

Diagnosing Darwin

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Darwin's Rooms, Christ's College, University of Cambridge, Cambridge, UK
Credit: Michael D. Barton.

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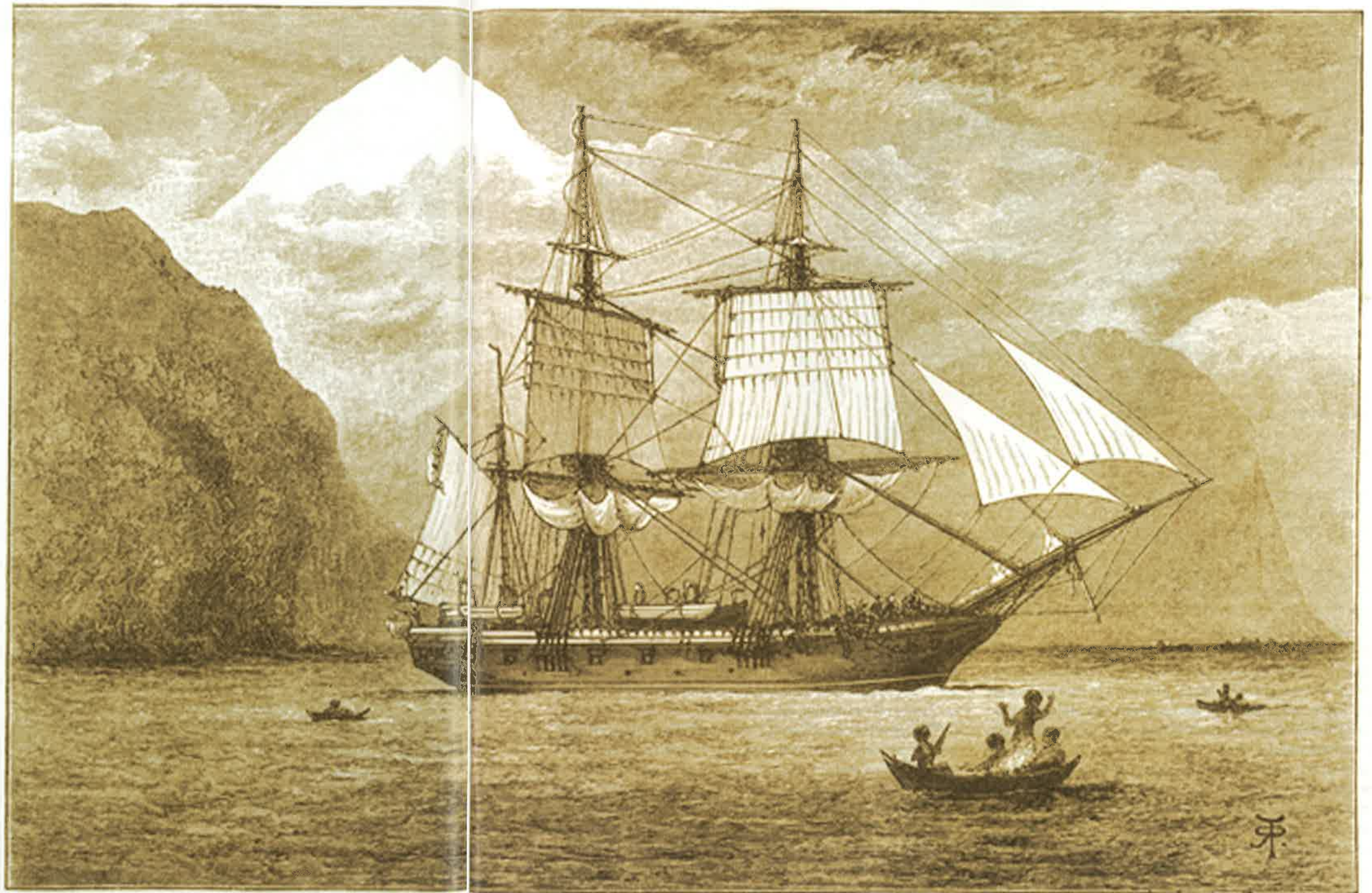
Charles Darwin (1809–1882) was a virtual invalid for most of his adult life. Until he developed evidence of cardiac dysfunction in his eighth decade, the doctors who cared for him could find no physical explanation for his chronic complaints and disagreed as to his diagnosis. Since that time, many have pondered the nature of Darwin's mysterious illnesses and proposed additional diagnoses to an ever-expanding list based on varying interpretations of the detailed description of Darwin's signs and symptoms that he obsessively recorded in his diaries and letters. Because of the absence of diagnostic laboratory test results, none has been accepted as definitive.

