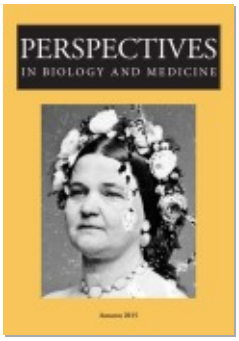
"What an Affliction": Mary Todd Lincoln's Fatal Pernicious Anemia



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Mary Todd Lincoln's fatal pernicious anemia

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ABSTRACT To date, no single diagnosis has unified the psychiatric illness and the numerous poorly defined physical complaints that Mary Lincoln (née Todd, 1818–1882) suffered in adulthood. Here, I show that her physical ailments spanned 30 years and included sore mouth, pallor, paresthesias, the Lhermitte symptom, fever, headaches, fatigue, resting tachycardia, edema, episodic weight loss, progressive weakness, ataxia, and visual impairment. Long thought hypochondriacal, these findings, plus their time course and her psychopathology (irritability, delusions, hallucinations, with preserved clarity), are all consistent with vitamin B12 deficiency. Pernicious anemia most probably caused this deficiency: she lacked risk factors for other causes, and her consanguineous parents both derived from a region of Scotland having a high incidence of pernicious anemia. A diagnosis of chronic multisystem pernicious anemia would clarify the conduct of Mary Lincoln as First Lady and widow, and illuminate challenges faced by her husband, President Abraham Lincoln. Her case highlights many forgotten features of the natural history of untreated pernicious anemia and is unique in the medical literature in demonstrating such a course extending over a lifetime.

From 1861 to 1865, Mary Lincoln (1818–1882) was First Lady of the United States. Intelligent, educated, astute, and ambitious when young, for 17

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years after the shattering murder of her husband (President Abraham Lincoln) she was socially isolated, mentally unstable, and, according to family, physicians, and newspapers, hypochondriacal. Except for suspicions of neurosyphilis, diabetic pseudo-tabes, and migraine, modern scholars disregard her physical complaints, offering only psychiatric diagnoses of either idiopathic or menstrual origin (Brussel 1941; Brust 2012; Burlingame 2008; Hirschhorn and Feldman 1999; Suarez 1966; Vidal 1993). Yet, her personal physician said, "While the whole world was finding fault with her temper and disposition, it was clear to me that the trouble was a cerebral disease" (Wilson and Davis 1998, 671).

The present study attempts to apply a single diagnosis to her entire illness, defined as her serious mental derangements, her major somatic complaints, and her death (at age 63). Not only has such a unifying diagnosis never been proposed, it has been considered infeasible (Hirschhorn and Feldman 1999), demanding instead a plurality of diagnoses to account for the totality of Mary's illness. However, were a single encompassing diagnosis found, it would, according to Occam's razor, be the preferred one (Jefferys and Berger 1992).[1]

The proposed diagnosis, pernicious anemia (PA), is a syndrome of vitamin B12 deficiency. It causes glossitis, anemia, pigmentary changes, edema, fever, and multiple neuropsychiatric abnormalities, including affective disorders, thought disorders, paresthesias, ataxia, muscular weakness, urinary dysfunction, and optic neuropathy—all of which Mary Lincoln developed, in a time sequence consistent with the typical natural history of untreated PA.

Because the natural history of PA changed markedly after Minot and Murphy introduced their Nobel Prize–winning dietary liver treatment in 1926 (Davidson 1957), physicians today have little familiarity with the untreated, inevitably fatal syndrome seen in Mary's time. Indeed, PA as it presents today could easily be considered a different disease from the classic "florid" form seen in the 1800s, and so has limited relevance in understanding her course. Thus, the present article devotes considerable space to describing the clinical features of the all-but-extinct "PA Victoriana" subtype of pernicious anemia, and largely ignores the much attenuated "PA Moderna" subtype. (Unless specifically noted, "PA" in text indicates PA Victoriana.)

To tell the decades-long story of patient and disease, this article necessarily adopts a nontraditional structure. It starts with a medical narrative of Mary Lin-

[1]Occam's razor is a 14th-century philosophical principle loosely translated as "multiplicity must not be posited without necessity." Applied to medical diagnosis, it stipulates that, all things being equal, diagnosing one disease to explain a patient's illness is more likely to be correct than diagnosing two. Although often regarded as merely a heuristic (a rule of thumb), Occam's razor has an objectively quantifiable form supported by Bayesian analysis: specifically, a diagnostic model having a greater number of adjustable parameters is statistically preferred over a model having fewer adjustable parameters only if its predictions are considerably more accurate (Jefferys and Berger 1992). Because fewer disease diagnoses generally translates to fewer parameters in a patient's overall diagnostic model, Bayesian analysis supports the clinical instinct to minimize the number of diseases in diagnostic models.

coln's life, follows with a short recap of PA's many clinical features, then relates her signs and symptoms to expanded descriptions of PA's features. It concludes with a general diagnostic discussion.

As a notoriously difficult-to-understand partner to one of the most consequential figures in world history, studies of Mary Lincoln are extensive (Williams and Burkhimer 2012). An identifiable medical cause for her unusual behaviors would significantly change scholarship about her, which has long viewed psychological and historical factors—such as upbringing, marriage, motherhood, loss, and sexism—as primary determinants of her actions.

Sources and Conventions

Excepting sparse notes during four months of psychiatric institutionalization and three paragraphs written six months ante-mortem (Hirschhorn and Feldman 1999), Mary Lincoln's medical records do not exist. Her case history, as reported here, originally derived from a 62-page compendium of her medical data, published before any suspicion she had PA (Sotos 2008). Drawn from approximately 100 historical sources, including 678 surviving letters (she and her son burned many other letters), the compendium has subsequently grown to book length (Sotos 2016). (Detailed citations of these historical sources have been omitted in this article at the editor's request,—but they are fully provided in Sotos 2016.)

As in the historical literature, Mary Lincoln is here called "Mary." Although overly familiar, calling her "Lincoln" would inevitably evoke her husband, and she did not use "Todd" after marrying.

Case History

Table 1 summarizes Mary's clinical course, dividing it into five increasingly severe chronological stages—reviewed below—plus a set of predisposing factors.

Stage 1: Before Washington (1818–1861)

Born in December 1818 as the fourth of seven children to consanguineous parents of Scottish extraction, blue-eyed, fair-complected, right-handed Mary Todd married Abraham Lincoln in Springfield, Illinois, in 1842. Except for recurrent springtime headaches ca. 1840 to 1847, and a tendency to "stoutness," she was otherwise generally healthy.

