regularity, particularly at night, patients awakening with pain night after night and week after week at a certain hour. However, they were not without pain during the waking hours in many instances. Associated with these headaches and ipsilateral to them were: vasodilatation, swelling of temporal vessels, engorgement of soft tissues of the eye, injection of the conjunctiva, plugging of the nose, profuse watering of the eye and nose with flushing of the side of the face. At least some of these phenomena were present in each case. Because of the clinical picture, Horton suggested the term "erythromelalgia of the head" be applied to the syndrome.

It was in this same article that Horton reported the successful use of histamine "desensitization" in treating his cases.

In 1941, Horton<sup>16</sup> reported 72 cases and discussed the ability

of histamine given subcutaneously to induce the typical headache syndrome in 35 of the patients. Horton was so impressed with the relationship of histamine to "erythromelalgia of the head" that he changed the name of the syndrome to "histaminic cephalalgia"<sup>13</sup> and went so far as to state that "...the spectacular manner in which patients respond indicates that histamine treatment is as specific for this syndrome as insulin is in the treatment of diabetes mellitus." It was this article and the previous article of 1939 that "captured the imagination of the medical world and focused attention on the syndrome."<sup>17</sup>

By 1955, Horton had diagnosed Cluster Headaches 1176 times and reported that 95% of patients will respond to histamine "desensitization" with cessation of attacks within 10 to 20 days.<sup>18</sup>

Other terms that have been used to describe Cluster Headaches are "periodic migranous neuralgia"<sup>19</sup> and "petrosal neuralgia."<sup>20</sup>

#### CLINICAL PICTURE

According to Horton<sup>21</sup> once Cluster Headaches are observed in its full blown form "...the clinical picture will never be forgotten." The typical appearance of the syndrome has been reported by many authors,<sup>2,3,8,12,13,19,21-32</sup> and all are in agreement that the syndrome consists of the triad of unilateral headaches with nose and eye signs on the ipsilateral side, with the tendency for the headaches to occur in batches or clusters that last weeks to months with headache-free intervals that last months to years.

PAIN: The pain reaches its peak in 10 to 20 minutes after onset of the headache and is excruciating, boring, constant and of such intensity that Roberts has referred to them as "suicide headaches."<sup>33</sup>

The pain strikes as suddenly as it ceases; often times the patient

will jump out of bed and pace the floor before he is fully awake<sup>21</sup> in contrast to most migraine attacks in which the patient prefers to lay still and quiet.<sup>13</sup> The pain is located typically in and around the orbit and temporal area but may spread into the upper jaw, face, neck, occipital area, the whole side of the head and even into the shoulder.<sup>18</sup> The headaches are usually unilateral during any one bout<sup>17</sup> but Graham has seen bouts in which the headache began on one side and switch<sup>20</sup> to the other side during the latter part of the bout.<sup>34</sup> Graham has also seen a case in which the headaches were bilateral<sup>34</sup> a finding not mentioned elsewhere in the literature.<sup>34</sup>

NOSE AND EYE SIGNS: These occur at the height of the head pain and consist of ipsilateral nasal stuffiness or rhinorrhea (in 95%) and mild to profuse tearing (in 95%).<sup>25</sup>

OTHER ASSOCIATED SIGNS AND SYMPTOMS: Occasionally there is ipsilateral sweating of the forehead,<sup>18,27,35,36</sup> dilatation and engorgement of the temporal vessels,<sup>3,35</sup> ipsilateral erythema of the face and forehead,<sup>3,16</sup> residual soreness over the involved side,<sup>3,16,18,27</sup> swelling of the soft tissues about the affected eye,<sup>3,16,18,27,35,36</sup> temperature increase of 1-3 degrees Centigrade on affected side,<sup>3</sup> and in a few patients there is occasional excessive salivation.<sup>22</sup>

CLUSTER FREQUENCY: Kunkle<sup>2</sup>, writing in 1954, was impressed with the curious tendency of this syndrome to present with headaches in bouts that would last anywhere from several days to months. He was the first to use the term "cluster." Eckbom<sup>23</sup> had noticed this feature in 1947 and remarked on the relevance of spontaneous remissions to any evaluation of long term therapy. Robinson<sup>17</sup> reporting on 20 patients, found an average of two bouts per year

with complete symptom-free intervals between these bouts.

CLUSTER DURATION: Duration of a bout lasted on the average from several days to a few months. Robinson,<sup>17</sup> reporting on 20 patients, found a range of 1 to 12 weeks with an average bout length of 2 weeks. Symonds,<sup>36</sup> in a study of 17 cases, had similar results. Kunkle<sup>2</sup> found that the bouts lasted "several days or weeks" with remissions of 2 months to 2 years in 30 cases of Cluster Headaches. Graham<sup>34</sup> found the shortest bout to be one day in one patient, the longest bout being 4 years in another with an average bout length being weeks to a few months.

CLUSTER TIMING: Horton<sup>18,27</sup> faintly suggests that the bouts of headaches are seasonal and Symonds<sup>36</sup> states that they seem to be related to the autumn and spring. Graham<sup>34</sup> feels that closer scrutiny of patients reveals that their bouts are more related to what the patients are doing in the autumn and spring, rather than to the seasons themselves. No other reference was made in the literature reviewed by this author as to a possible seasonal appearance of Cluster Headaches.

FREQUENCY OF HEADACHE ATTACKS: Most authors agree that a patient may have several attacks of headache within a 24 hour period. Robinson<sup>17</sup> reports a range of  $\frac{1}{2}$  to 6 headaches per day with an average of 2 to 4 (20 patients studied); Leider<sup>35</sup> reports 1-3 per day; Symonds<sup>36</sup> reports 1-8 per day (in 17 patients); Kunkle<sup>2</sup> reports that 70% of 30 patients had 1-5 per day; and Friedman<sup>13</sup> reports "more than one a day" in his patients.

HEADACHE DURATION: All authors mention the brevity of the headache attack itself with its sudden onset and just as sudden cessation. Horton,<sup>18</sup> reporting on 1,176 patients he had seen between 1937 and 1955, states that the attacks generally lasted

less than one hour; in another article, Horton<sup>16</sup> mentions 1-4 hours. Kunkle<sup>2</sup> found that 90 per cent of his patients (18 of 20) had attacks lasting less than 2 hours, often less than 30 minutes. Robinson,<sup>17</sup> in his 20 cases, found a range from 5 minutes to 8 hours with an average of 1-4 hours. Symonds<sup>36</sup> reports a range of 10 minutes to 3 hours for 17 patients studied. Graham,<sup>34</sup> reports on some unpublished data that the shortest headache was 3 to 10 minutes and the longest was two days (50 patients studied).

ATTACK TIMING: Many authors were impressed by the occurrence of headache attacks at night. Horton<sup>5</sup> was the first to mention that the attacks were usually nocturnal and that they tended to recur at the same time each day in any given individual. Friedman<sup>32</sup> mentions their clock-like regularity and tendency to awaken the patient from sleep. Symonds<sup>36</sup> found the attacks to be nocturnal in 12 of 17 patients and also noted that the bout usually began nocturnally and then spread to involve the daytime. Robinson<sup>17</sup> reports that 85% of his patients (17 of 20) had attacks mainly at night, but one (5%) had diurnal attacks only and two patients (10%) had attacks during both the day and night. Kunkle<sup>2</sup> reports that two-thirds (20 of 30) of his cases of Cluster Headaches always or commonly occurred at night.