Suppose Darwin were alive today and could be subjected to a modern diagnostic evaluation? What would it consist of? What would it conclude? And what is the likelihood that it would lead to a treatment regimen more effective than those applied by his physicians over a century ago?

Darwin's illnesses¹

Except for an upset stomach (mainly during breakfast) in his teens and brief eruptions (of unknown character) of his mouth and hands in his early twenties, Darwin enjoyed excellent health as a youth. During his five-year voyage on the *HMS Beagle*, from ages twenty-two through twenty-seven, he was frequently seasick, had several self-limited fevers, two instances of food poisoning, an inflamed knee and arm, intermittent boils, heat stroke, and a bout of "Chilean illness."^{1p13} Approximately a year after his return, he had a brief episode of palpitations but otherwise was healthy for eighteen months, when an attack of "gastric flatus" heralded the onset of a violent abdominal disorder that would plague him for the next three decades.^{1pp14–15} The disorder consisted of repeated, sudden attacks of abdominal pain, nausea, vomiting, and retching, typically occurring three hours after breakfast and most frequent and severe during times of emotional stress.^{1p30}

Assassin bug.
Sindair Stammers /
Science Source.



H.M.S. BEAGLE IN STRAITS OF MAGELLAN. MT. SARMIENTO IN THE DISTANCE.

Frontispiece.

Courtesy of the National Library of Medicine



Courtesy of the National Library of Medicine

During the worst periods, which lasted for years on end, he vomited after nearly every meal. Many of his friends thought him a hypochondriac. Because he seldom regurgitated food, “only acid & morbid secretion,”^{1p77} his vomiting did not interfere with his intake or digestion of food, his general nutritional status, or his professional productivity. His bowel movements were normal.^{1p22}

He was seen by over a score of England’s most prominent physicians for these complaints.^{1p279} Their diagnoses included hypochondriasis, excess gastric acid, suppressed gout, hyperventilation, allergies, and a complication of Chilean fever. To this list, the many physicians who since his death have pondered the cause of his invalidism have added the following diagnoses: Chagas disease, neurasthenia, a refractory anomaly of the eyes, mental overwork, schizophrenia, depressive psychosis, chronic appendicitis, a peptic ulcer, chronic cholecystitis, smoldering hepatitis, a diaphragmatic hernia, narcolepsy, hyper-insulinism, arsenicosis, lead poisoning, lactose

intolerance, Crohn’s disease, panic disorder with agoraphobia, repressed anger toward his father, systemic lupus erythematosus, and cyclic vomiting syndrome.¹⁻⁶

Darwin received a host of treatments for his gastric distress, which included small doses of arsenic, calomel, sugar-free diet, Indian ale, bismuth, hydrotherapy, Croton (an extract of flowering plants in the spurge family), mineral acids (a mixture of muriatic and nitric acids), aloes, lemons, a hydroelectric chain, pepsin, Condry’s ozinised water (potassium permanganate solution), magnesium carbonate of ammonia, phosphate of iron, ice therapy, strychnine, and codeine. Only Dr. Gully’s cold water cure (immersion in cold water) seemed to provide temporary relief of his gastric distress.^{1p279-280}

Whereas Darwin’s gastric dysfunction was his most distressing complaint, he had many others following his years abroad. These included insomnia, intermittent palpitations and headaches, episodes of numbness of the fingertips, a buzzing noise in the head, stars in the eyes, giddiness and

trembling hands (in his thirties), and weakness and a “touch of pleurisy” (at age fifty-one).^{1p68} He had unspecified trouble with his teeth beginning in his third decade, perhaps related to his recurrent vomiting. During his fifth and sixth decades, he wept a great deal while suffering with intermittent “rheumatism” and “lumbago,”^{1pp54,77,110,136} and also “boils and eczema” of the face and hands.^{1pp31,47,51,71} Interestingly, during his fits of rheumatism and eczema his gastric symptoms diminished.^{1pp74,77,81}