Mary delivered four sons in 11 years. In 1852, still breast-feeding 17 months after her third delivery, she developed "nursing sore mouth." A separate, unspecified "womanly" problem began after her final pregnancy and lasted for decades. A three-year-old son died in 1850, deeply affecting her.

Friends and family in Springfield described a marked change in Mary's personality over the years. For example, before her marriage, a cousin found her "lovely

TABLE 1 PERNICIOUS ANEMIA AS AN EXPLANATION OF MARY LINCOLN'S COURSE AND CLINICAL FINDINGS

Stage	*Major Physical Findings*	*Minor Physical Findings*	*Psychiatric Findings*
Predisposition	± Consanguinity from Scottish endemic zone	++Facial physiognomy (Fig. 1) ++Plumpness ++Blue eyes, light complexion	+ Mental illness in first- and second-degree blood kin
1. Initial (before 1861)	++Nursing sore mouth	+ "Womanly" problem ++Remarkably infection-free x Seasonal headaches	++Irritability
2. Early (1861–1865, ages 42–46)	++Pallor ++Sallow ++Transiently haggard	++New headaches ++Fatigue ± "Indispositions"	+ Spending ++Hallucination + Deficient self-control + Unethical conduct + Run-on speech
3. Middle (1865–1877, ages 46–58)	++Pallor ++Paresthesias ++Lhermitte symptom ++Edema (Fig. 2) ++"Feebleness" ++"Neuralgia" ± Boils	++Graying ++Borderline tachycardia ++Rare pain ++Fever accompanies ill health x Coughing episodes x Eye pain ++Near syncope, palpitation ++Continued headaches + "Disabled hand" ± "Indispositions"	++Delusions ++Depressive symptoms + Marked hallucinations + Paranoia ++Institutionalized (4 mos.) + Continued spending + Alienation of family + Suicide attempt ++Largely preserved clarity
4. Late (1877–1882, ages 58–63)	++Pallor ++Urinary incontinence ++Ataxia ++Marked weakness ++Visual loss ++Weight loss ++Continued "neuralgia"	+ Fall ± Hyperphagia? ++Edema resolves? ++Headaches ± Diabetes? ± "Indispositions"	+ Social isolation ++Continued hallucinations ++Continued delusions ++Depressive symptoms + Probable spending ++Largely preserved clarity
5. Terminal (July 1882, age 63)	++Marked edema ± Boils ++Weak, then locked-in		

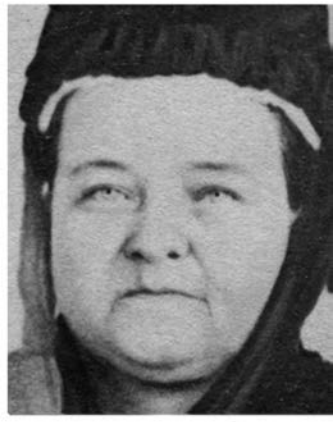
Note: The top segment lists findings from Mary Lincoln's case history consistent with a predisposition to pernicious anemia. Lower segments define five temporal stages in her illness, each with its associated case findings. Divisions between major and minor findings are ad hoc.

Key: ++ = finding is typical of PA; + = finding compatible with PA; ± = finding possible in PA; x = finding unexplained by PA; ? = finding's existence is uncertain.

(A) 1848±

(B) 1861

(C) 1863



(D) 1872

Figure 1

Mary Lincoln across the years

(A) Earliest known photograph, ca. 1848 (age 29±). Note wide-set eyes, wide face, wide jaw. (B) Age 42 in 1861. Note large ear lobes and fleshy face. Surface artifact is visible. (C) This haggard woman, blurrily photographed at a formal White House meeting in March 1863, "is often identified" as Mary Lincoln. She would have been 44 years old. Her hair style, facial structure, facial lines, submandibular fat, and clothes (mourning wear) match Mary's. Assuming this is Mary, then based on the reliably dated photographs closest in time before this one, she became haggard in 14 months or less. Whether such a dramatic change resulted from bereavement anorexia (one of her sons died 13 months earlier), or from pernicious anemia, or both, cannot be determined. (D) Last known photograph (age 53 in 1872), once again showing a fleshy face, with peri-ocular puffiness. Figure 2 presents this photograph in two other views. No reliably dated photograph between (C) and (D) is known.

Photo credits: (A) Library of Congress #LC-USZ6-2094; (B) Library of Congress #LC-DIG-cwpbh-01025; (C) Library of Congress #LC-USZ62-11880-3a14264u; (D) Lincoln Financial Collection, courtesy of the Indiana State Museum and Historic Sites.

in disposition [with] a natural kindness of heart," but, by 1848, she "changed from the pleasant woman I remembered to one rather sour of aspect and sharp of tongue, especially when addressing her husband, who seemed to take it as a matter of course when she berated him." Dozens of Springfielders left firsthand descriptions of her extreme irritability, frenzied outbursts, and "ungovernable temper," reported with unsympathetic clarity by modern historians (Burlingame 2008).

Desirous of fine clothes since childhood, her extravagant spending during a January 1861 New York City shopping trip as First-Lady-elect is sometimes identified as the earliest sign she was "not mentally 'right.'"

Stage 2: In Washington (1861–1865)

In February 1861, future President James Garfield described Mary as "sallow." Over the remainder of her life, 10 more descriptions of her complexion are known. All mention pallor, sometimes emphatically. No blood counts are known.

Mary's complaints of chills and a "racked frame" in September 1861 heralded two decades of symptomatic bodily discomforts that others interpreted as hypochondria. October saw the first of the 14 never-detailed "indispositions" she would mention in letters for the next 17 years (Turner and Turner 1972).

Any physical complaints, however, were soon overshadowed by severe, protracted grief over her third son's death from an acute infectious illness in February 1862. A March 1863 photograph (Figure 1C) shows Mary so haggard that historians have been uncertain it is her.

In July 1863, she struck her head on a rock after leaping from an out-of-control carriage, leaving her "stunned and severely bruised." The wound became infected and was drained. Her oldest son thought she "never quite recovered" from the injury. For the next 10 years, she complained of severe headaches, once noting associated nausea and eye pain.