AGE In general, the highest incidence of Cluster Headaches seems to occur in the later decades of life, or at least somewhat later in life than does typical migraine which very often begins in early adolescence.<sup>21,37</sup> However, the issue is not settled. Graham,<sup>34</sup> in a study of 73 patients, found there were headaches in patients at an early age of 10 years and to begin in others as late as 59 years of age. Friedman. in 1958 states the average

age of onset was 28 years, but in 1959<sup>32</sup> states Cluster Headaches are more common in middle and old age. Bickerstaff<sup>19</sup> found the highest incidence in the late third decade though 23 of the 30 cases studied had their first attack before the age of 40 years. Harris<sup>9</sup> reporting on 23 cases, found the highest incidence in the 40-50 age group. Robinson,<sup>17</sup> reporting on 20 cases, finds highest incidence in the 20-50 age group. Symonds<sup>36</sup> found average age of onset to be 26.7 years (17 patients) with a range of onset between ages 14-43 years. Kunkle<sup>2</sup>, reporting on 30 patients, finds the onset in 27 patients to have been between ages 17 and 40 years with one-half of the patients having onset between ages 21 and 25.

SEX: There is unanimous agreement that Cluster Headaches is an affliction predominantly of the male. Horton,<sup>18,27</sup> reporting on 1,176 cases found 87% were males. Others quoting a male predominance are: Bickerstaff,<sup>19</sup> 70% (21 of 30); Robinson,<sup>17</sup> 90% (18 of 20); Tucker & O'Neill,<sup>38</sup> 94% (15 of 16); Hansel,<sup>39</sup> 72% (23 of 32 patients); Symonds,<sup>36</sup> 82% (14 of 17); Kunkle,<sup>2</sup> 80% (24 of 30 patients); Eckbom,<sup>23</sup> 87% (20 of 23 patients); Friedman,<sup>15</sup> "...4-5 times more common in the male." The grand total of the above figures shows a male predominance of 86% (1,158 of 1,344 patients).

RACE: The only reported study of this is by Robinson<sup>17</sup> who reports that 19 of 20 patients were Caucasian, the other being a negro.

INCIDENCE: This issue is unsettled. Horton<sup>18,27</sup> collected the impressive number of 1,176 patients between the years 1937 and 1955. Hansel,<sup>25</sup> an otolaryngologist, reports 38% of 701 headaches he had seen were Cluster Headaches. Dalsgaard-Nielsen,<sup>30</sup> on the other hand, reports only 4% of his patients with a chief complaint

of headache had Cluster Headaches. Ogden<sup>39</sup> reports an incidence of 0.1% in survey of 4,634 patients with or without headaches and Friedman<sup>13</sup> states that Cluster Headaches are not as common as the literature would lead one to believe.

FAMILY HISTORY: Whether or not there is a significant incidence of headaches in other members of the family of a patient with Cluster Headaches is an unsettled issue. There seems to be general agreement, however, that there is a greater incidence of headaches in family members of patients with migraine (greater than 65%) than in family members of patients with Cluster Headaches.<sup>13</sup> Robinson,<sup>17</sup> Horton,<sup>16</sup> and Leider<sup>35</sup> state a family history of headaches is uncommon in Cluster patients. Friedman<sup>13</sup> states 25% have a family history of headaches in one section of his article and states less than 20% in another section. Bickerstaff<sup>19</sup> reports "many" had family history of migraine and reports of one case of "periodic migrainous neuralgia" in siblings-- the only reported example of Cluster Headaches in siblings except for Graham<sup>34</sup> who has a family in treatment with a distribution of headaches as follows: Father with Cluster Headache, Mother with common migraine, daughter with Cluster Headaches and elements of common migraine, and a son with common migraine and elements of Cluster Headaches. Swansberg<sup>41</sup> finds 52% of 21 patients with family history of migraine which coincides with same figures reported by Dalsgaard-Nielsen.<sup>30</sup> Symonds<sup>36</sup> found a family history of migraine in one third of his 17 patients and Kunkle<sup>2</sup> reports one third of his 30 patients had a family history of migraine with one patient having a close relative with Cluster Headaches.

SOCIAL STATUS: Though most authors mention that Cluster Headaches occur in general in white collar workers and people in positions

requiring a good deal of responsibility,<sup>13</sup> Robinson<sup>17</sup> is the only author found by this writer to report on the social status of a group of such patients. He reports (20 patients) that 30% were in the upper class, 65% were in the middle class, and 5% were in the lower class.

PERSONALITY: Though extensive studies have not been performed on the role of psychogenic factors in the syndrome of Cluster Headaches, there is agreement among many that patients with Cluster Headaches are prone to be ambitious, efficient, overconscientious, perfectionistic and meticulous persons with a constant striving for approval.<sup>13,42,43</sup> They also have a tendency towards compulsive behavior and sustained emotional states, and though they are in positions of responsibility they lack confidence.<sup>13</sup> Often there are conflicts of a hostile-aggressive nature with the chief character structure being masochistic.<sup>13,42</sup> Some had difficulties with sexual adjustment.<sup>42</sup> Graham<sup>22,34</sup> feels this type of headache is seen in active, intense men after prolonged periods of strain and in men who take few vacations, and maintains rest is necessary to get them out of a cluster. Friedman,<sup>13</sup> however, found few patients could associate onset of clusters with emotional stress; "...they occur when the patient is at work, on vacation, land, ocean, desert, warm or cold weather, dry or wet climates," and suggests "...patients with migraine type of vascular headache react by a delayed response.."

Steinhiber et al<sup>43</sup> administered the Minnesota Multiphasic Personality Inventory (MMPI) to 50 patients with Cluster Headaches and to 50 patients with other types of headache. These authors found 60% of both groups had abnormal profiles in that both groups showed a pattern consistent with conversion hysteria, ie,

peaks on the hypochondriasis scale, hysteria scale and depression scale. Cluster Headache patients, interestingly enough, differed from patients with other headaches in that they showed a greater elevation of the hypochondriasis score in relation to the hysteria score.

Kunkle,<sup>2</sup> in a "brief personality study," found evidence of chronic tension in 53% of 30 patients and states that 23% had onset of Cluster Headache after periods of tension. Robinson<sup>17</sup> reports 10% of 20 patients had clusters related to stress and Wolff<sup>44</sup> states psychotherapy helped some patients when aimed at reducing tension, desperation or exhaustion in the patient's life situation.

This author interviewed one patient with Cluster Headaches and found his clusters to occur after periods of prolonged tension. For example, this patient was a liquor wholesaler and his latest bout began on New Year's Eve of 1960-61, the moment the season for big liquor business had ended. In addition, this patient's original cluster began in Germany during World War II just after it was announced to him that Germany had surrendered. During his latest bout, the patient states that he had an attack of headache immediately after reaching climax while having intercourse with his wife.