Darwin’s mother died suddenly of an unknown disorder when he was eight years old. His father, who lived to the age of eighty-two, was morbidly obese and, like his own father and grandfather, suffered with gout. An older brother struggled with depression before dying at age seventy-seven of unknown cause. Three sisters died at ages fifty-six, sixty-three, and eighty-eight of unknown causes.^{1p119} A paternal great-grandfather and grandmother were alcoholic. A maternal uncle and a paternal half-cousin had digestive problems of unknown character or etiology.

Darwin’s wife, a first cousin, was deeply religious, whereas he was not; some have speculated that this difference might have had a role in the origin of his invalidism. They had ten children (seven male and three female). Three died young. Five developed hypochondriacal concerns about their health, possibly prompted by their father’s expressed conviction that his own disorder was hereditary. Four had fluctuating digestive troubles less severe than their father’s,^{1pp120-121} and several exhibited a “tendency for irregular pulses,” possibly precipitated by repeated examinations by their father.^{1p64}

Darwin was six feet tall and lean as a youth, with a light complexion and reddish-brown hair that receded rapidly after puberty. He was addicted to snuff, which he used several times a day from age eighteen. He drank brandy, wine, and port in moderation. Walking was his only exercise.

During his final decade, Darwin’s physical health improved markedly, with absence of “serious exacerbations of vomiting.”^{1p90} However, by his seventh decade, his memory was beginning to fail. He began to complain of constant attacks of “swimming of the head” and “some pain in the heart.”^{1pp90,93} While rock climbing at the age of seventy-two, he experienced a sudden “fit of dazzling.” The precise character of the fit is uncertain but likely involved “giddiness and an irregular pulse,” in that he reported these three months later.^{1p93} He then developed a cough, which quinine seemed to alleviate. Shortly thereafter, he developed pre-cordial pain, giddiness, exhaustion, and insomnia. Amyl nitrate provided little relief. Sitting at dinner one evening, he was seized with giddiness and fainted while trying to reach a sofa. Within minutes he regained consciousness, drank some brandy and seemed to recover. He then became nauseated and began vomiting and retching violently. This lasted until the next day, when he again lost consciousness and died. He was seventy-three years and two months old. The cause of death was listed as “angina

attacks with heart failure and degeneration of the heart and greater blood vessels.”^{1pp94-96}

Of the myriad diagnoses offered over the years to explain Darwin’s long suffering, given the nature of his complaints, we believe only three merit serious consideration: cyclic vomiting syndrome, hypochondriasis, and Chagas disease.

Cyclic vomiting syndrome^{7,8}

Cyclic vomiting syndrome is a little-known, yet surprisingly common and disabling disorder characterized by recurrent episodes of nausea, vomiting, and abdominal pain separated by asymptomatic intervals. Migraine headaches are common (and are often found in family members), as are cardiac arrhythmias and other manifestations of dysautonomia (as for example, Darwin’s palpitations, numbness of his fingertips and nervous tics). The intense anxiety precipitated by uncontrollable episodes of emesis occasionally induces behavior mimicking an affective or anxiety disorder (two of the many psychiatric disorders attributed to Darwin) or an endocrine disorder, such as hypothyroidism or hypoglycemia.

The syndrome is in essence a diagnosis of exclusion, in which standard diagnostic tests for recurrent vomiting are uniformly negative. Many patients, however, exhibit evidence of mitochondrial dysfunction on examination of body fluid metabolites and muscle biopsy, at least some of whom are shown to possess a mitochondrial gene mutation designated A3243G. Considerable evidence supports a matrilineal pattern of inheritance of the disorder, in which case Darwin likely inherited it from his mother, a Wedgewood, and his children from their mother, also a Wedgewood.