At best, Mary demonstrated a political tin ear while First Lady. At worst, historians have documented serious misdeeds, including influence peddling and massive unauthorized expenditures. Her temper continued to alienate others. More obviously pathological incidents occurred as well. In late 1863, she earnestly described her recently deceased son appearing nightly as a comforting, speaking apparition. Then in April 1865 she exhibited baseless jealous rage, public loss of self-control, and incessant run-on speech during a several-day visit with her husband to General Ulysses Grant's field headquarters.

Overcome with grief after President Lincoln was shot beside her on April 14, 1865, Mary did not vacate the White House until five weeks later, having already sold her husband's shirts for $84 and filled dozens of trunks with appropriated household goods (Burlingame 2008).

Stage 3: Post-Washington (1865–1879)

After leaving the White House, Mary and her surviving two sons moved to Chicago. Lincoln's estate, faithfully administered by a Supreme Court justice, was able to provide well for them.

Her physical condition soon worsened. In 1866, she mentioned aching limbs. In 1867, she described herself as "pale, wretched, [and] haggard," with her dresses fitting her "like bags." In 1868, she wrote a friend: "Tell your wife, whom I have always loved so much, that I intend gathering all the needles that are now running through my body, & send them to her, in a handsome, European pincushion" (original emphasis). Many of her later letters refer to "neuralgia" and other disagreeable sensations. For example, she complained in 1869–1870 of a "great & burning pain in my spine" and "A fearful cold, appeared to settle in my spine & I was unable to sit up, with the sharp, burning agony, in my back."

She remained physically active. In 1867, she could climb four flights of stairs—pantingly—and in 1870 considered taking a third-floor apartment. But she had near-syncope while seated in 1868 and, in 1871, had palpitations.

In 1868, 49-year-old Mary wrote that recent stresses had "almost whitened every hair of my head." All five subsequent descriptions of her hair color invoke grayness.

All the while, she continued her extravagant shopping. She had unshakable delusions of impecuniousness, and manifested several depressive symptoms. Yet she lived independently and mothered her youngest son, with some periods of relative happiness (Turner and Turner 1972), though not without scandal-causing lapses in judgment.

Her medications about this time included chloral hydrate, inorganic mercury, paregoric, camphor, and perhaps laudanum (Kunhardt 1959; Turner and Turner 1972). Their frequency of use is wholly unknown. No records show her drunk or imbibing. Her correspondence obsesses about money, but never substances.

Mary's youngest son died in 1871. Quarreling with her single surviving son's wife soon after, she became itinerant, with months-long travels in which economy was no doubt a prominent concern. Figure 2 shows Mary in 1872 with hand and facial edema, not long before seeking relief from "a dropsical condition" at a Wisconsin spa.

In her itinerant years (1873–1875), Mary had auditory hallucinations, paranoia, confusion, somatic delusions, and other delusions, sometimes with fever. For example, she complained there "was an Indian removing the bones of her face and pulling wires out of her eyes" and "that someone was taking steel springs from her head." She felt her scalp was being lifted and experienced cutting sensations. She would sometimes sit in a "perfectly dark" room.

The climax came in spring 1875. She had "general feebleness," was thin and shrivel-faced, and had marked delusions and hallucinations. Fearing for her safety,

Figure 2

Mary, edematous

Spirit photograph of 1872, purporting to show presence of dead husband (hands on shoulders). Note Mary's puffy hand and face. Within months of this photograph, she sought treatment at a spa for "a dropsical condition."

Photo credit: Lincoln Financial Collection, courtesy of the Indiana State Museum and Historic Sites.

her surviving son had her tried for insanity. Hours after the verdict committing her to an asylum, and with surprising resourcefulness and energy, Mary attempted suicide by opiate overdose. But for a pharmacist's quick thinking, she would have succeeded.

Mary's son selected an upscale, progressive, bucolic institution for his mother's care. She ate her meals at the director's family table, walked the extensive grounds, and was allowed escorted trips into town. Her pulse rate, measured twice at the asylum, was 100/min and 90/min. Physically, institutionalization "greatly improved" her. After four months at the asylum—during which she continued hallucinating—acquaintances successfully pressed for her release, though her physician still thought her insane. She regained control of her finances nine months later, being declared "restored to reason," though no family members thought her sane.

After her release, Mary moved to France for four years. Her letters from there are rational and clear, if overwrought (Emerson 2007; Turner and Turner 1972). She had a temporarily "disabled hand" in 1877, and then, after taking the waters at Vichy in July 1878, developed "boils" under her left arm, plus "continual running waters, so disagreeable and inconvenient." No further details of the complaint are known.

Stage 4: Last Years (1879–1882)

In October 1879, still living alone in France, Mary wrote that "many pounds of flesh have departed" and "my great bloat has left me." Three months later she was "down to 100 pounds exactly"—corresponding to a body mass index of 17.7 kg/m^2. Nothing suggests she ever followed a faddish diet.

Mary fell while standing on a chair (or ladder) in December 1879, injuring her back. Soon after, her longstanding complaints of fatigue increased. By June 1880, she could not descend stairs unassisted, owing to "weakness." She therefore returned to her sister's home in Illinois, bringing 8,000 pounds of belongings, which threatened to collapse the upper level of the home. She lived two more years, not leaving her usually darkened room once in a six-month span. She still expressed bizarre somatic complaints, was suspicious, always wore a money belt, believed herself poor, exasperated her relatives, and reportedly heard her husband's voice.

Mary sought medical help for her physical infirmities. In October 1880 her physician (and childhood friend) Dr. Lewis Sayre reported to the press that her limbs "were so devoid of muscular tonicity as to give her the appearance when walking of a person under the influence of liquor," so that onlookers would think her "addicted to drink." He further described her limbs as "swollen and dropsical," and suspected kidney disease.

Circa October 1881, she could not rise to stand unassisted and, feeling "thoroughly exhausted," had to be lifted into a cab and into her hotel. Weakening further, by January she could "walk but a very few steps." Mary's last letter, in March 1882, requests "an invalid's chair" and laments "my limbs in so paralyzed a state."

Despite occasional complaints of painful eyes, Mary remained an avid reader until December 1881, when she had marked difficulty reading and writing. Only as sight and gait both failed did she seem defeated, writing, "to be lame & almost without the least eyesight—what an affliction."

In January 1882, a committee of four physicians in New York City—including Dr. Sayre—examined her, to help Congress determine whether her medical condition warranted a federal pension (Hirschhorn and Feldman 1999). The physicians diagnosed her with an unnamed progressive spinal disease, supposedly caused by the fall in France two years earlier. The physicians also found a "commencing cataract of both eyes" and an unnamed progressive eye disease "connected with the spinal disease." She had vision "one-tenth natural standard," "much narrowing of the field of vision," and "reflex paralysis of the iris."

