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Cyclic Vomiting Syndrome:
Evolution in Our Understanding of a Brain-Gut Disorder*

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ABSTRACT

Cyclic vomiting syndrome (CVS) remains a mysterious disorder despite our increasing knowledge since its classic description by Gee in 1882. Its hallmark feature of recurrent, explosive bouts of vomiting punctuating periods of normal health causes substantial medical morbidity (50% of patients require intravenous therapy), as well as significant time lost from school (20 school absences per year) and work. Limited epidemiologic data indicate that CVS may occur more commonly than previously thought, affecting as many as 1.9% of school-aged children. Besides the relentless vomiting, the child usually has pallor (87%), lethargy (91%), anorexia (74%), nausea (72%), and abdominal pain (80%). There is evidence of clinical and physiologic overlap among

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CVS, abdominal migraine, and migraine headaches. We propose revised criteria for abdominal migraine that include pain as the predominant and consistent symptom, lack of abnormal screening tests, and in retrospect, either subsequent development of migraines or positive response to antimigraine medication. Besides migraines, other etiologic possibilities include mitochondrial DNA mutations, ion channelopathies, excessive hypothalamic-pituitary-adrenal axis activation, and heightened autonomic reactivity. The differential diagnosis includes idiopathic CVS (88%); gastrointestinal disorders (7%), including serious surgical disorders (eg, malrotation); and extraintestinal disorders (5%), including serious surgical (brain stem neoplasm) and metabolic disorders (eg, fatty acid oxidation disorder). Within the idiopathic group, there may be migraine, Sato's neuroendocrine, mitochondrial, and other subgroups. Treatment includes avoidance of triggers, prophylactic medication, supportive care, abortive medication, and family support. In the future, investigation into mitochondrial DNA mutations, ion channel defects, corticotropin-releasing factor, and serotonin and tachykinin receptor physiology and pharmacology may help discover the etiology and pathogenesis of this disorder.

Cyclic vomiting syndrome (CVS) remains a mysterious but increasingly understood disorder at the onset of the third millennium. Vomiting is a common index symptom in many disorders affecting children and adults and has been recently reviewed. CVS appears to be a singularly severe and unique temporal pattern of emesis that is characterized by recurrent, discrete, stereotypical episodes of intense vomiting punctuating periods of completely normal health (Table 1). Its peak intensity, a mean of six emeses per hour, is among the highest known in humans. That severity coupled with 22 recurrences over the life of the disorder results in significant medical morbidity, as well as academic and work disability. This review on CVS is timely because of new clinical and scientific insights into the disorder. In the last decade of the 20th century, two international scientific symposia, two published proceedings, and one conference on collaborative research were organized and 62 relevant papers were published. Despite the ongoing suffering of patients, the future is indeed brighter for affected patients and their families.

In this review, we describe the history of CVS from its first descriptions through the recent symposia. Our review of the epidemiology suggests that it may be a common disorder which often goes misdiagnosed or undetected. The clinical characteristics of CVS, especially the cyclic pattern of recurrent emesis, ar
### TABLE 1.
Consensus Diagnostic Criteria for CVS

<table>
<thead>
<tr>
<th>Essential Criteria</th>
<th>Supportive Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent, severe, discrete episodes of vomiting</td>
<td>Pattern</td>
</tr>
<tr>
<td>Varying intervals of normal health between episodes</td>
<td>Stereotypical: each episode similar as to time of onset, intensity, duration, frequency, associated symptoms and signs within individuals</td>
</tr>
<tr>
<td>Duration of vomiting episodes from hours to days</td>
<td>Self-limited: episodes resolve spontaneously if left untreated</td>
</tr>
<tr>
<td>No apparent cause of vomiting (negative laboratory, radiographic, endoscopic testing)</td>
<td>Associated symptoms</td>
</tr>
<tr>
<td></td>
<td>Nausea, abdominal pain, headache, motion sickness, photophobia (+ lethargy)</td>
</tr>
<tr>
<td></td>
<td>Associated signs</td>
</tr>
<tr>
<td></td>
<td>Fever, pallor, diarrhea, dehydration, excess salivation, social withdrawal</td>
</tr>
</tbody>
</table>

(Data from the International Scientific Symposium on Cyclic Vomiting Syndrome [CVS] held at St Bartholomew's Hospital, London, July 29-30, 1994.)

Described, as is its natural history with resolution in adolescence and frequent progression to migraines. We attempt to differentiate CVS and abdominal migraine. The current speculations on brain-gut relationship are summarized. We describe the differential diagnosis of episodic vomiting and appropriate exclusionary laboratory testing, as well as clinical subgroups and a proposed clinical pathway. Past and present therapeutic adventures are reviewed. Lastly, we review future research and therapeutic directions.

**HISTORY**

It is instructive to review the history of the clinical understanding and research efforts in CVS because many of the current etiologic possibilities simply represent rediscovery and elaboration of earlier century-old speculations.

**1806-1990**

CVS has puzzled physicians for nearly two centuries. Early reports of recurrent or periodic vomiting include those by Heberden.\(^5\)
(1806), Gruere⁶ (1840), and Lombard⁷ (1861). The description by Samuel Gee⁸ was the first in English and remains as apt today as it was in 1882. He noted:

> These cases seem to be all of the same kind, their characteristic being fits of vomiting, which recur after intervals of uncertain length. The intervals themselves are free from signs of disease. The vomiting continues for a few hours or a few days. When it has been severe, the patients are left much exhausted.

In this succinct passage, he captured the three hallmarks of the disorder: severe, discrete episodes of vomiting, interval wellness, and a stereotypical pattern.

Although the cause of CVS has remained elusive since its early descriptions, many theories were developed in the late 19th and early 20th century, and some remain valid today. The relationship of migraine headaches to CVS was recognized early on and remains an active area of investigation. In 1898, Whitney⁹ recognized the analogy between episodes of CVS and those of migraine. In 1904, Rachford¹⁰ noted that some children with recurrent vomiting had migraine headaches in their later years. Many others have confirmed similarities in symptomatology between migraine and CVS, have observed the progression from CVS to migraine headaches, and have noted an increased incidence of family members with migraines in those with CVS.¹¹-¹⁹ In fact, Wyllie and Schlesinger¹¹ in 1933 and Barlow²⁰ in 1984 described CVS and migraine as part of a “periodic group of disorders” that were thought to have a common origin.

A metabolic cause of CVS has frequently been sought. Early discussions involved the roles of hypoglycemia and ketoacidosis in these episodes.¹⁴ Ross and Josephs²¹ described a child with CVS with hypoglycemia and ketosis who responded rapidly to intraperitoneally or rectally administered glucose. Josephs²² subsequently demonstrated a greater decrease in serum glucose concentration in those with recurrent vomiting as compared with fasted controls. Similarly, Osman²³ believed that CVS was caused by depleted hepatic glycogen stores and advocated giving children extra sugar throughout the day. However, Miller²⁴ and others argued that ketoacidosis was a result of prolonged vomiting and inability to retain calories rather than the cause of the episode. Instead, he, Griffith,²⁵ Rachford,¹⁰ and Langmead²⁶ implicated acute poisoning of the liver, or the liver’s inability to handle toxins (eg, “intestinal toxemia”). Howland and Richards²⁷ suggested that the problem was a diminished capacity for oxidation of a vari-
ety of substances, one of which Langmead\textsuperscript{26} believed was fat. Recently, urea cycle defects, fatty acid oxidation disorders, and mitochondrial respiratory chain enzymeopathies have again been considered potential causes of CVS.\textsuperscript{28-31}

Abdominal epilepsy, an epileptic equivalent, also has been considered extensively. Gibbs and Gibbs\textsuperscript{32} (1951), Millichap et al\textsuperscript{33} (1955), and Kellaway et al\textsuperscript{34} (1959) reported a 14- and 6-per-second positive spike pattern in children affected by a convulsive equivalent manifested primarily by recurrent pain, vomiting, or both.\textsuperscript{32-34} Chao et al\textsuperscript{35} (1964) and Papatheophilou et al\textsuperscript{36} (1972) subsequently demonstrated that this electroencephalographic (EEG) pattern did not correlate with these epileptic equivalents and was common in recurrent abdominal pain; abdominal epilepsy therefore appears to be an uncommon cause of CVS.

Cullen and MacDonald\textsuperscript{16} believed that many of the characteristics of the periodic group of disorders supported a disturbance of the autonomic nervous system as a cause, a notion supported by recent studies.\textsuperscript{37,38} Additional suggestions as to etiology have included infections, food allergies, poor body mechanics, recurrent volvulus, chronic appendicitis, adrenal insufficiency, and eye strain.\textsuperscript{12,23,39-42} However, in hindsight, some of these appear to be precipitants of episodes rather than the cause.