Although commonly presenting during the preschool to early school age years, cyclic vomiting syndrome can begin any time from infancy to adulthood, with reported ages of onset ranging from two to forty-nine years. Darwin’s episodes of vomiting began in his teens, when he had an upset stomach mainly after breakfast. In adult patients, episodes are typically stereotypical (i.e., similar in duration and character from one episode to the next) over months to years, with attacks most often arising between midnight and noon. In men, vomiting is commonly triggered by noxious stress, pleasant excitement, and infections, whereas in women, triggers include menstruation, noxious stress, pleasant excitement, and fatigue. In Darwin’s case, episodes of vomiting were frequently triggered by noxious stress and pleasant excitement, but were alleviated by his skin eruptions.

The differential diagnosis for cyclic vomiting syndrome is broad. In addition to the alternative diagnoses mentioned above, many others are pursued in the diagnostic evaluation of these patients. In the state of Maryland today, the Hospital Services Cost Review Commission (HSCRC)/Medicare-approved charges for the studies listed in the accompanying table would total \$11,220 if performed only once, and would not include professional fees paid to a primary care provider

Diagnostic Evaluations of Patients with Cyclic Vomiting Syndrome ^{7,8}		
Alternative Diagnosis (Subspecialty Consultation Obtained)	Diagnostic Tests	Potential Harm
Esophageal reflux (gastroenterology)	EGD, UGI, PPI trial	Bleeding, cardiopulmonary complications of sedation, bowel perforation, aspiration
Gastritis/peptic ulcer disease/acholasia (gastroenterology)	EGD (with biopsy), antibody assay and/or stool antigen or breath test for <i>H. pylori</i>	Bleeding, cardiopulmonary complications of sedation, bowel perforation, aspiration
Pancreatitis (gastroenterology)	Seum amylase and lipase, endoscopic ultrasound	Bleeding, cardiopulmonary complications of sedation, bowel perforation, aspiration
Gall bladder disease (gastroenterology, general surgery)	Abdominal ultrasound, endoscopic retrograde cholangio-pancreatography	Bleeding, cardiopulmonary complications of sedation, bowel perforation, aspiration, pancreatitis
Partial bowel obstruction (gastroenterology, general surgery)	UGI (with small bowel follow through), colonoscopy, abdominal CT scan (with contrast)	Bowel perforation, bleeding, radiation exposure, contrast-induced ARF
Pyelonephritis (infectious diseases)	Urinalysis, urine culture and sensitivity	None
Appendicitis (gastroenterology, general surgery)	CBC, abdominal CT scan (with contrast)	Radiation exposure, contrast-induced ARF
Delayed gastric emptying (gastroenterology)	Radionuclide gastric emptying study	Radiation exposure
Porphyria (endocrinology)	Urine porphyrins	None
Plumbism (hematology, nephrology)	Whole blood lead concentration	None
Abdominal epilepsy/migraine (neurology)	EEG, head CT (with contrast), and MRI (with gadolinium, anti-migraine drug trial)	Radiation exposure, contrast-induced ARF, gadolinium-induced nephrogenic sclerosis
Crohn's disease (gastroenterology)	EGD, abdominal CT (with contrast), colonoscopy, capsule endoscopy	Bleeding, bowel perforation, radiation exposure
Systemic lupus erythematosus (rheumatology)	Assays for antinuclear, anti-double-stranded DNA and anti-Sm nuclear antigen antibodies	None
Psychiatric disorder (psychiatry)	EEG, head CT (with contrast), and MRI/MRA (with gadolinium)	Radiation exposure, contrast-induced ARF, gadolinium-induced nephrogenic sclerosis
Chagas disease (infectious diseases)	<i>T. cruzi</i> antibody assay	None

Abbreviations: EGD = esophago-gastric duodenoscopy, UGI = upper gastrointestinal barium study, PPI = proton pump inhibitor, CBC = complete blood count, CT = computed tomography, MRI = magnetic resonance imaging, MRA = magnetic resonance angiography, EEG = electroencephalogram, ARF = acute renal failure.

or subspecialty consultants, or charges associated with emergency room visits or hospitalizations.