The committee issued a report sympathetic to Mary. Although one of her several obituaries later reported that she had sought treatment for diabetes in New York City, the committee's report did not mention it.

Stage 5: Death (July 1882)

Mary eventually developed "sedentary habits." She also "puffed up," requiring removal of her wedding ring. In the weeks before her death she "gradually failed," with loss of "vitality" while afflicted with boils "on every part of her body."

Two days before her death, "she was up and walked across the room." The next day, "she was able to move around her room with assistance until afternoon, when her strength failed her completely." She was still conscious in the evening, "and remarked that she was dying. Her mind was not then entirely clear. . . . Later, she lost control of her vocal organs, and answered questions by the opening and closing of her eyes, which was the only sign she was able to make" (*Chicago Tribune*, July 17, 1882). She became stuporous at about 1 a.m. At 8 a.m. her physician announced there was no hope. She died about 12 hours later—approximately 30 hours after her "strength failed."

One obituary described her course as "a rapid wasting away of her vital energy, resulting in death." The death certificate listed "paralysis" as the cause of death. Eight years afterwards, her physician clarified: "In the late years of her life certain mental peculiarities were developed which finally culminated in a slight apoplexy, producing paralysis, of which she died."

Her physician found her "bright and sparkling in conversation . . . to the very close of her life."

Historical Understanding of Pernicious Anemia

Vitamin B12 is an essential co-enzyme that helps synthesize fatty acids and tetrahydrofolate, the latter needed to make DNA precursors and, it is suspected, certain neurotransmitters (Antony 2009; Stahl 2007). Lack of gastric intrinsic factor, causing gastrointestinal malabsorption of vitamin B12, defines PA.

Mary's physicians labored in near-total ignorance of PA. Originally described in 1855 by Thomas Addison (1868), the term "pernicious anemia" first appeared in English in 1874—just eight years before Mary's death (Castle 1980). The spinal cord lesions of PA—subacute combined degeneration of the posterior columns and the lateral corticospinal tracts (SCD)—were described in 1887, five years after Mary died (Victor and Lear 1956). Similar brain lesions were described in 1902, and the importance of a sore tongue in 1897 (Castle 1980; Holmes 1956). As late as 1896, "mental symptoms" in PA were appreciated only in the last months of life (Cabot 1896). They are now known to occur at any time in the disease course, even at presentation (Langdon 1905). The 1870 discovery of gastric atrophy became central when a study of 150 PA patients in 1921 showed that 99% had gastric achlorhydria, later determined to result from autoimmune gastritis (Castle 1980; Levine and Ladd 1921). Vitamin B12 was isolated only in 1948 (Castle 1962).

Until 1926, PA was indeed a pernicious disease, being 99.8% fatal (Cabot 1915). As late as 1915, the diagnosis was generally applied only when muscular weakness appeared, making it seem a disease that struck predominantly at age 40–60 years and that had a mean post-diagnosis survival of just one to three years (Cabot 1915). The subsequent recognition that muscular weakness appears late in the course, and that gastric achlorhydria can precede symptomatic nervous system involvement by 25 years or more, showed that the PA disease process could span an entire adult lifetime (Hershko et al. 2006; Hurst 1927; Riley 1925).

Osler called PA "a common and widespread disease" whose prevalence was largely "a matter of keenness on the part of the practitioners of any district" (Osler and McCrae 1919, 733). Rough comparisons suggest that hospital inpatients in the early 1900s were twice as likely to have PA than diabetes mellitus (Levine and Ladd 1921; Osler and McCrae 1919). In 1960, PA's prevalence in Scotland was 50% above the British national average, with even higher rates in a region between Glasgow and Edinburgh (Scott 1960). Glaswegians over 65 had a 2.5% prevalence in 1973 (Chanarin 1979). In 1996, 4% of white American women aged 60 or above had undiagnosed biochemical PA (Carmel 1996).

The pre-therapeutic literature additionally emphasized many features of PA Victoriana absent from textbooks today, including a "spontaneously" relapsing/remitting course, pallor with preservation of the fat layer, a non-sickly appearance, striking freedom from previous illness, preserved physical vigor in some patients despite severe anemia, an exacerbating effect of infection, and occasional postpartum or pregnancy onset (Cabot 1896, 1915, 1928; Castle 1962; Elsom 1937; Graham 1926; Osler 1907; Osler and McCrae 1919; Russell, Batten, and Collier 1900; Strauss and Brokaw 1951; Ungley and Suzman 1929; Victor and Lear 1956). Nursing care and diet were considered critical, Osler (1907) stating flatly: "the outlook depends on the stomach" (729, 731). Later work showed that dietary variability explains some, but not all, "spontaneous" fluctuations in course (Castle 1962).

Signs and Symptoms of Pernicious Anemia in Mary Lincoln

This section relates Mary's signs and symptoms to those of pernicious anemia. It is not a differential diagnosis of her clinical findings.

Skin and Hair

Patients with PA may have a characteristic "lemon tinged pallor" or grapefruit color that combines anemic pallor and a less-than-icteric sallowness (Cabot 1896, 1928; Minot 1926; Osler 1907; Putnam and Taylor 1901), the latter caused by lysis of red cell precursors. The few descriptions of Mary's complexion after 1861 all refer to either sallowness or pallor.

Some persons with pernicious anemia gray prematurely; most gray between ages 40 and 59 (Hardgrove et al. 1944). Mary probably grayed from 49 to 56. At age 61 a friend described her as "prematurely gray."

Oral

In the 1850s, "nursing sore mouth" (also known as "stomatitis materna" and "stomatitis nutricum") was a prevalent, easily recognized syndrome of glossitis or stomatitis in pregnant or nursing women. Especially common on the American frontier in multiparous mothers, it was sometimes life-threatening but generally responded quickly to weaning or delivery (Hutchinson 1857). Understood by 1909 to resemble a deficiency disease, it seems afterwards to have vanished from the medical literature (Blackwood 1909). Modern lactation textbooks do not mention it, although cases still occur in developed countries (Lawrence and Lawrence 2011; Onozawa et al. 2007).

Occurring after prolonged lactation, Mary's stomatitis was probably glossitis, and it is hard evidence of a nutrient deficiency, most likely iron, folate, or vitamin B12. Other nutrient deficiencies may cause glossitis, but typically only when malnutrition is generalized (Thomas and Mirowski 2010). Nothing suggests Mary was grossly malnourished in 1852.