The role of psychiatric or psychogenic factors in precipitating episodes of CVS has long been discussed. As early as 1898, Whitney\textsuperscript{9} concluded that CVS was a "gastric neurosis." Dods\textsuperscript{43} (1935) and Smith\textsuperscript{14} (1937) both described their patients with CVS as nervous or high-strung. In the 1970s, Davenport et al\textsuperscript{44} and Reinhart et al\textsuperscript{45} described psychopathology and disturbed family relationships in a few selected patients with CVS. Most recently, Withers et al\textsuperscript{18} found a higher incidence of anxiety, depression, and attention difficulties in CVS patients than in controls. However, all noted that these psychological problems are possibly the result of the distress of recurrent episodes of vomiting rather than the cause.\textsuperscript{15} Finally, it has been frequently observed that either emotional or physical stress can bring on an episode, which can include excitement over positive life events such as holidays, vacations, or birthdays.\textsuperscript{8,10,14,22,26,43}

Despite having been rethought for nearly two centuries, CVS remains an enigma today. With the resurgence of clinical and basic science interest in this disorder in the last decade, several of the current speculations on pathogenesis reprise those conjectured nearly a century ago, including migraine, metabolic and autonomic pathways.
1990-2000

The recent history of patient and physician interest is instructive as to how one can initiate a lay and scientific attack on a medical disorder in which there is limited knowledge as well as scant awareness among the public and professionals. In the early 1990s, Ms Kathleen Adams’ search for answers for her daughter led her to organize the inaugural conference for affected children and adults, their families, and a handful of physicians in 1993. At that conference, she founded the Cyclic Vomiting Syndrome Association (CVSA), dedicated to family support, advocacy, and education about the disorder. Ms Adams was elected president and Drs David Fleisher and B Li were appointed as primary medical advisors, and this began a productive patient-physician partnership. In short order, a regional infrastructure was built and support meetings were organized around the United States. Simultaneously, associations were formed in the United Kingdom and Australia; since that time international chapters have been formed in 14 countries.

As the first critical step of professional outreach, Dr Li proposed a scientific meeting to further understanding of this disorder. In 1994, Drs Li and John Walker-Smith organized the first international symposium at St. Bartholomew’s Hospital in London where Dr Samuel Gee wrote his classic description; the proceedings were published in the *Journal of Pediatric Gastroenterology in Nutrition* in 1995. As the second step, the advisory board recommended that CVSA support relevant research which might not otherwise be funded, and it consequently added support of research to its mission in 1997 and funded six peer-reviewed clinical and laboratory-based research projects in 1998. As the third step, the advisory board recognized the need of greater expertise in gut motility, nausea and emetic pathways, hypothalamus, corticotropin-releasing factor (CRF), stress response, mast cells, fatty acid oxidation, mitochondrial disorders, ion channels, serotonin and tachykinin receptors, genetics, and chronobiology. Funded largely by the National Institutes of Health (NIH), Drs Li and Sushil Sarna organized the second international symposium at the Medical College of Wisconsin in Milwaukee in 1998 to expand the basic science perspectives; the proceedings were published in *Digestive Diseases and Sciences* in 1999. This collaborative patient-physician partnership has been remarkably productive in raising more than $300,000 over a 6-year period not only for support and education but also for scientific interchange and research. This partnering has spurred the publication of 62 relevant articles in the last decade compared with 24 in the preceding two centuries.
EPIDEMIOLOGY AND DEMOGRAPHICS

The true incidence and prevalence of CVS is unknown. The current estimate of pediatric prevalence is 2%. In 1963, Cullen and MacDonald\textsuperscript{16} first estimated the prevalence of periodic vomiting in Western Australia to be 2.3% of 3440 children. Abu-Arafeh and Russell\textsuperscript{50} recently observed a similar prevalence of 1.9% in 2165 children aged 5 to 15 years queried in a cross-sectional school survey in Aberdeen, Scotland. These figures actually estimate the children who had the cyclic vomiting pattern rather than the syndrome,\textsuperscript{51} the former being a historical pattern of vomiting and the latter being a diagnosis of laboratory exclusion. Because no exclusionary testing was performed, some of those could have had a specific underlying diagnosis, which could have resulted in an overestimate of CVS. Also, these two estimates in white individuals may not reflect the frequency in other racial and ethnic populations. In our experience, all races are affected and substantial numbers have been reported in Japanese children.\textsuperscript{52,53}

Before the development of the consensus diagnostic criteria in 1994, we encountered 2 to 8 new cases per year from 1987 to 1992 at Columbus Children's Hospital; afterwards, 35 to 41 new cases from 1995 to 1999.\textsuperscript{4,52} Despite this striking increase that we attributed to better awareness and detection, that figure remains a log order lower than the anticipated 2000 to 3000 new cases per year based on a 2% prevalence in our pediatric catchment area of 900,000. How do we explain this large discrepancy? Some represents the difference between the higher prevalence of the cyclic vomiting pattern than that of the syndrome. In addition, because individual episodes are often evaluated by different physicians—primary care, partner on-call, urgent care, emergency department, gastroenterologist—many are misdiagnosed as resulting from acute illnesses (eg, gastroenteritis or food poisoning) because the overall pattern of recurrence is not appreciated. Other mildly affected children may not be detected because short nighttime episodes that do not result in school absences or doctor's visits may only be detected by surveys of nonclinic children or on careful reviews of systems.

A slight predominance of girls over boys (55:45) is present in our series.\textsuperscript{19} The median age of onset of symptoms is 5.2 years. Unfortunately, the median interval from onset of symptoms to proper diagnosis in a tertiary pediatric gastroenterology clinic is 2.5 years.
CLINICAL CHARACTERISTICS OF CVS

Several large series of patients with CVS have been described, including those by Smith¹⁴ (65 patients), Hoyt and Stickler¹⁵ (44), Fleisher and Matar⁵⁴ (71), and Li et al¹⁹ (214). The symptoms and signs are summarized in Table 2. Because our cohort of CVS is the largest, most of the percentages cited below represent those from our series.

MORBIDITY

The contrast between well and ill periods is striking. In the physician's office in between episodes, children are completely healthy.

<table>
<thead>
<tr>
<th>TABLE 2.</th>
<th>Phenomenology of CVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>55:45</td>
</tr>
<tr>
<td>Age of onset</td>
<td>5.2 years</td>
</tr>
<tr>
<td>Morbidity</td>
<td>20 days of missed school per year, 50% intravenous rehydration</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 times per hour at peak, with bile (76%) and blood (32%)</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Lethargy (91%), pallor (87%), fever (29%), salivation (13%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain (80%), retching (76%), anorexia (74%), nausea (72%), diarrhea (36%)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache (40%), photophobia (32%), phonophobia (28%), vertigo (22%)</td>
</tr>
<tr>
<td>Temporal pattern</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>24 hours</td>
</tr>
<tr>
<td>Periodic</td>
<td>47% have regular intervals, usually every 2 to 4 weeks</td>
</tr>
<tr>
<td>Circadian</td>
<td>Nighttime or early morning (34%)</td>
</tr>
<tr>
<td>Stereotypical</td>
<td>98%</td>
</tr>
<tr>
<td>Precipitating events</td>
<td>Infection (41%), psychological stress (34%), dietary (26%), menstrual (13%)—some trigger identified (68%)</td>
</tr>
<tr>
<td>Natural history</td>
<td>Duration, 2.34 years; 27% progress to migraine headaches</td>
</tr>
<tr>
<td>Family history of migraine</td>
<td>82%</td>
</tr>
</tbody>
</table>

(Data from references 14, 15, 18, 19, 52, and 54.)
Yet in the emergency department, they appear much sicker than those with gastroenteritis and are often curled up into a fetal position in severe pain and are pale, listless, incommunicado, and vomiting relentlessly. Despite being well approximately 85% of the time, the 15% of the time spent ill in 22 episodes over 3.4 years causes substantial medical morbidity, and academic and work disability. School-aged children older than 7 years missed 20 days of school during the past year.\(^5\) Because of repeated school absences, many children are required to receive home tutoring or be home schooled. Because of their episodic incapacity and many work absences, some adults have lost jobs. Compared with the rate of dehydration (<1%) associated with rotavirus gastroenteritis, 50% of the children with CVS require intravenous therapy during episodes, of whom 28% require it with each episode. Often, because these episodes unexpectedly ruin birthdays, holidays, and out-of-town vacations, some families have dispensed with family vacations altogether. Several children have been misdiagnosed and hospitalized on psychiatric wards for up to 6 months for treatment of presumed bulimia and psychogenic vomiting. Including the cost of visits to the physician, care in the emergency department and inpatient unit, diagnostic tests, and missed worked days to care for the child, we estimated the average annual cost of care to be $17,035 for a child with CVS.

CYCLIC VERSUS CHRONIC PATTERN OF VOMITING

The hallmark clinical feature of CVS is the recurrent, discrete, severe episodes of vomiting. We demonstrated that children with recurrent vomiting could be qualitatively and quantitatively differentiated into two main temporal patterns: cyclic and chronic (Fig 1).\(^5\) The cyclic group had an intense but intermittent pattern (ie, peak intensity ≥4 emeses per hour and ≤2 episodes per week), whereas the chronic group had a low-grade, but nearly daily pattern (ie, <4 emeses per hour and >2 episodes per week). These two quantitative criteria were 92% sensitive and 100% specific for children with CVS. These two groups differed both in severity and key symptoms. Consonant with the more intense vomiting, the cyclic group more often required intravenous hydration (62% vs 18%). Consonant with the postulated relationship with migraine headaches, the cyclic group had a significantly higher prevalence of family members with migraine headache (72% vs 14%), associated headaches (41% vs 19%), and photophobia (18% vs 4%). These distinct patterns carry implications for the diagnostic profile and evaluation. Among those with the cyclic pattern of vomit-
Cyclic versus chronic temporal patterns of vomiting. The number of emeses is plotted over a 2-month period. The chronic pattern represented by a dashed line has low-grade, nearly daily episodes, whereas the cyclic pattern represented by the solid line has high-intensity episodes every several weeks. (Adapted from Li BUK: Cyclic vomiting syndrome: New understanding of an old disorder. Contemp Pediatr 13:49, 1996. With permission.)