#### PRECIPITATING FACTORS:

HISTAMINE: Since Horton's original description of Cluster Headaches in 1939, there have been arguments pro and con as to the specificity of histamine to precipitate attacks of typical Cluster Headaches in patients with this affliction. It should be mentioned that when anyone speaks of precipitating an attack of Cluster Headache with histamine, he must be sure he is not referring to the

generalized headache that results in normals 30-60 seconds after injection.<sup>45</sup> When one precipitates Cluster Headache in a patient with Cluster Headaches by the injection of histamine there is a delay between injection and the headache of 30 to 60 minutes.<sup>18</sup>

With this caution in mind, Horton<sup>18</sup> reports that 0.35 mg histamine subcutaneously precipitated typical cluster headaches in 60% of 1176 patients with the affliction. Such precipitation with histamine was "apt" not to occur during the remissions or headache-free intervals between clusters. Robinson<sup>17</sup> found histamine precipitated an attack in 10 of 11 patients and felt that "a positive histaminic provocative test is pathognomonic for this disorder." A negative test, however, is less significant as it does not rule out a diagnosis of Cluster Headache.

VonStorch<sup>46</sup> reports equivocal results with the "histamine test." He produced headache in 92% of 36 patients with "migraine headaches" but in no case was it unilateral.

Northfield<sup>48</sup> likewise reports equivocal results. He produced headaches in 11 of 14 patients with headaches secondary to tumors. In each case the headache produced was similar in quality and distribution to that produced by the tumor. However, the headache produced by histamine injection apparently occurred a few seconds after injection.

Friedman and Brenner,<sup>47</sup> however, produced headache in 13 of 32 patients with post-traumatic headaches by histamine injections. In each of the 13 cases, the headache produced was identical to that complained of by the patient. Because of these results, the authors argue that histamine is not specific for production of Cluster Headaches and that its tendency to produce headaches in Cluster patients is due to its rather non-specific vasodilating

action.

ALCOHOL: Many authors are in agreement that alcohol can precipitate typical attacks of headache in the Cluster patient if the patient is in a cluster; headache is not precipitated during the remissions or headache-free intervals between clusters. <sup>3,22,23,25,32,35,44</sup> Horton<sup>3</sup> reports alcohol precipitated attacks in 40% of patients; Friedman<sup>13</sup> reports alcohol has this ability in 50%. Robinson,<sup>17</sup> however, found alcohol to precipitate an attack in only one of 20 patients.

OTHER VASODILATORS: Bickerstaff<sup>19</sup> and Graham<sup>22</sup> report amyl nitrite reproduced typical attacks of headaches in Cluster patients. Dalsgaard-Nielson<sup>30</sup> found nitroglycerin as good as histamine in producing attacks but Horton<sup>3,21</sup> finds histamine better than nitroglycerin.

FACTORS WHICH RELIEVE CLUSTER HEADACHE (other than drugs): Brickner<sup>8</sup> and Horton<sup>3</sup> report that dipping the hands of the patient in cold water often aborted or relieved the intensity of the headache. Hansel,<sup>25</sup> Horton,<sup>3</sup> Wolff<sup>44</sup> and Kunkle<sup>2</sup> report that pressure on the common carotid artery ipsilateral to the headache occasionally gave relief or reduced the intensity of the headache. In a few cases, compression of the ipsilateral temporal vessels gave some relief.<sup>25</sup> Most patients prefer to be propped up or remain upright during an attack.<sup>24</sup> Bending over and putting the head in a dependent position exacerbated the headache.<sup>3</sup>

PEPTIC ULCERS: The relationship of peptic ulcers to Cluster Headaches is an interesting, albeit unsettled issue. Horton<sup>49</sup> reported on 10 cases of duodenal ulcers with demonstrable craters in the same number of patients with Cluster Headaches. Horton felt that these ulcers were evidence of a hypersensitivity to histamine and

that a higher incidence of ulcers could be expected in these patients since he found that high gastric acid levels could be obtained with histamine injection of small amounts as compared to the amount of histamine required to stimulate comparable levels of gastric acidity in normal subjects. On treatment with histamine "desensitization" Horton<sup>49</sup> claims to have cured the headaches and ulcers of these 10 patients within 2 weeks.

Many authors, however, feel that any increase in gastric acid levels in patients with Cluster Headaches is due, not to a hypersensitivity to histamine, but rather to a non specific stress response.<sup>17</sup> Robinson<sup>17</sup> states "... acute duodenal ulcers are uncommon complications. As most patients with histamine cephalgia are adult males, the existence of duodenal ulcer may be either coincidental or a non-specific response to pain and stress."

Graham,<sup>22</sup> on the other hand, cautions against the use of steroids on patients with Cluster Headaches: "These patients have a propensity for duodenal ulcers, so don't use steroids without previous GI x-rays, atropine derivatives, antacids and ulcer diet." In some unpublished data, Graham<sup>34</sup> has found that 25 of 76 patients state they have trouble with indigestion, 27 of 74 have sought doctor's advice because of indigestive problems and 38 of 75 patients have had x-rays of their stomach at some time in their lives.

Alford et al<sup>50</sup> report a case of duodenal ulcer developing in patient three years after onset of Cluster Headaches. The patient demonstrated high gastric acidity during attacks but normal levels during headache-free periods.

HORNER'S SYNDROME: Horner's syndrome ipsilateral to the affected

side is not uncommon,<sup>18,21</sup> and may disappear or remain permanent after the headache attack. Bickerstaff<sup>19</sup> reports on three (of 30 patients) who developed Horner's during attacks of head pain and on one patient in whom the Horner's became permanent. Robinson<sup>17</sup> reports one permanent Horner's syndrome in 20 patients studied. Kunkle<sup>31</sup> found that 14 of 90 patients had mild to moderate miosis and mild ptosis on side ipsilateral to the headache and discusses the possibility of a sympathetic paresis, as opposed to parasympathetic stimulation, as the cause. The significance of Horner's syndrome in Cluster patients is unknown and any theory explaining Cluster Headaches will have to explain the occasional occurrence of this phenomenon.<sup>34</sup>

ALLERGY: The interest in the allergic history of the Cluster Headache patient and the allergic history in his family probably stems from Horton's original theory of a hypersensitivity of these patients to histamine. That allergy plays a role is disputed by most. However, Dalsgaard-Nielson<sup>30</sup> reports allergy (unspecified) in 50% of his Cluster patients, and Swanberg<sup>41</sup> reports a comparable 43% with a family history of allergy. Three of Symonds's<sup>36</sup> seven patients had hay fever. Unger<sup>40</sup> reports on the only 3 patients with Cluster Headaches he claims to have seen in 18 years of practice. Two of these patients were allergic (one to pork, the other to milk) and the third had focal tooth infection. Removal of the offending foods and tooth extraction, respectively, cured these patients of their headaches. Long term follow up of these patients, however, is fundamental to reaching any conclusions as to the allergic nature of the headaches in Unger's three patients. Hansel<sup>25</sup> cautions, however, that there is an allergic headache and that it must not be confused with headaches of the vascular type (see DIFFERENTIAL DIAGNOSIS). Hansel<sup>25</sup> reports that allergy is

uncommon in migraine in his experience. Similarly, Diaz<sup>51</sup> "has studied migraine for 25 years and has found no evidence to support allergy as an important precipitating factor."