Pregnancy and lactation increase maternal demands for B12, folate, and iron (Antony 2009; Baker et al. 1962; Casterline, Allen, and Ruel 1997). Elsom (1937) produced a classic syndrome of B12 deficiency in 85% of normal pregnant subjects by restricting dietary B-vitamins after the fourth gestational month. Maternal B12 demands are higher in lactation than pregnancy, and deficiency is more common after prolonged lactation (IOM 1998; Shapiro et al. 1965).

Owing to poor iron absorption caused by gastric achlorhydria, iron deficiency occurs frequently in PA (Carmel, Weiner, and Johnson 1987). Iron deficiency anemia is now recognized as a sign of incipient PA in young women (teens and 20s) (Hershko et al. 2006)—long before classic PA symptoms develop.

Mary's sore mouth occurred nine years before she developed pallor. No evidence suggests it recurred. In PA, "soreness of the tongue occurs early in the disease before an anemia of any degree has developed," and soreness "tends to decrease as the anemia increases in severity" (Graham 1926, 882). Ten years may elapse between glossitis and the development of anemia (Mark 1927).

Overall, therefore, Mary's sore mouth and its timing are fully consistent with the natural history of PA.

Neurological (Sensory)

Neurosensory symptoms are significant and early manifestations of spinal SCD in PA. Pins and needles paresthesias are the most common. They are usually acrodistal, constant, steadily progressive, and vexing. Many other peculiar sensations—often vaguely described, such as numbness, stiffness, deadness, tightness,

and shooting pains—can also occur (Victor and Lear 1956). Mary unmistakably and repeatedly describes such sensations, from the aching limbs early in her illness, to the striking pincushion metaphor, to the many "neuralgia" references to her longstanding cutting sensations.

True pain is classically absent or atypical in PA (Cabot 1896; Woltman 1924). Her physician commented "she did not often experience pain," and Mary's few references to non-cranial "pain" generally do not elaborate. An exception was from 1868 to 1870, when she complained of "great . . . pain in my spine" that was both "burning" and "cold." This unusual sensation, which never again appeared in her letters, fits the Lhermitte symptom: a disagreeable "electric" sensation that travels down the spine or limbs after neck flexion. It is "a common early symptom of subacute combined degeneration of the cord," occurring in 25% of SCD inpatients from 1962 to 1971 (Gautier-Smith 1973, 861). Generally brief and non-painful, it may sometimes be pervasive, "violent," and enervating (Lhermitte, Bollak, and Nicholas 1924; Olkon 1933; Pearce 1994). Descriptions of the Lhermitte symptom, starting with the original in 1924, invariably cast it as "electric" (Lhermitte, Bollak, and Nicholas 1924). Mary, living before the age of household electricity, appears to have used close non-electrical metaphors. (Jumping into cold water, for example, can feel like an electric shock.)

Excepting the Lhermitte symptom, Mary's other neurosensations had a slow tempo, such as the bilateral "neuralgic" wrist pain she wanted to prevent from "creeping into my fingers, so that they may use the pen." Thus, her known symptoms do not support claims that she had typical tabetic lightning pains (Hirschhorn and Feldman 1999).

Neurological (Motor)

Abnormal movement in PA—usually of the legs—can arise from sensory impairment (posterior column disease), spasticity (lateral column disease), or muscular weakness, typically occurring in that sequence. Sensory and spastic ataxia may, however, be minimal in an individual, as when peripheral nerve involvement adds flaccidity to spasticity (Antony 2009). Muscular weakness often heralds the final stage of the disease and progresses to flaccid tetraplegia and fatal "exhaustion" (Strauss and Brokaw 1951), leaving the patient "bloodless from pallor and scarcely capable of a movement of hand or foot" (Putnam and Taylor 1901, 86).

Mary's "general feebleness" was first mentioned in 1875. Her last four years saw steadily increasing weakness, "feebleness," and "paralysis" in her "limbs" (not just her legs), plus physical exhaustion. She was ataxic in her last two years. Absent firsthand descriptions, the type of ataxia is not discernible, but Dr. Sayre's description of hypotonic limbs in association with her "drunken gait" makes weakness more likely. Ataxia or sensory impairment could have contributed to her fall from the stepladder in December 1879. Her weakness crescendoed before her death, closely following the classic end-course for PA (see "Death" below).

Although many disorders can gradually sap strength in a 62-year-old woman, there can be little doubt that Mary's progressive weakness was compatible with advancing PA.

Psychiatric

Because mental symptoms can arise at any time in PA, the gradual, pre-Washington changes in Mary's personality would not be inconsistent with PA. Anemia (evidenced by pallor) appears to have become established by the time her more prominent mental symptoms began in 1861. Severe psychiatric symptoms (1863–1865) followed a head injury that produced an infected and purulent scalp wound, from which she "never quite recovered." As noted earlier, infections exacerbate PA (Victor and Lear 1956).

Psychiatric abnormalities in untreated PA are common and protean (Edwin et al. 1965; Henderson et al. 1966). They span slight irritability and suspiciousness to a marked confusional psychosis known as "megaloblastic madness" or "pernicious psychosis" (Holmes 1956; Kunze and Leitenmaier 1976; Smith 1960). Thus, in a 1930s series of PA inpatients (Goldhamer et al. 1934), 64% had irritability, 58% had mild depression, 18% had delusions, 16% had hallucinations—auditory predominates (Kunze and Leitenmaier 1976)—and 60% had memory disturbances. Mania occurs, too (Goldhamer et al. 1934; Smith 1960). Remarkably, Mary had all of these features, except memory impairment.

A widely noted feature of Mary's psychopathology was her generally high mental functioning—except with money, according to her son. Suarez (1966) thought this ruled out organic disease. Clarity, however, is characteristic of untreated PA, where there is "no marked [mental] deterioration, and comprehension and orientation were usually clear, except for a rare episode" (Woltman 1918, 797).

Persecutory delusions in PA are "usually influenced by the somato-neurologic findings" (Woltman 1924). Thus, Mary's long-standing delusions of cutting—probably arising from paresthesias—have been multiply described in PA (McAlpine 1929; Woltman 1924).