In many adult patients, prolonged showers or baths lessen the intensity of attacks. However, in contrast to Darwin's hydrotherapy, which afforded him temporary relief, most current patients report benefit from exposure to hot rather than cold water. Although no experimentally validated treatment for the disorder has been established, many are prescribed in an effort to relieve the suffering of these patients. They include intravenous hydration, anti-migraine drugs (e.g., amitriptyline, propanolol, cyproheptadine), anxiolytics/antiemetics (e.g., ondansetron, lorazepam, alprazolam), analgesics (e.g., ibuprofen, oxycodone), and H₂ blockers and proton pump inhibitors. Emergency room visits are frequent, hospital admissions less so. Many patients undergo cholecystectomies to no avail; a few are subjected needlessly to appendectomies, exploratory

laparotomy, pyloroplasty, gastrostomy and jejunostomy, and fundoplication.

One can only guess how many of these tests and treatments Darwin would receive if he were a patient today. Given the severity of his gastric disorder and his obsession with it, it is likely that he would be subjected to most, if not all. Although his episodes of vomiting lasted substantially longer than those delineated in the Rome III diagnostic criteria for cyclic vomiting syndrome,⁹ we believe the preponderance of evidence contained in his medical history is more consistent with the syndrome than any other diagnosis yet proposed for his "gastric flatus." If this, in fact, were his problem, none of the tests and treatments listed above would either diagnose or cure his ailment.

Hypochondriasis¹⁰

Hypochondriasis is classified under the somatization disorders in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).¹¹ It is characterized by an obsessive irrational fear of having a serious medical condition despite the failure of a comprehensive medical evaluation to identify any such condition. Although the belief is not of delusional intensity, attempts at reassurance fail to alleviate the patient's fear.

Unlike Darwin, patients suffering with hypochondriasis typically are reluctant to acknowledge the role of psychological factors in causing their symptoms, misinterpret benign physical sensations as evidence of serious illness, tend to respond to reassurance with anger rather than relief, and frequently are functionally severely impaired by the disorder. Darwin, in fact, recognized the role of anxiety caused by his revolutionary concepts in precipitating his gastric distress, had physical sensations that were hardly benign, was a compliant and grateful patient, and in spite of his symptoms continued to

DSM-IV Diagnostic Criteria for 300.7 Hypochondriasis ¹¹	
A.	Preoccupation with fears of having, or the idea that one has, a serious disease based on the person's misinterpretation of bodily symptoms.
B.	The preoccupation persists despite appropriate medical evaluation and reassurance.
C.	The belief in Criterion A is not of delusional intensity (as in Delusional Disorder, Somatic Type) and is not restricted to a circumscribed concern about appearance (as in Body Dysmorphic Disorder).
D.	The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E.	The duration of the disturbance is at least 6 months.
F.	The preoccupation is not better accounted for by Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Panic Disorder, a Major Depressive Episode, Separation Anxiety, or another Somatoform Disorder.

function effectively as husband, father, friend, colleague, and scientist.^{1pp19,52,71,72}

Like patients with cyclic vomiting syndrome, those with hypochondriasis have high rates of visits to physicians, subspecialty consultations, laboratory tests, and surgical procedures, all of which lead to high health care costs. Despite such intense medical attention, their symptoms generally remain unabated. Although cognitive, pharmacologic, and several other therapies have been recommended for the disorder, proof of clinical efficacy has yet to be demonstrated for any of these treatments.

Chagas disease¹²

In October 1959, Professor Saul Adler, a world-renowned

parasitologist, proposed Chagas disease as the cause of Darwin's prolonged gastric distress, citing a previously unnoticed passage in the *Beagle* narrative, in which Darwin describes being bitten by "the great black bug of the Pampas," the principal vector for the infection.^{2p113} For years this theory dominated thinking as to the etiology of Darwin's "gastric flatus," but has since fallen into disfavor.¹³ We believe that Darwin might have suffered with Chagas disease but, if so, in the form of a cardiomyopathy rather than one of the digestive mega syndromes proposed. Chagas disease, we believe, might explain his terminal cardiac dysfunction, perhaps also his gastric disorder, but only indirectly, by predisposing him to infection with *H. pylori* (see below).

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi*.¹² The microbe is transmitted to humans and many other animals mainly by blood-sucking bugs belonging to the subfamily Triatominae, of which only a small number are competent vectors.