Some unpublished data by Graham<sup>34</sup> reveals that only 3 of 71 Cluster patients had asthma, 17 of 74 had hives at one time or another, 3 of 72 had hay fever and 1 of 62 Cluster patients ever had eczema, rather convincing evidence that allergy plays little, if any, role in Cluster Headaches.

PHYSICAL EXAM: Physical exam of Cluster patients when they are not having an attack of head pain is unremarkable and there is nothing in the literature pertaining to this feature of the Cluster patient. Graham,<sup>34</sup> however, is of the impression that many of his patients present with thick, furrowed skin of the leonine type and that they are often red faced and of high color.

LABORATORY FINDINGS: Lab findings are unremarkable to date except for the recent findings of increased neurokinin in the CSF of Cluster patients (see ETIOLOGY).

However, Friedman<sup>13</sup> reports that the 17-ketosteroids in the urine are increased during the headache attack (as opposed to the migraine patient in which these levels are decreased). He has also found an increased excretion of lysine during the headache.

Graham<sup>34</sup> finds that 21 of 52 patients had hematocrits greater than 46. He also found abnormal EEG patterns in two patients who had an attack of headache of the cluster type while EEG's were being taken. He feels these findings may be important since there is a question of "hypothalamic seizures" of some kind in these patients.<sup>34</sup>

MISCELLANEOUS:

Graham,<sup>34</sup> in some unpublished data, finds 64 of 74 patients smoked one package or more cigarettes per day.

## DIFFERENTIAL DIAGNOSIS

The diagnosis of Cluster Headache is dependent primarily on its clinical picture as previously described. Though recent authors are beginning to view Cluster Headache as a variant of migraine or vascular headaches (see ETIOLOGY), Cluster Headaches can be differentiated on clinical basis from typical or common migraine. In a way, Cluster Headaches seem to be a telescoped migraine.<sup>34</sup>

### CLUSTER VS MIGRAINE HEADACHES:

Family History: Migraine patients have a family history of headaches in 65 to 90% of the cases<sup>15,16</sup> as opposed to the Cluster patient with 20% or less.<sup>13</sup>

Age of onset: Migraine usually begins in childhood and adolescence.<sup>16,37</sup> Cluster Headaches seem to occur more often in middle or late adult life (see CLINICAL PICTURE).

Bouts: These are a feature peculiar to Cluster Headaches only. They last weeks to months with spontaneous remissions in between bouts (see CLINICAL PICTURE).

Frequency of attacks: The migraine patient usually has one or less headaches per week<sup>13</sup> as opposed to the Cluster patient who has several in one day. The migraine patient usually has his attacks in the day as opposed to the nocturnal preference of the Cluster Headache.

Eye and nose signs: These are peculiar to Cluster Headaches only (see CLINICAL PICTURE). They are rare to absent in migraine.<sup>17</sup>

Aura: This is peculiar to the migraine patient only and consists of euphoria or excitement in a few cases but more commonly consists of irritability, depression and mental confusion.<sup>37</sup>

Prodromata: These are also peculiar to migraine and rare to absent in Cluster Headache. They are felt to be due to initial vasoconstriction of the internal carotid and/or its branches and consist of scintillating scotomata, hemianopsia, transient hemiparesis and tingling of the tongue and fingers.<sup>13,17,37,44</sup> All these occur contralateral to the headache in the migraine patient.

Gastro-intestinal disturbances: Nausea, vomiting and occasional diarrhea are common in the migraine patient at the peak of head pain.<sup>37</sup> Such signs are rare or absent in Cluster patients.<sup>2,3,16,17,18</sup>

Sex: Migraine is much more common in the female<sup>17</sup> as opposed to the Cluster patient who is typically male (see CLINICAL PICTURE).

Menses: The patient with migraine often gains relief from attacks during pregnancy.<sup>37</sup> The Cluster patient shows no such relation to the menses.<sup>3,16,25,35</sup>

Headache duration: The migraine attack may last anywhere from hours to weeks with an average duration of 10-12 hours.<sup>17</sup> The Cluster headache is of shorter duration, often less than an hour (see CLINICAL PICTURE).

Other helpful differentiating features are the tendency for migraine patients to prefer the lying position during head pain,<sup>37</sup> whereas the Cluster patient may pace the floor.<sup>13</sup> Photophobia is common in migraine at the height of the head pain<sup>37</sup> but rare in Cluster Headache.<sup>17</sup>

It must not be forgotten that as distinctive as the clinical picture of Cluster Headaches may be, features of migraine may be present in the Cluster attack and visa versa.<sup>44</sup>

#### TYPICAL NEURALGIA (IE, TIC DOULOUREUX)

The pain of tic douloureux is limited to the distribution of

the fifth cranial nerve or one of its branches. The typical sharp, shooting and paroxysmal pain can be precipitated by pressure on "trigger zones." The pain is short and fleeting (therefore the expression "tic") and lasts seconds to minutes. There are no eye or nose signs so typical of Cluster Headaches. Vasoconstrictors, vasodilators and narcotics give inadequate relief whereas chemical or surgical disruption of the cranial nerve involved is the treatment of choice. Neurotic traits in these patients are uncommon.<sup>13,17,37</sup>

#### ATYPICAL NEURALGIA:

This headache is more common in females, especially in females with neurotic traits. The pain is bizarre and doesn't conform to nerve or blood vessel distribution. The pain is described as diffuse, deep-seated, pulling and gripping and is poorly localized. The pain may last for hours or days and there are no trigger zones. Vasoconstrictors and narcotics give relief frequently. Eye and nose signs are absent but this headache may be difficult to differentiate from Cluster Headaches.<sup>13,17</sup>

#### HYSTERIA

Like atypical neuralgia, the hysterical headache may be difficult to differentiate from Cluster Headaches. However, the hysterical headache is usually seen in females. The headache is vague and bizarre and there are a great variety of other coexistent somatic complaints. Sometimes there are frank conversion symptoms such as aphonia, fainting and paralysis.<sup>13,17</sup>

#### ALLERGIC HEADACHES

In this patient one finds a past history and a family history of allergy. There are usually other manifestations of allergy such as urticaria, angio-edema, eczema, B.I. allergy, hay fever and in-

halant allergy of the respiratory type. Prodromal symptoms are common in the first 12-24 hours and usually consist of G.I. upsets, vomiting, distention, polydipsia, edema of the hands and feet, face swelling, marked gain in weight and urticaria. Visual prodromata are rare. The headache is generalized with a sense of pressure, dizziness and mental confusion (cerebral edema). Vasoconstrictors give no relief and the headache itself lasts 12-24 hours although the complete cycle from onset to termination is 48 hours. The terminal phase of the attack is characterized by polyuria and a parallel return of the weight to normal. Attacks of allergic headache are prevented by anti-histamines given prior to exposure to the allergen which is in contrast to the Cluster patient in whom anti-histamines are of no value (see TREATMENT). The entire syndrome of the allergic headache can be reproduced repeatedly with ingestion of causative food.<sup>25</sup>