VOMITING

The vomiting found in CVS is unusually rapid fire and relentless. In our first series of 34 patients, the mean peak intensity (peak number of emeses per hour during worst hour) was 13 times per hour or once every 5 minutes. With our expanded series of 225 patients that includes more mildly affected children, the mean peak intensity remains at 6 emeses per hour or once every 10 minutes. The high peak intensity exceeds even that seen with mechanical small bowel obstruction and appears to be matched only by those who have Bacillus cereus food poisoning or have received apomorphine. The median and mean totals of 11 and 22 emeses per episode also reflect the severity. The emesis typically is projectile (50%) and contains bile (76%), mucus (72%), and blood (32%), the latter resulting most commonly from propulsive
gastropathy in which the gastric cardia herniates retrograde through the gastroesophageal junction, or less commonly from a Mallory-Weiss tear. The persistence of emesis even when the stomach contains only mucus and bile supports the notion that CVS is centrally mediated and progresses largely independent of gastric feedback.

**AUTONOMIC SYMPTOMS**

Autonomic symptoms are common, especially lethargy (91%) and pallor (87%). Although the pallor may simply accompany severe nausea and vomiting, the origin of the lethargy is unknown. The lethargy can be so profound that affected patients are unable to walk or talk and may appear comatose; the EEG correlate is δ waves as if the child is in metabolic coma. In other children, a premonitory sleep heralds full recovery and is part of the rationale for use of sedatives to facilitate rest and recovery. Excess salivation with drooling is dramatic but is not common (13%).

**GASTROINTESTINAL SYMPTOMS**

Besides the vomiting, the sine qua non in all patients, abdominal pain (80%), retching (76%), anorexia (74%), and nausea (72%) are the most common symptoms. Early on, the abdominal pain can be excruciating and mimic an acute abdomen. Whether the target organ of the pain is actually brain or gastrointestinal tract is unknown. If the episode lasts for several days, epigastric pain usually results from vomiting and retching-induced injury to the esophagus and stomach. The anorexia like the nausea is minimally relieved by emesis and may represent the effects on both the chemotrigger zone and the gastric motility. The nausea by all accounts is the most distressing symptom because there is no temporary relief whatsoever until the episode is over. Many of the behavioral features (eg, rendering a fetal position, social withdrawal, compulsive drinking, and turned off lights and television) are intended to reduce nausea. As one 17-year-old patient wrote, "As the attack progresses the nausea becomes constant. Nothing will relieve it—I can only describe it as absolute hell and I feel so awful that I honestly want to die."

The fact that a third of the patients have fever (29%) and diarrhea (36%) coupled with the vomiting contributes to the frequent and understandable misdiagnosis of gastroenteritis. Although low-grade fever can usually be attributed to dehydration, the few cases that repeatedly reach 104°F have been conjectured to involve cytokine release. The diarrhea has been suggested to be the result
of autonomic discharge, but whether the diarrhea is from intestinal hypersecretion, increased motility, or both is unclear.

NEUROLOGIC SYMPTOMS
The observation that neurologic symptoms occur in a significant number of individuals lends support to the proposed relationship between migraines and CVS.\textsuperscript{15,18,19,54} But because classic symptoms of headache (40\%), photophobia (32\%), and phonophobia (28\%) are found in less than half of the affected children, the standard migraine criteria cannot be used to establish this diagnosis. Yet, the significantly higher occurrence of these criteria in patients with CVS than in control patients with chronic vomiting underscores the association between migraines and CVS.\textsuperscript{56}

"ON-OFF" STEREOTYPICAL PATTERN
The syndrome is characterized by severe episodes between which the child returns to normal, an "on-off" pattern with no partly ill state (Fig 2).\textsuperscript{55} This square wave pattern is so typical that if a patient has any symptoms in between episodes, it usually implies that the patient either does not have CVS or has a superimposed chronic vomiting disorder such as gastroesophageal reflux.\textsuperscript{56} Sixty-eight percent of patients have a short one-half hour pro-

![Figure 2](https://example.com/figure2.png)

**FIGURE 2.**
Pattern of individual episodes of CVS. Two discrete episodes of CVS are depicted schematically, with the height of the line presenting the intensity of vomiting. The separate phases of the well interval, prodrome before the onset of vomiting, the vomiting episode itself, and the recovery phase from last emesis to the turning point where the child can begin to keep food down and be playful are indicated.
drome, consisting of nausea and pallor without visual aura, before the onset of vomiting. The vomiting usually reaches its peak intensity within the first hour and begins to decline after the first 4 to 8 hours, and lasts a median and mean of 24 and 41 hours, respectively. The recovery period from the end of vomiting to the point of turning the corner and being able to eat lasts a mere 5 hours. The recovery is often so brief that parents have stated "it was like turning off a switch." Almost all parents (98%) describe the attacks as stereotypical as to time of onset, intensity, episode duration, and associated symptomatology. Because stereotypy is so expected, we have found that when the pattern changes, a complicating disorder may be uncovered on testing. Once this latent disorder is triggered, it appears to follow the same cascade and ends in clinically similar episodes within individuals.

PERIODIC AND CIRCADIAN OCCURRENCE
One of the intriguing aspects of CVS is its chronobiology. Despite the terms "periodic" and "cyclic" as the principal descriptors of the disorder, they are slight misnomers. Actually less than half of patients (47%) have a stable periodicity, whereas the remainder have an intermittent, but variable timetable. The two most common regular intervals between onset of attacks were every 2 weeks (24%) and 4 weeks (23%). Although 4-week intervals raise the possibility of a relationship to follicle-stimulating hormone and luteinizing hormone, most affected girls were prepubertal. However, we have seen eight postmenarchal girls who have episodes only with the onset of their menses, a catamenial CVS. Remission during the summer months is the most common seasonal variation, for which we have postulated a role for reduction in exposure to infectious, allergic, and school-related stressors.

A circadian pattern occurs in which the most common period of onset is in the early morning (eg, 2-4 AM and 5-7 AM) in 34% of patients. We have suspected that the early morning surge of CRF and vasopressin may contribute to that circadian susceptibility.

TRIGGERS OF EPISODES
Various stressors appear to precipitate episodes of CVS. By history, 68% of the parents can identify a repetitive proximate event such as a psychological or physical stress, or infection. Using questions from studies on migraines, various events have been identified: infections (41%) were the most common, especially chronic sinusitis; psychological stresses (34%) including
both positive experiences (eg, birthdays, holidays) and negative ones (eg, family and school related); dietary triggers (26%) including chocolate, cheese, and monosodium glutamate; physical exhaustion or lack of sleep (18%); atopic events (13%); and motion sickness (9%). Among menstruating girls, 13% identified the onset of menses as the typical proximate event.

**NATURAL HISTORY AND DEVELOPMENTAL PATTERN**

There are no definitive studies on the natural history of CVS. Hoyt and Stickler\(^1\) noted that episodes ended before 14 years of age in 43 of 44 patients, and the median duration of the illness was 6 years. Fleisher and Matar\(^5\) characterized the course in 16 patients who had been episode-free for more than 1 year and found that the mean age of onset, mean duration of illness, and mean age of resolution were 8.0, 5.7, and 13.7 years, respectively. Suggesting that the illness can last well into adulthood, Hammond\(^6\) found that of 12 young adults who had CVS as children, 6, 7, and 8 continued to have abdominal pain, vomiting, and headache, respectively, up to 10 years later.

A substantial percentage of children trade their CVS for migraine headaches sometime during their adolescent years. In our series of 88 children whose episodes had ended for 1 year or more, two thirds (65%) did not have other symptoms, whereas one third (27%) had migraine headaches.\(^5\) Only 7% subsequently had abdominal migraines and 5% progressed through all three phases, from CVS to abdominal migraine and migraine headaches. We found that the younger the age of onset, the longer the duration of illness: ages of onset earlier than 3 years, between 3 and 8 years, and later than 8 years were associated with durations of illness of 5.8, 4.9, and 2.9 years, respectively. Using survival analysis of 277 patients including those with ongoing episodes, there was a 50% chance of outgrowing CVS by 4 years after onset. Although 27% of those with CVS have developed migraines so far, the survival model would predict that 50% would develop headaches by 15 years of age.

CVS occurs in adults.\(^6\) \(^1\)-\(^6\) Judging by curbside consults, we know that small numbers of cases are being recognized and evaluated by family physicians, internists, and adult gastroenterologists. However, because this clinical entity is so poorly recognized and studied in adult patients, the prevalence rates, although likely to be substantially less than in children, are completely unknown.

If it is predominantly a pediatric disorder, what regulates its resolution by adolescence? The only current tenable hypotheses are
Cyclic Vomiting Syndrome

TABLE 3.
Key Diagnostic Questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has your child had 3 or more attacks of vomiting like this before?</td>
<td>Yes (100)</td>
</tr>
<tr>
<td>Is your child completely normal in between?</td>
<td>Yes (100)</td>
</tr>
<tr>
<td>Is each episode similar to the others?</td>
<td>Yes (98)</td>
</tr>
<tr>
<td>Does the vomiting occur more than every 15 minutes at its peak?</td>
<td>Yes (71)</td>
</tr>
<tr>
<td>Is there associated pallor and lethargy?</td>
<td>Yes (91, 87)</td>
</tr>
<tr>
<td>Is there associated abdominal pain, anorexia, and nausea?</td>
<td>Yes (80, 74, 72)</td>
</tr>
<tr>
<td>Is there a family history of migraine headaches?</td>
<td>Yes (82)</td>
</tr>
</tbody>
</table>

(Data from references 4, 19, 52, 54, and 56.)