In March of 1835, Darwin was bitten by one such bug (a great black "Benchuca" bug)² while residing in the Pampas of Argentina. More than likely he was bitten repeatedly by such bugs during his excursions in both Argentina and Chile, and might well have been infected by *T. cruzi* in the process.²

Recent surveys, however, indicate that only a small percentage of people at risk of *T. cruzi* infection (i.e., those exposed to Benchucas harboring the parasite) are actually infected (17.4 percent), and of those infected, less than half develop clinically apparent disease.¹² The acute phase of symptomatic infections lasts four to six weeks and is characterized by prolonged fever, malaise, hepatosplenomegaly, lymphadenopathy, and occasionally cardiac arrhythmias. Darwin had an attack of "Chilean fever" in 1834 that lasted from September to November and could have been a bout of acute Chagas disease.

The chronic phase of the disease usually does not manifest clinically until ten to thirty years after the initial infection. The digestive form, which develops in only ten to fifteen percent of chronically infected patients, consists of mega-esophagus, mega-colon, or both. Darwin never exhibited signs or symptoms of either. The cardiac form of the disease, the most serious and frequent manifestation of chronic Chagas disease, develops in twenty to thirty percent of chronically infected patients. It typically produces abnormalities of the cardiac conduction system, as well as bradyarrhythmias, tachyarrhythmias, apical aneurysms, cardiac failure, thromboembolism, and sudden death.¹² Thus, Chagas cardiomyopathy might have been the cause of Darwin's terminal cardiac dysfunction and death. However, given his age at the time his heart began to fail, his failing memory, and the infrequency with which persons exposed to Benchuca bugs develop the chronic form of the disease, it is more likely that he died of atherosclerosis of his heart and his brain. In the chronic phase, Chagas disease is diagnosed by demonstrating the presence of IgG antibodies against *T. cruzi*. If alive today, Darwin would certainly be tested for these and more than

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likely also have his cardiac and cerebral symptoms extensively evaluated with an EKG, holter monitor, stress test and cardiac catheterization, along with a CT scan and MRI of his head.

Although benznidazole and nifurtimox are effective against acute Chagas disease, they are not recommended for patients with advanced cardiac disease. Cardiac symptoms are managed with amiodarone, a cardiac pacemaker and implantable defibrillator, and diuretics and beta blockers, even though their efficacy has not been confirmed in clinical trials.¹² Today, Darwin, no doubt, would be given many, if not most, of these in managing his cardiac symptoms.

For reasons yet to be determined, patients with Chagas disease are prone to infection with *H. pylori*,¹⁴ which in its acute phase is associated with vomiting, abdominal pain, and weight loss. During the chronic phase of such infections, a small minority of patients develop gastritis, peptic ulcer disease, gastric cancer, or lymphoma. Dr. Barry Marshall, the co-discoverer of *H. pylori*'s role in peptic ulcer disease, believes that Darwin's gastric distress was caused by the bacterium.¹⁵ If so, Darwin's particular disorder more likely would have been a peculiarly persistent form of *H. pylori*-induced chronic gastritis (i.e., non-ulcer dyspepsia) than a peptic ulcer, gastric cancer, or lymphoma. Unfortunately, current treatments have little if any effect on the course of such dyspepsia.¹⁶

Conclusion

According to a descendent of the great man, in Darwin's home, "it was a distinction and a mournful pleasure to be ill."^{17p543} Darwin might have been a hypochondriac, as implied by this statement, and today would be seen by a psychiatrist in consultation and also subjected to psychological testing. However, we believe he also suffered with cyclic vomiting syndrome, which although severe, never seriously interfered with his scientific productivity and resolved spontaneously in his seventies. We also believe that he died of atherosclerotic cardiovascular disease. Although his physicians, some of the finest Britain had to offer at that time, could find no physical abnormality to explain his gastric symptoms, they had only Darwin's history and physical examination to guide them in their evaluations.

If Darwin were alive today, no doubt a wide array of sophisticated laboratory examinations would be added to his work up. We believe those directed at his "gastric flatus" would be uniformly negative and point to cyclic vomiting syndrome as a diagnosis of exclusion. We suspect that those directed at his terminal cardiac dysfunction would reveal advanced atherosclerosis of both his heart and his brain. Though a host of treatments would be given, we doubt that any would prove more than marginally better in relieving his suffering or extending his life than those administered by his own physicians.

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