#### OTHER HEADACHES AND FACE PAIN

Other headaches and face pain can be excluded by careful examination of the head and neck and by their clinical course, ie, mastoiditis; facial abscess; tumors of the nasopharynx, cranial nerves or cerebellopontine angle; dental sepsis; deviation and spurs of the nasal septum or disease of the paranasal structures; ocular lesions; post-herpetic neuralgia; temporal arteritis; aneurysm and anomalies of blood vessels; abnormalities of the temporomandibular joint; and post-traumatic headache.<sup>13,17</sup>

Cephalgias secondary to upper cervical nerve injury can be reproduced by hyperextension of the neck or rotation of the occiput to the painful side. Also, a history of trauma will be present and procainization of the second cervical root will give relief.<sup>13</sup>

Tension headaches can be diagnosed without difficulty.<sup>13</sup>

ASSOCIATED ANATOMY AND PATHOPHYSIOLOGY

An understanding of the anatomy and pathophysiology of head pain is pre-requisite to any understanding of the etiology of headaches.

Pain sensitive structures of the head are:<sup>17,29,44</sup>

1. Tissues covering the cranium such as skin and vasculature.
2. Cranial periostium and endosteum.
3. Intracranial structures such as: great venous sinuses and tributaries, parts of dura at the base of the brain, arteries of the dura and cerebrum, cranial nerves 5, 9, and 10, and the first three cervical nerves.

Pain insensitive structures within the cranium are: all the pia and arachnoid, choroid plexus, ependyma, most of the dura and the brain itself.

Basic mechanisms by which pain may arise in these pain sensitive structures are:<sup>29</sup>

1. Traction and displacement of the longitudinal sinuses and contributing veins.
2. Traction on the middle meningeal arteries, the Circle of Willis and its branches.
3. Distention and dilatation of intracranial and extracranial arteries and their branches.
4. Direct pressure on cranial nerves 5, 9, and 10 and the first three cervical nerves.
5. Inflammation in or about any of the above structures.

Stimulation of painful structures above the tentorium refers pain anterior to a plane joining the ears and is transmitted by the fifth cranial nerve. Stimulation below the tentorium refers pain

posterior to a plane joining the ears and is transmitted by cranial nerves 9 and 10 and cervical nerves 1, 2 and 3.<sup>17</sup>

The blood supply to the extracranial structures is from the external carotid artery. That to intracranial structures is from the internal carotid and vertebral arteries.<sup>17</sup>

The sympathetic supply to the head comes from the neck (cervical ganglia) and is distributed along the arterial pathways. Sympathetic stimulation causes vasoconstriction (ipsilateral), dilatation of the pupils, and contraction of the levator palpebral muscle.<sup>17</sup>

Much interest has been focused on the parasympathetic supply to the head and related structures and the relation of the parasympathetic system to etiology of Cluster Headaches. This supply arises within the cranium and is distributed via the III, VII, IX, and X cranial nerves.<sup>17</sup>

The fibers of the seventh nerve are of particular interest since parasympathetic fibers travel via this nerve in the greater superficial petrosal nerve and the chorda tympani and supply the lacrimal gland and its secreto-motor apparatus, the nasal mucosa, and along with the vagus, send vasodilator fibers to the ipsilateral cerebral hemispheres.<sup>17,44,52,53</sup> There is evidence that the greater superficial petrosal nerve also carries pain fibers.<sup>55</sup> Sweet and White<sup>55</sup> stimulated the distal and proximal ends of the sectioned greater superficial petrosal nerve with resultant pain in the ipsilateral ear, eye and adjoining parts of the head and face in 4 of 5 patients with Cluster Headaches and in 5 of 9 subjects without headaches. This work of Sweet and White gives some support to Gardner's earlier hypothesis<sup>20</sup> that discharges over the greater superficial petrosal nerve may be the cause of Cluster

Headaches. Gardner<sup>20</sup> sectioned this nerve in 13 patients with Cluster Headaches with resultant relief for approximately 50% of the patients. However, there were recurrences of attacks in these patients and Gardner has given up this method of treatment for Cluster patients.<sup>34</sup>

The III cranial nerve carries fibers to the ciliary muscle and sphincter pupillae of the eyeball and parasympathetic stimulation along this pathway causes miosis.

In general, then, parasympathetic stimulation can be expected to cause lacrimation, rhinorrhea and dilatation of the cerebral arteries (via greater superficial petrosal nerve and the vagus), salivation (via the chorda tympani), and miosis (via III cranial nerve). All are signs and symptoms common in Cluster Headaches and therefore one can better understand the interest in the parasympathetic supply to the structures of the head.

### TREATMENT

#### HISTAMINE "DESENSITIZATION"

Since Horton's original description of Cluster Headaches in 1939 and 1941 up until his later publications around 1956, histamine therapy was to Horton the *sin qua non* method of prophylactic and long term management of Cluster Headaches.<sup>3,16,56</sup>

In 1939 and 1941, Horton's original articles reported his observation that 0.5 mg of histamine precipitated typical attacks of Cluster Headaches. If this amount was given on subsequent days Horton noticed that "...succeeding attacks seemed progressively less severe and more difficult to precipitate. The possibility of desensitization with histamine was thus suggested."<sup>16</sup> Horton then postulated that a local release of histamine was the provoking factor in Cluster Headaches<sup>3</sup> with a resultant local anaphylactic re-

action.<sup>21</sup>

Other rationale for treatment with "desensitization" was based on facts that: 1. Gastric acidity increased during headaches (due to absorption of histamine into the blood stream from the local area of anaphylaxis);<sup>21</sup> 2. Standard doses of histamine produced a greater rise in gastric acidity in headache patients as opposed to normals;<sup>17</sup> 3. Horton felt that patients responded to histamine "desensitization;"<sup>3</sup> 4. Evidence that a "tolerance" can be established to histamine, ie, 50% of guinea pigs injected with histamine over a period of 2-3 weeks tolerated a large dose of histamine I.V. that otherwise was sufficient to kill 37% of controls;<sup>3</sup> 5. With histamine "desensitization" over a period of time, the wheal produced by intracutaneous injection of histamine decreased in size.<sup>3</sup>

Horton's method of "desensitization" was to use the contents of a 1 cc ampule of 0.275 mg histamine diphosphate per cc which contains 0.1 mg of histamine base. Two injections were given subcutaneously daily about 6-8 hours apart, the first injection being 0.05 cc until a maximum of 0.5 cc to 1.0 cc was reached. Adequate dosage was determined by the patient's response; if flushing of the face or throbbing occurs, the dose was reduced by half and the regimen started again until the dose is reached which wouldn't precipitate symptoms. This "maintanance dose" is given 2-3 times daily, according to Horton, and "...may be continued for a lifetime, if necessary, without harm."<sup>27</sup> With such therapy, Horton quotes that 95% of his patients responded with cessation of attacks within 10-20 days.<sup>27</sup> In the same article, however, Horton states that "...histamine therapy is neither simple or commonplace, and it is fraught with many pitfalls. He found especial

problems when the patient had to be desensitized for the second and third time, for in these cases the patient was often made worse by desensitization.<sup>21</sup> In such cases he found adjunctive use of cortisone and/or ACTH made it possible to re-institute histamine therapy.<sup>21</sup>