Short of psychosis, Mary's personality had clear features relatable to PA. For example, she showed the "exaggeration of native traits" or "endogenous disposition" seen in PA (Kunze and Leitenmaier 1976; Putnam and Taylor 1901). Her later-life obsessions with shopping, clothes, money, grudges, and status all accentuated earlier-life traits (Williams and Burkhimer 2012). The following snapshot of one PA patient's personality in 1901 is uncannily similar to Mary's: "In general her memory remained good, but she was subject to violent outbreaks of passion under slight provocation, and showed considerable lack of judgment as to her own condition and her obligations to those around her. Except in these respects, she retained a high degree of keenness to the last" (Putnam and Taylor 1901, 86).

Finally, the tragic events in Mary's life—watching three sons and her husband die—cannot be overlooked. Often cited as contributing to her psychopathology,

an interesting mechanism could (speculatively) tie her grief to physical illness. Bereavement-associated anorexia, which Mary developed at least once, in 1850, would reduce her intake of vitamin B12, potentially exacerbating PA. Inadequate dietary intake of vitamin B12 is well known to cause hypovitaminosis in poor and vegetarian populations (Antony 2009).

Given the wide range of psychopathology seen in PA, it is not surprising that Mary's history is compatible.

Edema and Weight

Changes in both edema and dry weight occur during relapses and remissions of PA. Edema in PA is common (Cabot 1915). It resembles nephrotic edema, in that facial accumulation occurs, venous pressure is not elevated, and osmotic pressure is low (Muelengracht, Iversen, and Nazakawa 1928; Stewart, Crane, and Deitrick 1937). However, renal dysfunction is mild, if present at all (Muelengracht, Iversen, and Nazakawa 1928; Stieglitz 1924). Edema accumulates during relapses and may worsen early in remission, before decreasing later in remission (Vaughan 1931).

Although data are sparse, Mary's edema did wax and wane. She was "dropsical" in 1872, saw her "great bloat" resolve in 1879, and was dropsical again by late 1880. Notwithstanding edema, overall weight tends to drop during relapses of PA, and rise during remissions, sometimes markedly (Minot 1926;Vaughan 1931). The fat layer is generally preserved until emaciation and anasarca occur terminally (Cabot 1896, 1915; Russell, Batten, and Collier 1900).

Interpreting Mary's weight is complicated by possible bereavement-associated anorexia after her major psychological traumas (1850, 1862, 1865, 1871) and by the uncertain dates of her later photographs. There is, however, good evidence she was "stout" in 1871–1872 but became "a quite slender lady [with a] shriveled face" by the time of her insanity trial in 1875, when her psychiatric disease peaked. This is fully consistent with PA, as is her "greatly improved" physical and mental state after four months of monitored eating at the asylum, where she took her meals with the director and his family. Her body mass index of 17.7 kg/m^2 two years ante-mortem, plus her pre-terminal anasarca, are also consistent with PA.

Cardiovascular and Energy

Fatigue is nearly universal in PA and dyspnea is very common, although Osler and others describe paradoxical patients who retain remarkable physical vigor despite very low hematocrits (Cabot 1915; Chanarin 1979; Osler and McCrae 1919).[2]

Beginning in 1861, Mary developed unexplained weakness and feebleness, culminating in thorough exhaustion as death approached. Although her surviving

[2]In this "not rare" phenomonenon, PA patients show "a degree of muscular and mental power altogether astonishing when compared with the impoverishment of the blood" (Cabot 1915, 629)—for example, a man with an erythrocyte count below 2 million (male normal: 4.5 to 5.9 million) who each day walked six miles and swam 90 minutes.

letters do not mention breathlessness explicitly, she often bemoaned her fatigue and feebleness. Climbing four flights of stairs in 1867 might suggest paradoxical vigor, but it is unrevealing without detail (speed and degree of dyspnea).

Cardiomyopathy and palpitations are frequent in PA (Cabot 1915). By current criteria, her heart rates of 90 and 100/min at the asylum are top-normal and tachycardic, respectively (Spodick 1993). They would also fit many common disorders, including anemia, anxiety, heart failure, hyperthyroidism, or autonomic instability. Perhaps Mary's "palpitations" were anxiety-related, but her episode of near-syncope rings genuine.

Ocular

The marked deterioration of Mary's vision during her final months exceeded that which "beginning cataracts" might have caused. Instead, it better fits the "dimness of vision" (due to central scotoma) and narrowed visual fields caused by optic nerve atrophy in advanced PA (Benham 1951; Hamilton, Ellis, and Sheets 1959; Holmes 1956). Even into the post-liver era, 5% of SCD cases had such atrophy (Benham 1951).

Miscellaneous Physical

Fever occurs commonly in PA, especially during relapses (Cabot 1915; Graham 1926; Russell, Batten, and Collier 1900). Mary reported fevers in 1869, 1873, and 1875.

Most PA patients have headaches, sometimes migrainous (Cabot 1915; Hartfall 1939; Smith 1960), perhaps reflecting vitamin B12's effect on folate and, therefore, homocysteine metabolism (Lea et al. 2009). Mary's severe nonseasonal headaches began at about the same time as her first hallucinations and still occurred in her last year.

In women with PA, "sanguineous vaginal discharges frequently occur" (Cabot 1915, 632; Fagge and Pye-Smith 1891, 644), which is compatible with Mary's longstanding "womanly" problem.

Death

Mary's attending physician diagnosed "a slight apoplexy" as causing her death. Among mid-20th-century deaths from PA, 33% were sudden and unexpected, and cerebrovascular disease caused 12–20% (Chanarin 1979).

Mary's end did not, however, seem to be a classic syndrome of cerebrovascular accident. "Her strength failed her completely" does not evoke a hemispheric ischemic stroke, nor does her later locked-in inability to move save for eye blinks. Instead, Mary's end better matches the deaths from PA that Addison (1868) described: "the patient can no longer rise from the bed; the mind occasionally wanders; he falls into a prostrate and half-torpid state, and at last expires" (211–12).

Descriptions of Mary's last days suggest that her weakness progressed markedly in the day before her tetraparesis, a tempo generally observed in fatal PA, where the lower limbs "in the course of twenty-four hours became absolutely paralyzed [with] complete flaccidity" (Russell, Batten, and Collier 1900, 51). Moreover, paresis in end-stage PA tends to spare muscles innervated by cranial nerves, as Mary experienced. Mary's pre-terminal anasarca also fits the end stage of PA (Russell, Batten, and Collier 1900).

Overall, therefore, it is reasonable to conclude that her death was not "apoplexy" in the modern sense of the word, and that her course was compatible with fatal PA. Whether the "boils" of her final illness contributed directly to her death is unclear. However, indirect contribution is possible because of infection's exacerbating effect in PA.