The greater susceptibility to motion sickness between 2 and 12 years of age in humans, when CVS is most prevalent, and an age-related decline in the early morning circadian peak of CRF rhythm seen in experimental animals. 65,66

DIAGNOSTIC QUESTIONS
In lieu of any validated laboratory markers, making the diagnosis of CVS depends on fulfilling the consensus historical criteria.4 Using the clinical phenomenology of our large series and comparing it with symptoms in children with the chronic pattern of vomiting, we have come up with seven key diagnostic questions that will detect most patients with CVS (Table 3).19,56

RELATIONSHIP AMONG CVS, ABDOMINAL MIGRAINE, AND MIGRAINE HEADACHES
The precise relationship among these entities cannot be definitively settled until validated laboratory markers become available. However, in an attempt to provide answers to the questions of how these three entities are interrelated and when each diagnostic label should be used, we describe the clinical and physiologic overlap, and attempt to clarify the nosology of these disorders.

EVIDENCE OF A LINK BETWEEN CVS AND MIGRAINES
As early as 1898, Whitney9 recognized a potential connection between migraines and CVS. The link between CVS and migraine headaches was based on the overlap in clinical characteristics, the
concurrency of both disorders in the same child, and the family histories of migraines. Five decades later, Farquar in 1956 coined the term “abdominal migraine” to identify a group of children with a another migraine variant manifested primarily by recurrent episodes of abdominal pain. However, Axon et al and Hockaday have recently and independently questioned whether it is a distinct clinical entity.

Based on family history and therapeutic responses, the more recent literature reinforces the migraine linkage. Pfau et al found a positive family history of migraine more frequently in children with CVS (72% vs 14%) compared with those with chronic vomiting, and found that 75% responded to antimigraine prophylaxis with cessation of episodes. Similarly, Anderson et al found that 83% and 91% of their cohort with CVS responded to prophylactic antimigraine treatment with cyproheptadine and amitriptyline, respectively. Using a case-control method, Withers et al also demonstrated a higher prevalence of migraines (37% vs 9%) in cases than in controls. Li et al recently reported that those with CVS who met the criteria of migraine-associated CVS (positive family history, subsequent development of migraine headaches, or both) had double the positive response rate (79% vs 36%) to antimigraine therapy as did the nonmigraine CVS subgroup.

OVERLAP IN CLINICAL PRESENTATION
When the three core symptoms of vomiting, abdominal pain, and headache are compared, there are notable parities in occurrence across all three conditions (Table 4). By definition, the index symptom occurs in 100% of children in their respective group (eg, vomiting in CVS). In addition, the finding that the two other core symptoms were found in 3% to 81% of patients (ie, abdominal pain or headache in CVS) lends further credence to the association. Using the current diagnostic criteria, between one third and four fifths of each group could also be reclassified as a second one (eg, CVS as abdominal migraine).

When the associated symptoms are compared, an even greater clinical overlap among conditions was noted. Across the board, three quarters of each group experience pallor, anorexia, and nausea. Because the profiles of associated symptoms were nearly identical, the core symptom appeared to dictate which primary label was used (eg, abdominal pain in abdominal migraine). Although vomiting intensity (the number of emeses per unit time) is one of the distinctive features of CVS, there is no objective corollary of
Cyclic Vomiting Syndrome

TABLE 4.
Comparison of Symptoms Among Patients With CVS, Abdominal Migraine, and Migraine Headaches

<table>
<thead>
<tr>
<th></th>
<th>CVS* (%)</th>
<th>Abdominal Migraine† (%)</th>
<th>Migraine Headache‡ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>100</td>
<td>39-72</td>
<td>40-69</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3-81</td>
<td>100</td>
<td>10-55</td>
</tr>
<tr>
<td>Headache</td>
<td>38-59</td>
<td>31-50</td>
<td>100</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>87</td>
<td>90-100</td>
<td>23-88</td>
</tr>
<tr>
<td>Lethargy</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>74</td>
<td>91-98</td>
<td>13-93</td>
</tr>
<tr>
<td>Nausea</td>
<td>72</td>
<td>73-91</td>
<td>46-100</td>
</tr>
<tr>
<td>Photophobia</td>
<td>32</td>
<td>1-42</td>
<td>27-81</td>
</tr>
</tbody>
</table>

*Data from references 15, 18, 19, 54, and 60.
†Data from references 71-74.
‡Data from references 72, 74, 76-81.

intensity for symptoms of abdominal pain or headache other than disruption of normal activity.56

The observation that CVS can progress sequentially to abdominal migraine and migraine headaches supports the notion that there may be several distinct age-dependent presentations of migraines. Retrospectively comparing adult migraineurs to controls, Lanzi et al61 noted that 40% vs 11% had attacks of cyclic vomiting and 30% vs 3% had episodic abdominal pain in the past. In a cross-sectional school survey in Scotland by Abu-Arafeh and Russell,72 the mean respective ages of children with CVS, abdominal migraine, and migraine headaches of 5.3, 10.3, and 11.5 years suggested a sequential progression among the entities. In our series of 88 children whose episodes have ceased, nearly one third have subsequently had migraine headaches.52

OVERLAP IN PHYSIOLOGIC MEASURES
There is circumstantial evidence that CVS and migraines share some physiologic characteristics. The autonomic nervous system is thought to mediate a number of key symptoms (e.g., pallor, lethargy, and salivation) common to children with migraine.16,54 Meossi et al83 demonstrated diminished baroreflex (heart rate) responses to postural changes in children with periodic abdominal pain,
vomiting, and headaches compared with those of control subjects. Rashed et al\textsuperscript{37} recently reported higher sympathetic responses to postural changes in children with CVS and adults with migraine headaches compared with adult control subjects. To et al\textsuperscript{38} recently described a predominance of sympathetic adrenergic over parasympathetic cholinergic tone in children with CVS between episodes compared with that found in healthy subjects.

Migraine-type neural and vascular changes have also been documented in affected children. Mortimer and Good\textsuperscript{71,84} have established parallel visual evoked encephalographic responses (VER) in children with abdominal migraine and migraine headaches that differed from healthy control subjects. This would imply VER patterns are also found in some patients with CVS because some patients with abdominal migraine also manifest vomiting. Altered cerebral blood flow has been found on transcranial ultrasound studies in adults with migraines.\textsuperscript{85,86} Oki et al\textsuperscript{87} have documented interictal bitemporal hypoperfusion by positron emission tomography scan in one child with CVS.

In summary, there are parallels in autonomic, neural, and vascular functioning that help support the clinical similarities among the three periodic entities. Further study of these physiologic parameters is required to establish the consistency and significance of these findings. Although we suspect that these autonomic perturbations are central to the pathophysiologic cascade, they may simply be epiphenomena of nausea, vomiting, and severe abdominal and headache pain. If validated, it is possible that these measures could be used to diagnose CVS, abdominal migraine, and migraine headache in a positive rather than exclusionary fashion.

**CRITERIA FOR ABDOMINAL MIGRAINE**

Some clinicians have used the labels CVS and abdominal migraine interchangeably because of the extensive overlap in clinical criteria. Both diagnostic labels are based solely on historical criteria without support of objective laboratory markers. Because of the lack of consensus agreement, the less established of the two diagnostic labels is abdominal migraine. In chronological order, diagnostic criteria have been put forward by Lundberg,\textsuperscript{88} Symon,\textsuperscript{17} Abu-Arafeh and Russell,\textsuperscript{72} the Rome Criteria for functional gastrointestinal disorders,\textsuperscript{89} and us (Table 5). The key diagnostic tenets are recurrent, stereotypical, severe episodes of abdominal pain between which the patient is well, usually accompanied by autonomic symptoms and a family history of migraine headaches. Because symptoms of vomiting and abdominal pain are often coin-
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Migraines</strong></td>
<td>Family history of migraine headaches</td>
<td>One of the following: family history of migraine or subsequent development of migraine headaches</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Pattern</strong></td>
<td>Stereotypical, discrete episodes (≥3) of vomiting that are self-limited</td>
<td>Stereotypical, ≥ 5 discrete attacks</td>
<td>≥ 5 discrete attacks</td>
</tr>
<tr>
<td><strong>Interval history</strong></td>
<td>Complete resolutions of symptoms between attacks of varying intervals</td>
<td>Complete resolution of symptoms between attacks</td>
<td>Complete resolution of symptoms between attacks</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Hours to days</td>
<td>Each attack lasts for ≥ 2 hours</td>
<td>Each attack lasts 2-48 hours</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Severe vomiting, ≥ 4 emeses per hour</td>
<td>Pain is severe enough to interfere with normal daily activities</td>
<td>Pain is severe enough to disrupt normal daily activities</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>Midline abdominal pain</td>
<td>Periumbilical or poorly localized pain</td>
<td>Unilateral, pulsating, moderate-to-severe intensity</td>
</tr>
<tr>
<td><strong>Associated symptoms</strong></td>
<td>Pallor, lethargy, anorexia, excess salivation, nausea, headache, photophobia, dehydration</td>
<td>Two of the following: anorexia, nausea, vomiting, pallor, lethargy</td>
<td>One of the following: nausea ± vomiting, photophobia, phonophobia</td>
</tr>
<tr>
<td><strong>Laboratory evaluation</strong></td>
<td>No apparent cause of vomiting on laboratory, radiographic, and endoscopic testing</td>
<td>No apparent cause of vomiting on laboratory, radiographic, and endoscopic testing</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Therapeutic response</strong></td>
<td>NA</td>
<td>Positive response to antimigraine medication</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Data from references 4, 8, and 54.
†Data from references 17, 72, 88, and 89.
‡Data from reference 82.