A few others report beneficial effects of histamine "desensitization" with descriptions of their own particular regimen.<sup>35,39,56,57</sup>

On the other side of the therapeutic fence, however, are the many authors who have found histamine "desensitization" of no value in the treatment of Cluster Headache.<sup>2,13,20,22,23,24,36</sup> A major argument against the value of such treatment is the feeling of many that spontaneous remissions, a characteristic feature of Cluster Headaches, are the actual cause of "cures" in patients receiving histamine desensitization.<sup>2,17,23,36</sup> Also, there is no report in the literature of a control series or the use of double blind procedures to rule out the possibility that spontaneous remissions are behind "desensitization" cures. Such studies would also help rule <sup>out</sup> the therapeutic value that may be unwittingly afforded these patients because of the necessary daily attention and injections given to them by doctors or themselves.<sup>17,22</sup>

Others question the rationale of Horton for the use of histamine therapy. In the first place, vasodilators other than histamine precipitate Cluster Headaches and histamine can precipitate other types of headaches such as post-traumatic headaches and, possibly, headaches due to tumor (see CLINICAL PICTURE). Histamine, then, is not specific in its ability to precipitate Cluster Headaches. Also, there is no pharmacologic evidence that histamine can sensitize or desensitize in the true sense of the word since these phenomena require an antigen which is a protein or at least a poly-

peptide. Histamine is merely a decarboxylated amino acid.<sup>13,17,45</sup> In addition, the increased gastric acidity during the headache attack may not be due to absorption into the blood of locally released histamine as advocated by Horton, but is more likely the result of a non-specific stress response to a painful headache.<sup>2</sup> Lastly, if histamine release within the body was in any way responsible for Cluster Headaches, one would expect to gain some protection with anti-histamines. Anti-histamines, however, have been found ineffective by most authors (see below) in the treatment of this syndrome.

Conclusion: Horton has been the main and almost sole proponent of histamine "desensitization" in the long term management of Cluster Headaches. Most other authors find such therapy of little value.

#### ERGOTAMINE TARTRATE AND PREPARATIONS:

Ergotamine tartrate and its various preparations are regarded by many, including Horton, as the mainstay in the symptomatic treatment of the acute attack of headache of the Cluster (or migraine) type.<sup>8,13,18,19,21-25,36,46,58-60</sup> Ergotamine tartrate acts as a potent peripheral vasoconstrictor<sup>45</sup> and Pool<sup>61</sup> has published data indicating that it constricts the external but not the internal carotid artery. Ergotamine will stop the attack in 10-15 minutes after administration (?IM) in more than 90% of the cases<sup>17,22,58</sup> and administration can be accomplished today with parental injection, rectal suppository, oral ingestion, sublingual absorption and aerosol inhalation.<sup>60</sup> Some of the more popular preparations are Wigraine (tablets & suppositories), Cafergot P-B (tablets & suppositories), Gynergen (parental), Bellergal (tablets & space-tabs), D.H.E. 45 or Dihydroergotamine (IM or IV) and EC-110 (tab-

lets).

In addition to their use in the acute attack, ergotamine tartrate and its preparations have some prophylactic application and when given at bedtime often prevent night attacks.<sup>32,36</sup> The best procedure for treatment of the Cluster patient is to give daily morning and evening doses of ergotamine six days out of each week, stopping the dosage on the seventh day to see if the patient's bout has ceased. Stopping the dosage one day out of every seven also helps against side-effects of ergotamine.<sup>36</sup>

Contraindications to the use of ergotamine are coronary artery disease, sepsis, patients with vascular disease such as syphilitic arteritis, marked arteriosclerosis, thrombophlebitis, Raynaud's or Buerger's syndrome, diseases of the liver or kidney, and pregnancy (causes abortion).<sup>22,45</sup> VonStorch<sup>62</sup> has reviewed 42 cases of gangrene secondary to the use of ergotamine tartrate and its preparations.

#### OTHER VASOCONSTRICTORS

Octin: Peters et al<sup>59</sup> report that Octin (methyl-iso-octenylamine), a vasoconstrictor which may act directly on blood vessels or as a sympathomimetic, was successful in giving complete relief in 15 of 16 trials in patients with Cluster Headaches, and suggests its usefulness in patients who have abused ergotamine or in those in whom ergotamine is contraindicated. MacNeal<sup>65</sup> found Octin the drug of choice for Cluster patients.

Epinephrine: Epinephrine IV or SC is reported by many authors to be effective against the acute attack of head pain in the Cluster patient, especially when given early in the attack.<sup>7,13,15-18,25,35,42</sup>

Oxygen: Friedman<sup>13,42</sup> and Horton<sup>18</sup> found 100% oxygen had the ability to abort attacks of headache in some Cluster patients and

in others was a useful adjunct to the above vasoconstrictors.

### ANTI-HISTAMINES

Tucker and O'Neill<sup>38</sup> are the only authors in the literature that report benedryl, a potent anti-histaminic, to be effective in the treatment of the Cluster patient. These authors obtained excellent results in 70% of 16 patients with benedryl 50 mg b.i.d. over a two month period. All other authors report poor to ineffective results with anti-histamines.<sup>13,16,17,19,22,32,64</sup> Lee<sup>56</sup> used as much as 400 mg daily for 2 weeks in one patient with no results.

### SURGERY

Surgery has given uniformly poor results in the Cluster patient. Gardner et al<sup>20</sup> reported that pre-ganglionic resection of the greater superficial petrosal nerve in 13 cases of "petrosal neuralgia" gave 25% poor, 50% fair and 25% excellent results. There were recurrences of headaches, however, and Gardner has ceased this method of treating Cluster Headaches.<sup>34</sup> Similarly, White and Sweet<sup>55</sup> were unsuccessful with their neurectomies of the external greater and lesser superficial petrosal nerves.

Dandy,<sup>12</sup> in 1931, obtained relief for two cases of Cluster Headaches, as mentioned previously, with resection of the cervical ganglia. The number of cases is too small and the follow up too short for evaluation of this method.

Horton<sup>18</sup> reports that 90% of his patients had undergone one surgical procedure or another without benefit. Likewise, Friedman<sup>13</sup> reports that the following surgical operations had been done previously on his patients without benefit: cocainization of the spinal ganglia, supra-orbital block, ligation of veins under the chin, ligation of the temporal artery, removal of the sphenopalatine gang-

lion and avulsion of the occipital nerve.