Interestingly, even the vagueness of Mary's cause of death is compatible with PA: "What caused the fatal outcome in pernicious anemia in the pre-liver-treatment days is not altogether clear. It seems, despite the fact that repeated transfusions could maintain the hemoglobin level at a level which anemia per se was not lethal, that these patients died in a state of extreme exhaustion" (Strauss and Brokaw 1951, 801).

Predisposing Factors

Older literature often describes a physical stereotype in PA-afflicted northern Europeans that includes premature graying, blue eyes, large ear lobes, wide facies, wide-set eyes, and a wide jaw (Harvey, Bordley, and Barondess 1979; Hurst 1927; Minot 1926; Spivak and Barnes 1983). Figure 1 shows all of these features in Mary. Additionally, Addison (1868) found the disease "uniformly occurred in fat people" (213). Because it is hard to tie these features pathophysiologically to PA—except for graying and obesity—they may be better viewed as marking a predisposed Euro-American population cohort in that era. Familial clustering, long recognized in PA, occurs in 10–30% of patients (Antony 2009; Chanarin 1979; Minot 1926). DNA studies of Mary's present-day kin have localized both her paternal and maternal origins to the high-prevalence belt of PA between Edinburgh and Glasgow (McMurtry 2015; Scott 1960). Several of Mary's first-degree kin, including a look-alike sister, had mental difficulties (Evans 1932).

Diagnostic Discussion

Table 1 shows that a diagnosis of PA is compatible with virtually all significant elements from Mary Lincoln's medical history. All her well-described clinical events—sore mouth, pallor, paresthesias, Lhermitte symptom, ataxia, weakness, edema, impaired eyesight, weight changes, headaches, fever, cardiac symptoms, and all of her psychiatric symptoms—are encountered in PA. So, too, the poorly described events—"indispositions," "neuralgia," and the "womanly" problem—can be mapped to features of PA, although necessarily with less certainty.

Importantly, and additionally, Mary's illness evolved as PA does over time, namely: sore mouth as the initial symptom, which did not recur; sequential progression from pallor to paresthesias to motor symptoms (McAlpine 1929) to brain-and-oculoneural degeneration; insidious systemic onset (Cabot 1915); a striking relapsing/remitting course, often linked to fever or infection; increasing exhaustion; and death, in her 60s, within four years of muscular weakness commencing (Cabot 1896).

Mary's putative 30-year course (dating from her sore mouth) does not conflict with the few years' survival generally reported for PA Victoriana, because those survival times generally dated from the onset of marked symptoms occurring late in the disease (Addison 1868; Cabot 1896; Osler 1907; Osler and McCrae 1919). When gastric achlorhydria marks disease onset, survival longer than 20–25 years was multiply described in the pre-liver era (Hurst 1927; Riley 1925). It is now known that achlorhydria may start in childhood (Castle 1962).

Of note, PA does more than simply explain Mary's clinical course. First, it adheres to the old psychiatric truism calling for evaluation of PA "in primary neuroses and psychoses occurring after the age of 35" or even in all psychiatric patients (Holmes 1956; Kunze and Leitenmaier 1976; McAlpine 1929). Second, it fulfills a prediction of increased risk that could reasonably have been made in Mary's 20s, based on her appearance, which corresponded to the classic PA physical phenotype in northern Europeans, and her parents' origins in Scotland's PA-enriched belt.

Overall, therefore, it is reasonable to conclude that PA satisfies the demanding requirement of accounting for Mary's extensive clinical course.

Missing Pieces

If PA could be confidently ruled out, its ability to explain Mary's course would become irrelevant. This, however, is difficult to do on clinical grounds. PA has no bedside sine qua non and, even if a highly prevalent feature of PA were absent from records, absence-of-mention rarely proves absence-of-feature in historical research.

Nevertheless, of PA's major symptoms, only gastrointestinal involvement went unmentioned in Mary's case. Probably an artifact of her Victorian propriety, it would not be surprising if her numerous "indispositions" referred to abdominopelvic symptoms. Indeed, in her only letter mentioning her "womanly" problem the confessing sentence is "violently crossed out" (Turner and Turner 1972, 475).

Dyspnea, which afflicted 87% of Cabot's late-stage PA patients in 1915, is not a prominent part of Mary's history, if present at all. However, potentially synonymous complaints, such as fatigue, feebleness, and exhaustion, are prominent. Less likely, PA's paradoxical vigor syndrome could have masked dyspnea.

As expected, therefore, available evidence does not rule out PA.

Differential Diagnosis

Although no substitute for a detailed differential diagnosis, Table 2 summarizes previous investigators' medical hypotheses for Mary Lincoln's clinical course, plus other relevant possibilities. None succeed as a single, unifying psychophysical explanation.

Without gastric surgery, a restricted diet, generalized malabsorption, childhood onset, or exposure to the Diphyllobothrium fish parasite, a non-PA cause of hypovitaminosis B12 is unlikely for Mary. Implicitly, any syndrome in which PA is a component, such as autoimmune polyendocrine syndrome type I, would merit consideration in a formal differential diagnosis.

Some features of Mary's clinical course are unexplained by PA. They can, however, be explained by relatively obvious "accessory" diagnoses, including prolonged grief disorder, seasonal headaches, traumatic back injury, respiratory infections, boils, and eye pain of uncertain etiology. Thus, these few commonplace and obvious diagnoses do not weaken the explanatory power of PA, but instead reaffirm the definition of "main findings" in Mary's case.

Limitations

Sparse clinical detail, nonexistent laboratory information, and old medical literature about an extinct disease (PA Victoriana) unavoidably limit the current study. The situation is far from bleak, however. Unlike PA Moderna, which today is almost always diagnosed in the laboratory, PA Victoriana was an easy-to-recognize clinical syndrome, diagnosed at the bedside, based on understandings from autopsy series. Osler taught that, despite its lack of pathognomic features, "Few diseases are more readily recognized at sight," and viewed even blood counts as just one of four major features of the condition (Osler and McCrae 1919, 739).[3]

Bias can enter historical diagnosis if, during assembly of the historical figure's case history, facts are filtered to suit a particular diagnosis. Here, that risk is low because Mary's unfiltered medical history was published years before vitamin B12 deficiency was entertained (Sotos 2008).

Unusually, the present study does not include an in-depth differential diagnosis. This is not limiting, however, because the study's principal aim was to identify a single disease able to explain Mary's main psychiatric and physical findings—an aim that does not require choosing between competing diagnostic hypotheses.