*Abbreviation: NA, not applicable*
incident, the majority of patients can be diagnosed as having either CVS or abdominal migraine.

To establish the specificity of each diagnostic term, we have encountered a few individual cases that have episodic vomiting without abdominal pain and vice versa that can only be classified as CVS and abdominal migraine, respectively. In addition, there are other patients in whom each disorder occurs sequentially, usually CVS first, then abdominal migraine. For diagnostic consistency, when vomiting and abdominal pain both occur, we operationally used the predominant and consistent symptom, whether vomiting or abdominal pain, to make the primary classification. We propose three additional supportive criteria to strengthen a diagnosis of abdominal migraine: (1) negative screening diagnostic tests so that common gastrointestinal, hepatobiliary, and renal disorders are excluded, and for making retrospective diagnoses; (2) subsequent development of migraine headaches; and (3) a positive response to antimigraine prophylactic or abortive medication (Table 5).

Identifying patients as having either abdominal migraine or CVS is useful because it points the clinician toward empirical trials of antimigraine therapy that are uncommonly used in gastrointestinal disorders which manifest either vomiting or recurrent abdominal pain. In the future, we will need to test diagnostic criteria to determine their sensitivity and specificity, just as we have done with CVS.

SPECULATIONS AS TO ETIOLOGY AND PATHOGENESIS

Several potential brain-gut pathophysiologic pathways may play a role in the etiology and pathogenesis of CVS including (1) migraine, which has neurogenic, mitochondrial, ion channel, and hormonal aspects; (2) stress, which involves hypothalamic discharge, CRF, and histamine release; and (3) autonomic dysfunction, which has both cardiovascular and gastrointestinal aspects. Each pathway could reflect separate or more likely interrelated pathophysiologic cascades. We attempt to integrate these into a single brain-gut schema.

MIGRAINE AND MIGRAINE-RELATED MECHANISMS

Because the clinical and physiologic links between migraine and CVS are extensive, it is pertinent to review several of the known mechanisms in migraine as they may relate to CVS. As recently reviewed by Welch, migraines at their core represent regional electrophysiologic and cellular metabolic events that result in postsynaptic neuronal hyperexcitability.
Brain excitability can result from cellular dysfunction through at least two identified mechanisms: reduced mitochondrial energy production and altered intracellular divalent cation concentrations. Classical migraines (with aura) appear to result from disordered energy metabolism in the cerebral cortex. Classical migraines also occur in MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like) syndrome, which results from a single point mutation at base pair 3243 that affects mitochondrial respiratory chain enzymes. Evidence from 31P-nuclear magnetic resonance (31P-NMR) studies in peripheral tissues of migraineurs indicates that a global defect in mitochondrial oxidation may be present. Cortical hyperexcitability may also be induced by alterations in voltage-dependent Ca\(^{2+}\) permeability caused indirectly by intracellular Mg\(^{2+}\) deficiency from local Mg\(^{2+}\) fixation. In patients with familial hemiplegic migraine, four characterized missense mutations of the \(\alpha_1\) subunit of a brain-specific voltage gated P/Q type neuronal Ca\(^{2+}\) channel (CACNL1Ar) are presumably responsible for this form of migraine.

Fluctuations in female hormones and stress also play a modulating role in brain hyperexcitability. Catamenial or menstrual migraines are believed to be triggered by the precipitous fall in estrogen level just before the onset of menses. These mechanisms probably apply to CVS as well as migraines. In MELAS syndrome, both classical migraine headaches and CVS occur presumably caused by the same defect in the mitochondrial respiratory chain. Boles et al has reported a large mitochondrial DNA (mtDNA) deletion in one child and has subsequently identified mutations in the D-loop portion of the mtDNA in others with CVS. Indirect support of the presence of a subtle mitochondrial defect comes from our finding that in 80% of children with CVS, migraines were found on the matrilineal side alone. Because ion channelopathies have been associated with episodic phenomena, it has been proposed that such defects could cause CVS as well. That hemiplegic migraine is caused by a Ca\(^{2+}\) ion channelopathy lends indirect credence to this possibility. Parallel to menstrual migraines, the response of catamenial CVS to low-estrogen-dose birth control medication suggests that the premenstrual decline in estrogen levels is also involved. However, the precise mechanism by which these electrophysiologic perturbations, ion gradients, and hormones result in vomiting is unknown.

There may be other links between energy metabolism and CVS. Disorders of fatty acid oxidation such as medium-chain acyl-CoA dehydrogenase deficiency are associated with a recurrent Reye-
like picture with metabolic crisis, hypoglycemia, hyperammonemia, and severe vomiting.\textsuperscript{29,106-108} It is possible that defective mitochondrial fatty acid oxidation in a child exposed to fasting stress could result in hyperexcitability in areas that impinge on the emetic cascade.

**HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND THE STRESS RESPONSE**

The stress response mediated by the hypothalamic-pituitary-adrenal axis (HPA) appears to play a role in CVS. Infectious, physical and psychological stressors have been identified as principal precipitants of episodes.\textsuperscript{14,18,19,54,55} Excessive HPA activation has been documented by Wolfe et al\textsuperscript{109} (1963), Sato et al\textsuperscript{53,110-112} (1980s), and Pasricha\textsuperscript{113} (1996) in both children and adults with CVS. Best characterized by Sato,\textsuperscript{53,110-112} the clinical syndrome is comprised of CVS, profound lethargy, and hypertension that occurs only during episodes. Levels of corticotropin (ACTH) and cortisols were documented to increase just before the onset of the episode, accompanied by subsequent increases in antidiuretic hormone (ADH), prostaglandin E\textsubscript{2}, and serum and urinary catecholamines. Secretion of other hypothalamic hormones (gonadotropin and thyrotropin-releasing hormone remained unperturbed. The exaggerated release of ADH and catecholamines may account for the hypertension and the fluid retention. Based on provocative tests in controls, Sato\textsuperscript{112} proposed that the etiology was the reduction in dopaminergic inhibition of central norepinephrine release. Neuroleptic agents (phenytoin, valproate, and phenobarbital) and prostaglandin inhibitors (indomethacin and ketorolac) appear to be the most effective in preventing and aborting episodes, respectively.\textsuperscript{53,109-113}

We have seen four children who fit Sato's clinical and neuroendocrine profile. They appear to be distinguished not only by the presence of hypertension but also by the greater severity of episodes. For example, compared with the rest of those with CVS, their mean number of emeses per episode was substantially higher (92 vs 26) and the mean duration of their episodes was longer (144 vs 36 hours).\textsuperscript{19} However, whether this greater severity simply reflected a selection bias in which more testing was performed in sicker hospitalized patients will require additional laboratory screening. This subgroup could have a distinct pathway involving the HPA axis or could conceivably represent the most severe end of the migraine spectrum.

There has been recent interest in the potential role of CRF acting as a brain-gut mediator. Sitting atop the stress cascade, hypothalamic CRF can induce in sequence pituitary ACTH, adrenal cortisol, and
catecholamine secretion. In animal models, Taché\textsuperscript{114} has demonstrated that CRF analogues acting on CRF-R2 receptors induce gastric stasis, emesis, or both via the vagus nerve.\textsuperscript{115,116} This pathophysiologic cascade could partly explain how a stressor induces a generalized response with vomiting and hypertension. How this becomes a self-sustaining process instead of a transient phenomenon is unclear. It appears that mast cells proximate to nerves, by releasing histamine and stimulating local CRF release, play a triggering role in migraines.\textsuperscript{117,118} CRF may help to explain the nocturnal susceptibility to episodes because CRF and vasopressin regulate human circadian rhythms by peaking in the early morning hours.\textsuperscript{119,120}

**AUTONOMIC DYSFUNCTION**

Autonomic nervous system dysfunction may play either a central or auxiliary role in the clinical expression of CVS.\textsuperscript{121} Many of the symptoms of CVS including pallor, flushing, fever, lethargy, excess salivation, vomiting, and diarrhea are mediated by the autonomic system.\textsuperscript{16,54,58} Although pallor and salivation can nonspecifically accompany nausea and vomiting, the link between CVS and autonomic dysfunction may be more specific. In an extreme example, Riley-Day familial dysautonomia can manifest discrete episodes of vomiting resulting from intermittent high-grade gastrointestinal dysmotility.\textsuperscript{122}

In direct support of its role in CVS, Rashed et al\textsuperscript{37} and To et al\textsuperscript{38} have recently demonstrated measurable heightened sympathetic cardiovascular tone in affected patients as compared with control subjects.

Preliminary data suggest the presence of an underlying gastric dysrhythmia that can be detected indirectly by electrogastrograms between episodes when the child is well.\textsuperscript{123,124} In support of this mechanism, Vanderhoof et al\textsuperscript{125} have successfully used low-dose erythromycin, a motilin analogue that enhances gastric motility, to prevent vomiting episodes.