### PSYCHOTHERAPY

This is the single most important method of long term management of the patient with Cluster Headaches.<sup>34,42</sup> The general plan of such treatment should attempt to give the patient insight into his behavior and attitudes that produce stress and he must learn to adopt those attitudes that reduce anxiety and tension in his life situations.<sup>42</sup>

### MISCELLANEOUS

It has already been mentioned that pressure over the ipsilateral common carotid and temporal artery, dipping of the hands in cold water and the upright position reduced the severity of head pain in the Cluster patient (see CLINICAL PICTURE).

Winchell,<sup>24</sup> an MD with Cluster Headaches, reports in 1952 that coffee and cigarettes, Tuamine (nasal decongestant) sometimes afforded relief and that cocainization of the mucous membranes of the nose sometimes aborted attacks.

Sluder,<sup>5</sup> in 1913, obtained beneficial results with application of cocaine to the sphenopalatine foramen.

Harris,<sup>9</sup> in 1936, obtained beneficial results with alcohol injections into the supra- and infra-orbital nerves. He reports obtaining more long lasting results with injection of the Gasserian ganglion.

Horton<sup>21</sup> summarized his experience with ACTH and cortisone in 1956 stating that they were ineffective when used alone.

Frohner,<sup>65</sup> on the other hand, in 1953, obtained relief for two patients with Cluster Headaches with cortisone therapy and Graham<sup>22,34</sup> feels these drugs help bring clusters to a close in refractory cases.

Discontinuation of alcohol during bouts, meprobamate at meals and at bedtime and lightening of the work schedule are beneficial.<sup>22</sup>

Aspirin, empirin, antipyretics & sedatives are of no value,<sup>13,25</sup> whereas demerol and codeine must do when ergotamine and other vasoconstrictors fails.<sup>13,22</sup>

UML 491 (1-methyl lysergic acid butanolamide)

Within the past couple of years, articles have appeared in the literature regarding a new drug, UML 491, and its usefulness in the prophylactic treatment of vascular headaches of the cluster and migraine type.

Doepfner,<sup>67</sup> in 1958, demonstrated UML 491 to be a most potent anti-serotonin agent. Sicuteri,<sup>66</sup> in 1959, knowing that ergotamine tartrate has anti-serotonin activity, wondered if perhaps it was this action of ergotamine which made it effective against headaches of the vascular type. With the idea that serotonin may play a role in vascular headaches, Sicuteri<sup>66</sup> treated 2 cases of Cluster Headaches and 18 cases of migraine with UML 491 with beneficial effects in all. Graham<sup>68</sup> confirmed Sicuteri's findings of the beneficial effects of UML 491 in a controlled and double blind study of 16 Cluster patients and 15 migraine patients.

Apparently, UML 491 has no vasoconstrictor or oxytoxic effects in animals, but Graham<sup>68</sup> and Dalessio<sup>69</sup> report the occurrence of anginal pain and intermittent claudication in patients receiving high doses of UML 491 and caution the use of this drug in patients with arterial disease.

Graham,<sup>68</sup> Friedman,<sup>70</sup> and Sicuteri<sup>66</sup> agree that UML 491 is of little value against the acute attack of head pain.

Dalessio<sup>69</sup> found UML 491 to possess an anti-inflammatory action and Friedman<sup>71</sup> suggests that this drug may act locally in the tissues about blood vessels preventing edema and/or breakdown of polypeptide substances (neurokinin) that Wolff et al have recently demonstrated in patients with headaches of vascular type (see

ETIOLOGY).

ETIOLOGY

Vallery-Radot<sup>7</sup> advanced the first theory in 1925 when he suggested that a decreased sympathetic tone to the branches of the external carotid artery was at the basis of the signs and symptoms of Cluster Headaches. This theory does explain the occasional Horner's but it does not explain rhinorrhea, lacrimation, erythema, etc, seen so often in the Cluster patient.<sup>17</sup> Also, blood vessels have intrinsic tone and do not dilate with the lack of sympathetic stimulation.<sup>17</sup>

Be that as it may, theories of sympathetic paresis have persisted here and there in the literature to the present time. Kunkle,<sup>31</sup> in 1960, for example, suggests that sympathetic paralysis is responsible for the Horner's syndrome in 8 of 14 patients with Horner's (all 14 had Cluster Headaches). He felt that persistent dilatation of the carotid in the vicinity of the siphon might be the source of sympathetic paralysis. In one patient, Kunkle demonstrated that neo-synephrine abolished the Horner's which indicates that a sympathetic paralysis rather than a parasympathetic discharge underlies the Horner's phenomenon.

Roberg,<sup>72</sup> in 1944, reports a case of Cluster Headache in a female patient who had an aneurysm of her internal carotid artery. He too postulated a sympathetic paralysis may play a role in the syndrome of Cluster Headaches, but also felt that a partial parasympathetic stimulation was necessary to explain such signs and symptoms as local vasodilatation, increased skin temperature, hyperemia of the conjunctiva, lacrimation and rhinorrhea. "It is difficult to explain localized, dynamic, vascular changes otherwise than by a disturbance of innervation."<sup>72</sup> Such local

disturbance may occur, according to Roberg, in the peri-arterial plexi as in the above case of aneurysm of the internal carotid artery or "...the origin of such disturbance may well be in the hypothalamus, that mysterious region in which the terms 'organic' and 'functional' become pale, confused and void of meaning."<sup>72</sup>

<sup>20</sup>  
Gardner et al, as mentioned previously, felt that parasympathetic discharge over the greater superficial petrosal nerve might be the responsible mechanism, but their results with sectioning of this nerve were equivocal (see TREATMENT).

### HISTAMINE THEORY

Horton's rationale for treating Cluster patients with histamine "desensitization" has already been discussed as has evidence contrary to any theory of hypersensitivity to histamine (see TREATMENT). To reiterate, the non-supportive evidence is: 1. Histamine is not specific in provoking attacks; 2. Histamine "desensitization" has not worked for many authors and in those cases in which it has resulted in "cures" there is the possibility that spontaneous remissions are the actual source of such cures; 3. The theory does not explain the occasional Horner's; 4. Anti-histamines should, but do not, provide protection; 5. There is no pharmacologic evidence that histamine can sensitize or desensitize; 6. Increased gastric acidity during an attack of head pain is more likely due to a non-specific stress reaction rather than to absorption of histamine into the blood stream from the local site of "anaphylactic" reaction around the branches of the external carotid artery.

### VASCULAR THEORY WITH NOXIOUS AGENT (NEUROKININ)

Most authors are in agreement that dilatation of the external carotid artery and its branches is a basic element in the production of vascular headaches of the Cluster and migraine type.<sup>13,17,22,25,32</sup>

Supportive evidence for a theory of vasodilatation consists of (see CLINICAL PICTURE and TREATMENT): 1. The fact that vasoconstrictors give relief, ie, ergotamine & epinephrine, cold water application to hands and face, Oxygen, etc; 2. Effectiveness of pressure over the carotid artery in giving relief; 3. Preference of the patient for the upright position during an attack; 4. Occasional temporal artery engorgement and residual tenderness; and 5. Diaphoresis and increased skin temperature ipsilateral to the head pain. In addition, Kunkle<sup>2</sup> found that intrathecal injection of saline does not abolish the head pain in Cluster Headaches which one would expect it to do if there were engorgement of the intra-cranial arteries and veins.