Furthermore, accepting that Mary had a unifying psychophysical disease would be sufficient reason for historians to begin reassessing not only Mary's actions and

[3]The others are "retention of fat, the insidious onset, [and] the absence of signs of local disease" (Osler and McCrae 1919, 739). Minot and Lee (1917) substantially agreed: "Important points in the diagnosis are: a history of an insidious onset, of remissions, of sore mouth and tongue, and of spinal cord symptoms, and the presence of achlorhydria without evidence of malignancy. The blood picture is, of course, important, but the diagnosis is not to be made upon this alone" (762).

TABLE 2 MAJOR CONSIDERATIONS IN DIFFERENTIAL DIAGNOSIS OF MARY LINCOLN'S CLINICAL COURSE

Diagnosis	*Reasons against*
Idiopathic psychiatric disease (1)	Does not explain neurological findings or death.
Menstrual disorder (2)	Does not explain neurological findings or death.
Grief	Does not explain neurological findings or death. "Grief alone . . . causes a different symptom picture. Though it creates great sadness, it would not cause the delusions and hallucinations she suffered in 1873 and other times." (1)
Migraine (3)	"Cannot explain the full range of Mary Lincoln's psychiatric symptoms." (1)
Traumatic myelopathy (4)	Does not explain psychiatric findings. (5)
Tertiary syphilis (6)	[Visceral lues] 10-year survivial with untreated symptomatic syphilitic heart or kidney disease unlikely. [Tabes dorsalis] No lightning pains. [Tabes dorsalis] Expected evolution into dementia did not occur. [General paresis of the insane] No dementia.
Diabetes mellitus (5)	20-year survival without insulin would be unprecedented. (7) Easily diagnosable in the 1800s, but no mention by any physician.
Diabetic pseudo-tabes (5)	"I doubt [it] could account for the full picture of Mary Lincoln's psychiatric symptoms. It would not cause her paranoid delusions, auditory hallucinations, or delusions of poverty." (1) Does not explain [early] psychiatric disturbances in Springfield. Doubts about diabetes mellitus (see above).
Substance abuse (8)	No historical evidence for substance abuse. Hundreds of letters almost completely devoid of substance allusions. Continued hallucinating during institutionalization. "The symptom picture is wrong" [for chloral hydrate] (1)
Inorganic mercury poisoning	All three hallmarks absent: intention tremor, erethism, hypersalivation. Would require multiple physicians to miss a then-common diagnosis. Mary herself knew symptoms of toxicity. (9) Four pregnancies and children all unaffected. No spontaneous abortions.
Atherosclerosis	Does not explain psychiatric findings. Unlikely to cause episodic course. 10-year survival with untreated symptomatic ischemic cardiorenal disease unlikely.
Hypothyroidism	Cognition not slowed. Incompatible with episodic course.
Folate deficiency	No evidence for general malnutrition. Isolated folate deficiency in adults has not been unequivocally shown to cause neurologic findings. (10)

Note: All listed diagnoses have major counterarguments if they were to be suggested as a single unifying diagnosis for Mary's psychophysical illness. Diagnoses with cited references—in parentheses—have been previously proposed for her in print. Counterarguments from the Lincoln literature are preferentially quoted. Cabot (1915) mentions hypothyroidism and atherosclerosis in the differential diagnosis of PA. By definition, multiple diagnoses would not be unifying, hence are not considered.

References: (1) Brust 2012; (2) Burlingame 2008, 625–26; (3) Brussel 1941; (4) Sayre et al. 1882, in Hirschhorn and Feldman 1999; (5) Hirschhorn and Feldman 1999; (6) Vidal 1993; (7) Osler 1892, 302; (8) Beidler 2009; (9) Turner and Turner 1972, 537–39; (10) Antony 2009.

their genesis, but also those of her family, who were the disease's secondary victims. If a unifying diagnosis other than PA better explains Mary's history, so much the better for historians: that would strengthen the reasons to reassess her actions.

Conclusion

Interest in Mary Lincoln's madness has overshadowed the chronic multi-system illness she simultaneously endured (Emerson 2007). Although not completely free of mental overlay, her descriptions of her own symptoms appear accurate and generally unexaggerated.

The present analysis demonstrates a strikingly high concordance between Mary Lincoln's medical history and the natural history of pernicious anemia. Modern physicians have not previously claimed—or even entertained—that a single disease accounted for her entire illness and her death, proposing instead that multiple diseases afflicted her. Thus, Occam's razor dictates that the single diagnosis of PA should now be regarded as the leading diagnostic hypothesis for her.

A diagnosis for Mary Lincoln of chronic, florid, untreated PA has several historical implications. First, it explains the sad, slow decay of her life, from extraordinary promise to chronic psychosis to early death. Second, it removes expectations of sound judgment from her: as First Lady and widow she was simply a woman with a biochemically injured mind struggling in a complicated, relentlessly demanding environment. Third, it illuminates yet another burden Abraham Lincoln carried as President: although endlessly patient towards Mary, he was acutely aware of the political damage that her impaired judgment could do him. History should additionally note how well all of the Lincolns (and some Todds) met the pernicious disease that assailed Mary's body and distorted her essential nature.

Despite the enormous attention that historians have devoted to Mary Lincoln, it is, surprisingly, a poet who seems to have understood her best. Although Carl Sandburg never explicitly names her disease, he accurately assesses its effects on her reputation:

> All the babblings about her are only a vain exercise of the tongues of those who misunderstand. . . . Under the progression of her malady, the hammering wear and tear of the repeated periods of hysteria and hallucinations, there was a fading of a brightness seen in her younger years. . . . If she is to be compared with other Presidents' wives, other White House ladies whose performances rate higher in history for conduct and sacrifice, it may be she has an alibi, apology so perfect that her ghost could answer "Did God in His infinite wisdom ever weigh down any White House woman with a devastating curse such as rode in my blood and brain?" There are crippled brains on which it is no more wise to visit impatience or excoriation or ordinary verdicts of guilty, than upon crippled bodies. We do not kick the clumsy for being what they are. (Sandburg and Angle 1932, 7, 76, 128–29)

Thanks to one of the great triumphs of scientific medicine, the terrible disease that afflicted Mary Lincoln now exists only as formes fruste. Her misfortune was living before treatment was available, and before physicians could make a diagnosis that would have prevented 150 years of misunderstanding about her. Disparaged as the "female wildcat of the age" (Hertz 1938, 134), the thorn in her paw may finally have been found.

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