At present, many questions remain. We do not yet know whether these autonomic perturbations are reproducible and, if consistent, whether they are temporally upregulated or hardwired into the system. We also do not know whether these phenomena are simply linked to nausea and vomiting, or whether they indicate a specific autonomic susceptibility to the disorder.

**PATHOPHYSIOLOGIC MODEL**

No comprehensive pathophysiologic model encompasses all three pathways and accounts for all the clinical manifestations of CVS. Using as models abdominal migraine and migraine headache that
can both be associated with vomiting, we suspect that CVS is also a brain-gut disorder of central origin (Fig 3). The postulated subclinical mitochondrial metabolism or ion channel defect could heighten the susceptibility to stress. If so, which neuropeptides translate cortical depolarization through the efferent vomiting center or via the postulated CRF pathway remains unclear. Also unknown is whether the self-perpetuation of the episode once triggered occurs centrally like a migraine or peripherally, perhaps enhanced by the sympathetic hyperreactivity.

The CVS episode often begins with an initiating stress and in some cases appears to activate the HPA axis. CRF may be the initial signal that leads to sequential release of excess ACTH and ADH, cortisols and catecholamines, as well as vagally mediated vomiting. These hormones could account for many of the autonomic symptoms of CVS. However, the exact interplay of central release of histamine, serotonin, dopamine, norepinephrine, and prostaglandin E₂ in initiating and modulating the episode needs further delineation.

The “siphon” model proposed by Harding et al.¹²⁶ may provide a conceptual framework that enables incorporation of many of the
Cyclic Vomiting Syndrome

inputs (eg, stress triggers) and modulating factors (eg, impaired mitochondrial energy production) that result in a final common output of episodic vomiting. In this model, a variety of infections, and physical and psychological stimuli could trigger episodes, and various underlying mitochondrial and autonomic disorders could increase susceptibility to episodic vomiting. This model could account for the additive effect of more than one stimuli and predisposing condition (eg, heterozygote metabolic states) on initiating episodic emesis.

DIFFERENTIAL DIAGNOSIS AND EVALUATION

In this section, we review the differential diagnosis of CVS and corresponding screening tests, as well as a proposed clinical pathway. Two key points can be made as a result of having systematically derived the final diagnoses from treatment responses in a large series of 225 children who had episodic vomiting.  

First, the cyclic vomiting pattern is not a diagnosis but rather a clinical presentation that can result from heterogeneous disorders affecting the gastrointestinal, hepatobiliary, pancreatic, neurologic, renal, metabolic, and endocrine systems. Second, although the majority of children received a diagnosis of idiopathic CVS, one in eight of those were found to have a specific disorder that could be diagnosed by systematic testing.

Among those who had the cyclic vomiting pattern, the three main diagnostic categories—idiopathic CVS (88%), gastrointestinal disorders (7%), and extraintestinal disorders (5%)—are discussed below. The CVS label was applied to those whose tests were negative or whose positive finding (eg, peptic esophagitis) did not respond to therapy (eg, H2 antagonists) and was therefore considered incidental to the CVS. Conversely, our criterion for rendering a specific non-CVS diagnosis (eg, intestinal malrotation) was a positive treatment response (ie, cessation of episodes) to specific therapy (ie, surgical fixation). We observed that 41% of those with CVS were also found to have a comorbid disorder, most commonly peptic esophagitis and chronic sinusitis, which based on an incomplete response to therapy was not deemed to be the primary cause of cyclic vomiting. These commonplace findings underscore the necessity of exclusionary testing and careful examination of the clinical outcomes to specific therapy.

GASTROINTESTINAL DISORDERS

Among the gastrointestinal disorders discovered, the most serious were 14 surgical lesions: small bowel malrotation (5 cases), chronic appendicitis (3), duplication cyst (1), small bowel
<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Blood*</th>
<th>Urine/Stool*</th>
<th>X-ray/Other</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Peptic injury (eg, esophagitis)</td>
<td></td>
<td></td>
<td>EGD with biopsy</td>
</tr>
<tr>
<td>Malformations (eg, malrotation)</td>
<td></td>
<td></td>
<td>UGI/SBFT x-ray</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>CBC, ESR</td>
<td>Stool guaiac</td>
<td>UGI/SBFT x-ray</td>
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<td>Chronic appendicitis</td>
<td>ESR</td>
<td></td>
<td>Abdominal CT</td>
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<td>Hepatobiliary disorder (eg, gallbladder dyskinesia)</td>
<td>ALT, GGTP</td>
<td></td>
<td>Gallbladder ultrasound + CCK</td>
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<tr>
<td>Pancreatitis</td>
<td>Amylase, lipase</td>
<td>VMA, HVA</td>
<td>Abdominal ultrasound</td>
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<tr>
<td>Dysautonomia, pseudo-obstruction</td>
<td></td>
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<td>UGI/SBFT x-ray, gastric</td>
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<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td>emptying scan</td>
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<tr>
<td>Abdominal migraine</td>
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<tr>
<td>Chronic sinusitis</td>
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<td>Sinus CT</td>
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<td>Increased subtentorial pressure (eg, neoplasm)</td>
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<td>Abdominal epilepsy</td>
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<td>Acute hydronephrosis</td>
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<td>Renal ultrasound</td>
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<td>secondary to UPJ obstruction</td>
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<td>Nephrolithiasan</td>
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<td>Metabolic/Endocrine*</td>
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<td>Addison's disease</td>
<td>Electrolytes, cortisol</td>
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<td>Diabetes mellitus</td>
<td>Glucose</td>
<td></td>
<td>Ketones</td>
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<tr>
<td>Condition</td>
<td>Test Parameters</td>
<td>Diagnosis/Other</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------</td>
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<td>Pheochromocytoma</td>
<td>Catecholamines pH, HCO$_3^-$</td>
<td>Organic acids</td>
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<td>Organic acidemias (eg, propionic acidemia)</td>
<td>Ester: free carnitine ratio</td>
<td>Organic acids, ketones</td>
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<tr>
<td>Disorders of fatty acid oxidation</td>
<td>Lactate, pyruvate</td>
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<td>Mitochondrial disorders (eg, MELAS)</td>
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<tr>
<td>Urea cycle defects (eg, pOTC)</td>
<td>NH$_3$</td>
<td>δ-ALA, porphobilinogen</td>
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<td>Hypothalamic surge</td>
<td>ACTH, ADH</td>
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<td>Disorders of ketolysis</td>
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<tr>
<td>Other</td>
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<tr>
<td>Munchausen-by-proxy (ipecac)</td>
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<td>Anxiety, depression, secondary gain</td>
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<tr>
<td>Pregnancy</td>
<td>HCG</td>
<td></td>
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<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All testing below obtained during the episode, except (†) in nonfasted state.

**Abbreviations:**
- EGD, esophagogastroduodenoscopy
- UGI/SBFT, upper gastrointestinal series with small bowel follow-through
- CBC, complete blood cell count
- ESR, erythrocyte sedimentation rate
- ALT, alanine aminotransferase
- GGTP, γ-glutamyl transpeptidase
- CCK, cholecystokinin
- VMA, vanillylmandelic acid
- HVA, homovanillic acid
- UPJ, ureteropelvic junction
- UA, urinalysis
- MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like syndrome
- pOTC, partial ornithine transcarbamylase deficiency
- NH$_3$, ammonia
- δ-ALA, δ-aminolevulinic acid
- ACTH, corticotropin
- ADH, antidiuretic hormone
- HCG, human chorionic gonadotropin

(Adapted from Li BUK: Cyclic vomiting syndrome: New understanding of an old disorder. Contemp Pediatr 13:55, 1996. Used with permission. Some data from references 127, 128, 141, and 152.)
obstruction from adhesions (1), Hirschsprung enterocolitis (1), choledochal cyst (1), cholelithiasis (1), and gallbladder dyskinesia (1) (Table 6). Using the diagnostic criteria above, two of the malrotations were not found to be the cause of vomiting; they nevertheless required surgical correction. Some less serious nonsurgical disorders were identified including a few atypical presentations of peptic injuries to the upper gastrointestinal tract and irritable bowel syndrome.

Despite our hope that we could distinguish children who were more likely to have a specific underlying disorder and who deserved more extensive diagnostic testing from those with CVS, none of the 79 analyzed clinical features enabled us to do so. Because not all testing was performed in all patients, the true positive and negative predictive values of any clinical parameter could not be determined.

In our reported series of 225 children, more than 500 radiographic, endoscopic, and EEG procedures (2.4 per child) were performed in an attempt to uncover an underlying cause. We did find the following. First, the two tests with the highest yield were the endoscopy (43%), revealing mostly peptic esophagitis, and small bowel radiography (28%), demonstrating mostly gastroesophageal reflux. Second, screening metabolic, liver, and pancreatic tests were optimally performed during the episode to maximize the yield in detecting an intermittent disorder. Third, surgical disorders were best detected by small bowel radiography and abdominal ultrasound or computed tomography (CT). The appropriate trade-off between performing all exclusionary tests in all patients and the potential morbidity of a missed surgical lesion remains up to one's clinical judgment. In our experience, the empirical criteria for performing radiographic studies were severe or prolonged episodes that required repeated intravenous hydration, atypical presentations with severe headache or unilateral pain, and intractable episodes that responded poorly to medical management.