Though the clinical pictures differ strikingly, Wolff<sup>44</sup> feels there is strong resemblance between Cluster Headaches and migraine, ie: 1. The distribution and character of the pain in "histaminic cephalalgia" is identical to that seen in some patients with migraine attacks; 2. A higher incidence of family history for headaches is not always demonstrable in migraine; 3. Migraine does not always begin in the earlier years; it can occur at any age; 4. No sharp differentiation can be made on the basis of presence or absence of nausea, vomiting, scotomata, etc; 5. Both patients often have nausea; 6. Lacrimation, redness of the conjunctiva, suffusion of the skin, rhinorrhea, nasal stuffiness characteristic of Cluster patients have also been found in migraine patients; 7. Cluster Headaches are said to be of short duration, minutes to less than an hour, but migraine is very variable, lasting minutes to days; 8. Migraine has been known to wake patient up at night; 9. Both types of headaches respond to vasoconstrictors such as ergotamine and epinephrine; 10. Both are reduced with common carotid artery

pressure; 12. And, both headaches have occurred and recurred in situations of tension, desperation or exhaustion and both headaches respond to psychotherapy.

Wolff concludes that Cluster Headaches is "...closely related to true migraine, and like migraine may be considered one of the many varieties of painful vascular disorders of the head."<sup>44</sup> Symonds,<sup>36</sup> Kunkle,<sup>2</sup> Friedman,<sup>13</sup> and Graham<sup>34</sup> are of the same persuasion.

Since this paper is a review of some of the literature pertaining to the syndrome of Cluster Headaches and since leaders in the field are beginning to view the syndrome as a type of vascular headache, brief mention is made here of the recent breakthrough of evidence and data indicating that a local agent may be responsible for the signs and symptoms of headaches of the vascular type.

Horton,<sup>3,16</sup> in 1939, was apparently the first to hypothesize a local active agent (histamine). Wolff,<sup>44</sup> in 1948, also suspected a local active agent but he disqualified histamine as that agent.

In 1956, Ostfeld, Chapman, Goodell & Wolff<sup>73</sup> obtained isotonic saline perfusates of the headache area in patients during an attack of migraine and found that these perfusates lowered the pain threshold of skin by 10-15% over control perfusates. This "headache fluid" caused contraction of the rat uterus which was blocked by ergotamine. Experiments also demonstrated that this headache fluid contained a substance whose spread was facilitated by hyaluronidase and not inhibited by anti-cholinergics or anti-histamine agents. In addition, the headache fluid contained increased amino acids (arginine and lysine) which indicated that tissue breakdown had occurred in the area of the headache.

In 1959, Chapman et al<sup>74</sup> performed some clever experiments in

which they demonstrated that higher CNS activity could alter the amount of the above pain-threshold-lowering substance. In one experiment, these authors produced an axon-reflex flare by the intradermal injection of histamine into the forearms of subjects. They then collected saline perfusates from the erythematous area of the axon-reflex flares (wheals) and compared the perfusates to those collected while the subjects were immersed in cold or hot water. They found an increased amount of pain-threshold-lowering substance in the perfusates of the latter group of subjects. This result indicated to the authors that CNS activity at the brain stem and hypothalamic levels could enhance inflammatory reactions (is, increase the axon-reflex flare). Sympathectomy had no effect on the results of this experiment.<sup>74</sup>

In another experiment these authors produced axon-reflex flares in hypnotized patients by suggesting to them that their forearms were being touched by a red hot metal rod (in actuality the rod was at room temperature). Again they demonstrated an increased amount of the pain-threshold-lowering substance ("bradykinin-like polypeptide") in the axon reflex flare as compared to controls.<sup>74</sup>

These authors conclude: "The individual's perception and attitudes may be relevant to neural activities that engender or enhance inflammatory reactions. Liberation or accumulation of proteolytic enzymes in the periphery and the subsequent formation of a bradykinin-like humoral agent is implicated in this reaction. Experiments with hypnosis (implicating highest levels of neural integration) demonstrate that activity within the CNS can augment the effects of the axon-reflex flare."<sup>74</sup>

<sup>75</sup>  
Chapman et al later isolated this "bradykinin-like" agent

from saline perfusates of axon-reflex flares produced by faradic stimulation of the forearm and it has also been collected during anti-dromic stimulation of dorsal nerve root. Since these experiments the bradykinin-like substance was called "neurokinin."

Neurokinin, in addition to the properties already mentioned, has been shown to be a potent vasodilator and a polypeptide and it has been differentiated from bradykinin, urinary kallikrein, urinary kallidin, plasma kallidrein, plasma kallidin, plasmin, trypsin, substances P, U & Z, adrenaline, noreadrenalin, oxytocin, cerebrotonin, hypertensin, pepsitensin, acetylcholine, histamine, serotonin, adenosine, ATP, K and isuprel.<sup>75</sup> It increases capillary permeability and heightens vulnerability to injury.<sup>73,76</sup> It is not released through vasodilatation alone although it is a potent vasodilator itself.<sup>75,78</sup> It has been found in the CSF of patients with severe and long-lasting vascular headaches of the migraine type.<sup>77</sup> Locally, in the area of head pain, there is 3 to 35 times more neurokinin than in controls and the amount closely parallels the degree of the headache.<sup>77</sup>

An enzyme has been indicated in the formation of neurokinin and it is specific for the nervous system, ie, it is increased in the CSF after convulsions in man and it is increased in cerebral perfusates during stimulation of the brains of lab animals. It is abnormally high in the CSF of schizophrenic patients and along with neurokinin it has been found locally in the subcutaneous tissues during vascular headaches of the migraine type.<sup>75</sup>

Chapman et al conclude: "The potent hypotensive and vasodilator action of neurokinin and its formation during neuronal excitation, suggest strongly that it serves in local vasomotor control of the nervous system. Migraine headache attacks are linked

to activity in the CNS since they often occur following long periods of alertness, striving, extraordinary effort or major frustration. The painful local reaction in the extracranial vessels may thus be an epi-phenomenon of the excessive operation of the normal mechanisms for functional vasodilatation within the CNS. A common innervation of the branches of the external and internal carotid arteries could lead to a simultaneous release of vasodilatory substances both intracranially and extracranially. The pain of vascular headache of the migraine type can be seen to be the outcome of combined effects of large artery dilatation plus the action of pain lowering substances accumulating in the blood vessel walls and perivascular tissue. The result is a sterile inflammatory reaction neurogenically induced."<sup>78</sup>

#### SUMMARY AND CONCLUSIONS

An attempt has been made to review some of the literature pertaining to the clinical syndrome of Cluster Headaches. The history, clinical picture, treatment, associated anatomy and pathophysiology, and etiology of this syndrome was discussed.

NOTE: Credit is due to Robinson<sup>17</sup> for the general organization of this paper into the major topics discussed, and appreciation is extended to Dr. John Graham for his discussion with this author of his unpublished data.

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