NONGASTROINTESTINAL DISORDERS
Among the most serious extraintestinal disorders found were 11 surgical lesions of the neurologic and renal systems: intracranial neoplasm (3 cases), Chiari malformation (3), nonfunctioning ventriculoperitoneal shunt (3), refractory chronic sinusitis (1), and acute hydronephrosis from ureteropelvic junction obstruction (1) (Table 6). Using the diagnostic criteria above, one Chiari malformation and one ureteropelvic junction obstruction were
not the causes of vomiting, but nevertheless required surgical correction.

Within the extraintestinal category, five serious nonsurgical disorders were discovered: two suspected mitochondrialopathies with developmental delay, multisystem involvement, and persistent lactic acidemia\(^\text{103,104}\); Addison's disease with recurrent vomiting and hyponatremia; acute intermittent porphyria presenting with recurrent attacks of abdominal pain, vomiting, and ataxia precipitated by fasting and alcohol\(^\text{132}\); and very long-chain acyl-CoA dehydrogenase deficiency coupled with the mutation for short-chain acyl-CoA dehydrogenase deficiency in one infant with recurrent bouts of hypoglycemia, lethargy, and vomiting.\(^\text{29,106-108}\) Individual cases of chronic sinusitis, asthma, nephrolithiasis, and abdominal epilepsy were also diagnosed.\(^\text{128}\)

The extraintestinal test with the highest yield was a sinus series, with 38% having air-fluid levels or mucosal thickening, followed by 20% of CTs or magnetic resonance (MR) images of the brain demonstrating either Chiari malformations or subtentorial neoplasms.\(^\text{128}\) The surgical disorders were best detected by cranial imaging and renal ultrasonography. The blood glucose, electrolytes, ammonia, and lactic acid, and urinary organic acids, carnitine, δ-aminolevulinic acid, and porphobilinogen must be performed during the episodes to maximize the chance of detecting an intermittent (eg, disorder of fatty acid oxidation) or heterozygous (eg, partial ornithine transcarbamylase deficiency) condition.\(^\text{28}\) Of those, the organic acid profile (50%), the sedimentation rate (42%), and the urine ketones (38%) had the highest positive yield.\(^\text{128}\) The typical findings included dicarboxylic aciduria related to ω-oxidation of fatty acids, a slight elevation in sedimentation rate caused by intercurrent illness, and ketosis from a fasting response, respectively. In those with abnormal organic acid profiles, with one exception of very long-chain acyl-CoA dehydrogenase deficiency, all plasma acylcarnitine and urine acylglycine profiles were normal.

Although psychological causes such as disturbed parent-child relationships,\(^\text{44,45,133,134}\) bulimia, and Munchausen-by-proxy (ipe-cac poisoning)\(^\text{135}\) have been thought to play a significant role in CVS, only four children (2%) were thought to have psychological factors including depression, secondary gain, and somatization.\(^\text{128}\)

**SUBGROUPS WITHIN CVS**

As we systematically analyzed our series of children with idiopathic CVS, it became clear that most (82%) fit into a migraine-
associated CVS group. As we looked further at the remainder (18%), we noticed clinical heterogeneity that may reflect the presence of additional subgroups. If so, subclassifying patients may enable us to sharpen our acumen to discover pathophysiologic mechanisms and detect outcomes to specific treatments by allowing us to analyze and compare specific subtypes of patients. For example, we have demonstrated the clinical utility of identifying those migraine-associated CVS patients because they are much more likely to respond to antimigraine therapy.

Those with Sato's profile of CVS characterized by vomiting, profound lethargy, hypertension, and elevated plasma ACTH and ADH levels tend to experience the most prolonged and severe episodes. In the acute episode, this group responds to parenteral nonsteroidal anti-inflammatory agents (indomethacin, ketorolac) and a combination of ondansetron and lorazepam. As a preventive strategy, neuroleptics (phenytoin) and tricyclic antidepressants (amitriptyline) have been the most effective.

A subgroup of patients characterized by developmental and growth delay, seizures, specific mitochondrial lesions (eg, retinitis pigmentosa), idiopathic multisystem disease, and persistent low-grade lactic acidemia is thought to have an underlying mitochondrial enzymopathy. In these patients, MELAS, large mitochondrial DNA deletion, and several mutations in the D-loop have been discovered. Anecdotally, these children have responded to tricyclic antidepressants.

There are several other miscellaneous subgroups. One subgroup has episodes during periods of fasting and illness, responds rapidly to intravenous glucose, and is suspected to have a disorder of fatty acid oxidation or ketolysis. On organic acid analysis, we have found some nondiagnostic dicarboxylic aciduria and remain suspicious that some patients could be heterozygotes for a disorder of fatty acid oxidation that renders them more susceptible to a comorbid disorder. Another subgroup is suspected to have gastric dysrhythmia, either a nonspecific form or one caused by diabetic gastroparesis or Riley-Day familial dysautonomia. Although low-dose erythromycin has been effective in the nonspecific form, those patients with acquired or congenital dysmotilities do not respond well to prokinetic drugs. Another subgroup has stable and predictable cyclic episodes that may ultimately be found to have a chronobiologic trigger that differs from those initiated by stress. Among patients in this group are postmenarchal girls who have catamenial CVS that responds to low-dose estrogen birth control pills.
CLINICAL PATHWAY
It is obvious what tests should be performed to exclude specific diagnoses; however, it is not clear how many tests should be performed in each patient (Table 6). Although to perform all tests in all children with the cyclic vomiting pattern is clearly not cost-effective, at stake is the possibility of missing serious, underlying correctable surgical and treatable nonsurgical disorders. Unfortunately there are insufficient data to answer the question definitively.

We compared the cost of two primary strategies: (1) performing all exclusionary testing first and then treating those with negative tests with antimigraine prophylaxis, or (2) administering empirical antimigraine treatment first with or without a small bowel radiograph to exclude malrotation.137 We calculated the costs of prophylactic antimigraine therapy, extensive diagnostic testing and, in the case of a child with missed malrotation with volvulus and significant small bowel resection, lifelong parenteral nutrition. The most cost-effective strategy was to use prophylactic antimigraine therapy and to perform small bowel radiography; if no therapeutic response occurred in 2 months, the patient should undergo systematic testing. Although this clinical pathway has to be studied, it suggests that extensive testing at diagnosis may not be necessary.

If the 2-month therapeutic trial fails, what constitutes appropriate diagnostic testing? Our first stage of testing includes metabolic screening during the next episode, esophagastroduodenoscopy, and sinus films. If that fails to reveal any potential cause, our second stage of testing includes an ultrasound of the kidney, gallbladder, and pancreas, and a head CT or MRI.

HERAPEUTIC ADVENTURES
Because the pathophysiology is still unknown, the treatment of CVS remains empirical.55,138,139 Although treatment to date has been a series of adventures, the use of both established and newer antimigraine and antiemetic agents have been increasingly successful. There are five management strategies to use for the child or adult with CVS: avoidance of triggers, prophylactic pharmacologic therapy, supportive care during the episode, abortive pharmacologic therapy, and general family support.

AVOIDANCE OF TRIGGERING EVENTS
In some instances, avoidance of precipitating events such as dietary chocolate or cheese can prevent episodes without the use
of prophylactic medication.\textsuperscript{55,138} In cases in which psychological stresses initiate episodes, acute stress management techniques or benzodiazepine anxiolytics (lorazepam or diazepam) can occasionally prevent the expected attack. Because stress is a well-documented trigger, it may be that both approaches can attenuate the afferent stress signal or the efferent autonomic response. In most situations, the avoidance of the trigger is impossible (eg, infections, car ride).

**PROPHYLACTIC PHARMACOLOGIC THERAPY**

Pharmacologic therapy includes prophylactic agents taken daily to prevent future episodes (Table 7).\textsuperscript{55,139} Most of these agents have been borrowed from medications used to treat other disorders, including migraines (antimigraines), epilepsy (neuroleptics), and gastrointestinal dysmotility (prokinetics).\textsuperscript{140} To justify the effort of taking daily medication, we select prophylactic therapy when the episodes occur more frequently than once a month or when the episodes are particularly severe and disabling (eg, episodes last 3-7 days).\textsuperscript{1,141} Particularly in patients with a family history of migraine, it is logical to begin with antimigraine prophylaxis. Defining efficacy as a greater than 50% decrease in number of episodes or episode severity (duration or emeses), we found antimigraine medications to be effective, including low-dose propranolol (57%), cyproheptadine (39%), and amitriptyline (67%), in our open experience.\textsuperscript{52,56,70} From the vantage point of fewest side effects, we typically begin with either propranolol or cyproheptadine. Pizotifen is a widely used medication in the United Kingdom and Australia that is similar to cyproheptadine, albeit with fewer side effects.\textsuperscript{142} We have generally used neuroleptic agents in those patients with epileptiform changes on EEG. However, phenobarbital had a 79% success rate in an open trial, and there are also anecdotes of success with carbamazepine and valproic acid.\textsuperscript{143} The use of erythromycin, a motilin agonist that promotes gastric motility, would be ideal when an underlying dysmotility is suspected. Erythromycin has been used in an open trial with approximately a 75% success rate.\textsuperscript{125}

**SUPPORTIVE CARE DURING THE EPISODE**

Supportive care includes intravenous fluids, management of abdominal pain, and relief from nausea. In our experience, intravenous administration of glucose and electrolytes alone has a 42% efficacy. Because a bolus of intravenous glucose without additional fluids can ameliorate episodes possibly by terminating the keto-
**TABLE 7.** Pharmacologic Approaches to CVS

<table>
<thead>
<tr>
<th>Medication, Route, Dose</th>
<th>Goal (Mechanism)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supportive measures</strong></td>
<td></td>
</tr>
<tr>
<td>D5/.45 NS + KCl or D10 W IV</td>
<td>Treat dehydration, Addison’s, disorders of fatty acid oxidation</td>
</tr>
<tr>
<td>Demerol IV or IM 1-2 mg/kg q4-6h</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Lorazepam IV 0.05-0.1 mg/kg q6h</td>
<td>Sedation, anti-anxiety, antiemetic</td>
</tr>
<tr>
<td>Diphenhydramine IV 1.25 mg/kg q6h</td>
<td>Sedation, antiemetic</td>
</tr>
<tr>
<td><strong>Abortive therapy (if &lt; 1 episode/mo at onset of episode)</strong></td>
<td></td>
</tr>
<tr>
<td>Ondansetron IV 0.3-0.4 mg/kg</td>
<td>Antiemetic (5-HT₃ antagonist)</td>
</tr>
<tr>
<td>Granisetron IV 10 µg/kg q4-6h</td>
<td>Antiemetic (5-HT₃ antagonist)</td>
</tr>
<tr>
<td>Ketorolac IV 0.5-1.0 mg/kg q6-8h</td>
<td>Antimigraine (NSAID)</td>
</tr>
<tr>
<td>Sumatriptan PO 25 mg (≥40 kg)</td>
<td>Antimigraine (5-HT₁D agonist)</td>
</tr>
<tr>
<td>Sumatriptan nasal 20 mg (≥40 kg)</td>
<td>Antimigraine (5-HT₁D agonist)</td>
</tr>
<tr>
<td>Ondansetron PO 4-8 mg qid</td>
<td>Antiemetic</td>
</tr>
<tr>
<td>Midrin PO q1h ≤ 5 doses/12 hours</td>
<td>Antimigraine</td>
</tr>
<tr>
<td><strong>Prophylactic therapies (if &gt; 1 episode/4 wk given orally daily)</strong></td>
<td></td>
</tr>
<tr>
<td>Propranolol 10 mg bid-qid</td>
<td>Antimigraine</td>
</tr>
<tr>
<td>Cyproheptadine 0.3 mg/kg/d divided q6-8h</td>
<td>Antimigraine</td>
</tr>
<tr>
<td>Amitriptyline 25-50 mg/d</td>
<td>Antimigraine</td>
</tr>
<tr>
<td>Loestrin 1.5/30</td>
<td>Antimigraine, antiepileptic</td>
</tr>
<tr>
<td>Phenobarbital 2-3 mg/kg/d divided qd-bid</td>
<td>Antimigraine, antiepileptic</td>
</tr>
<tr>
<td>Carbamazepine 5-10 mg/kg/d divided bid</td>
<td>Antimigraine, antiepileptic</td>
</tr>
<tr>
<td>Erythromycin 20 mg/kg/d divided bid-qid</td>
<td>Prokinetic</td>
</tr>
<tr>
<td>Cisapride 0.2-0.3 mg/kg/dose qid</td>
<td>Prokinetic</td>
</tr>
</tbody>
</table>

**Abbreviations**: 5-HT₃, 5-hydroxytryptamine₃; NSAID, nonsteroidal anti-inflammatory drug. (Data from references 55, 56, 70, 125, 138, 139, 143-145, 150, and 151.)

sis, glucose may be the key ingredient. Narcotic analgesics are used when more directed abortive approaches fail to attenuate the pain. Diphenhydramine, lorazepam (γ-aminobutyric acid inhibitor), and chlorpromazine can be used to sedate the child to allow rest and provide adjunctive antiemetic effect and relief from...
intractable nausea. In our and others’ experience, the use of diphenhydramine or lorazepam in conjunction with ondansetron (5-hydroxytryptamine$_3$ [5-HT$_3$] antagonist) appears to be more effective than the use of ondansetron alone in the most severe episodes (Table 7).

**ABORTIVE PHARMACOLOGIC THERAPY**

Among abortive medications taken at the onset of an attack to stop its progression, antiemetic and antimigraine agents have been used. We use the abortive approach when the child breaks through prophylactic therapy or when the episodes occur sporadically or less often than once per month. In general, these agents have to be administered parenterally because the intractable emesis precludes the use of oral medications. Using the criteria of a positive response signifying a greater than 50% reduction in number of emeses or duration of episode, intravenous ondansetron has a 62% efficacy in our open experience. Ondansetron has a wide safety window up to 0.3 to 0.4 mg/kg per dose. Although not commercially available, ondansetron is available in an orally dissolving sublingual form and has been reconstituted as a suppository by individual pharmacies. In especially severe cases, a constant infusion has provided greater relief than ondansetron administered every 6 hours. In contrast, phenothiazines ($D_2$ antagonists) have shown a low efficacy rate of 22%, suggesting that the mechanism of emesis in CVS may differ from that found in other common forms of emesis.

Sumatriptan, a 5-HT$_{1D/1A}$ agonist, has a 51% efficacy rate in our open label experience when administered as abortive strategy by subcutaneous injection, orally, or intranasally. Unfortunately, no pharmacokinetic studies have been performed to guide dosing in children. We favor the oral form during the prodrome and nasal form at onset of vomiting because of the unpleasant burning sensation in the chest and neck commonly experienced with the subcutaneous route. Other triptans are now available including zolmitriptan, naratriptan, and rizatriptan, although none have been tried extensively in CVS.

One major caveat in interpreting all the drug studies conducted to date is the occurrence of a striking placebo effect. Consultation alone without initiation of therapy has reduced the frequency of episodes in 70% of the patients. We have seen a similar effect in our own ongoing randomized, double-blind, crossover trial of ondansetron in which enrollment alone caused a nearly 10-fold reduction in frequency of episodes from the previous year. Because all the above trials cited were uncontrolled and mostly
retrospective in design, they must be cautiously interpreted. Future therapeutic trials should be rigorously designed.

Because the pathophysiology is unknown, the response to various classes of medication has given us a glimmer of insight. Although amitriptyline has 5-HT\textsubscript{2} receptor antagonist activity, its numerous pharmacologic actions preclude any firm conclusions on specific site of action. However, the triptan agents acting as 5-HT\textsubscript{1D} agonists on cerebral vasculature provide one known locus of action. That only 62\% of patients respond suggests that there could be other mechanisms or pathways. 5-HT\textsubscript{3} antagonists acting at the chemotriguer zone near the area postrema provide a second locus. Despite their presumed central sites of action, both 5-HT\textsubscript{1D} and 5-HT\textsubscript{3} agents appear to act peripherally to regulate gastric atony and efferent feedback to the brain, respectively.\textsuperscript{153,154}

Exciting new classes of agents other than serotonergic ones are on the horizon.\textsuperscript{155} Tackkykinin (NK\textsubscript{1}) receptor antagonists are now in phase II trials in adults with chemotherapy-induced emesis.\textsuperscript{156} Based on animal studies, these new agents are potentially more potent than the 5-HT\textsubscript{3} antagonists. CRF-R1 antagonists could theoretically prevent the vomiting by attenuating the stress response near its origin.

**FAMILY SUPPORT**

There is a high level of frustration in having an unpredictable, disruptive, unexplained illness that is often misdiagnosed, and for which few definitive answers exist. Family support is clearly needed. More often, the CVSA provides such support for the family by phone, e-mail, electronic bulletin board, website, literature, and newsletter.

- Mail address: Cyclic Vomiting Syndrome Association
  Ms Debra Waites, Administrator
  3585 Cedar Hill Rd, NW
  Canal Winchester, Ohio 43110
- Phone: 614-837-2586
- Website: http://www.breaker.iupui.edu/cvsa1
- Listserv: majordomo@jatek.net

Occasionally, the family dynamics are so disrupted that individual and family psychotherapy may be needed.\textsuperscript{45,133,134}

**FUTURE DIRECTIONS**

The potential for definitive understanding of CVS looks bright. The recently established CVSA has made great strides in advo-
eating for better recognition and proper diagnosis of the disorder by physicians. Stimulated by two scientific symposia, a growing number of clinical and basic scientists have joined interdisciplinary forces to solve this clinical mystery. The CVSA's support of individual research and collaborative investigative efforts into the pathogenesis and treatment of CVS will provide further insights.

New insights are likely to arise from several types of investigations. The continued input from clinicians that are subgrouping CVS patients and determining therapeutic outcomes will enable evidence-based approaches to treatment. Ongoing laboratory investigations into the inborn defects (eg, mitochondrial DNA, ion channel defects) and pathophysiologic cascade (eg, CRF) will provide greater understanding of molecular defects and brain-gut interactions involved. As more specific analogues become available for use in animals and humans, it is likely that more effective therapeutic agents will be forthcoming and will further delineate the vomiting pathways. As understanding of the role of ion channelopathies is gained, specific channel stabilizers may become useful. However as has been observed in migraine headaches, the agent with greater receptor specificity may not be the most clinically effective agent, as is the case of amitriptyline compared with the newer tricyclic antidepressants.

It is hoped that these collaborative (patient and physician) and interdisciplinary (clinical and basic scientists with various brain-gut expertise) efforts will lead to a definitive understanding of the mechanisms and treatments of CVS in the first decade of the new millennium.

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