

# Role of Iron Therapy and Hematology in Re-Conceptualizing Chlorosis to Hypochromic Anemia: A Historical Perspective

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## Abstract

Historically hypochromic anemia was known as chlorosis due to distinct skin shade in patients, in addition to symptoms similar to anemia such as a lack of energy, indigestion, headaches, shortness of breath, and loss of appetite. Chlorosis was considered a disorder common to adolescent females until approximately the second decade of the last century. Chlorosis was regarded as anemia of adolescent girls without definite etiology that commonly occurred in the inhabitants under poor hygienic conditions. Physicians anticipated seeing chlorosis in adolescent girls at the time of puberty and during the process of sexual maturation. Before the end of the nineteenth century, there was a dearth of published evidence about the prevalence of chlorosis.

However, the most important evidence was found from the records of the dispensaries and hospitals. These records depicted that chlorosis was commonly found among the pauper adolescent females during the latter half of the eighteenth and throughout the nineteenth centuries. The history of chlorosis is unique due to diverse explanations for its etiologies, including the environmental, psychological, and sexual causes, before it came to be known as iron deficiency anemia. The role of iron therapy in proper doses and development of hematology in the middle of the nineteenth century helped to re-conceptualize chlorosis as hypochromic anemia confined to young women. In addition, changes in diet and nutrition after 1900, along with an increased understanding of hemoglobin and red blood cells helped to understand disease as a form of iron deficiency anemia commonly found in young females.

**Keywords:** Chlorosis, Young Girls, Iron Therapy, Hematology, Iron Deficiency Anemia

## Overview of Chlorosis/Hypochromic Anemia

Chlorosis was a prevalent disease during the eighteenth and nineteenth centuries and is now believed to be iron deficiency anemia [1]. The name chlorosis is derived from the Greek word *chloros*, meaning green [2]. During the seventeenth century (1615), one of the Professors of Medicine at Montpellier, Dr. Jean Varandal, suggested this name due to a greenish shade discerned on his patients' skin [3]. Thus, a popular English term, "green sickness," became famous for chlorosis during

the seventeenth and eighteenth centuries. Hypochromic or iron deficiency anemia was historically known as chlorosis or green sickness not only because of the distinct green skin shade, but also due to other symptoms similar to anemia [4]. For instance, patients suffering from chlorosis presented with symptoms such as lack of energy, shortness of breath, indigestion, loss of appetite, and constipation [4].

Chlorosis was considered a curse of adolescent and young females until about the second to the third decade of the twentieth century [5]. Physicians anticipated seeing chlorosis in adolescent girls during



the process of sexual maturation and these young girls learned about this disease from family members, friends, media, and their clinicians [6]. There are numerous references to this disease in literature and art from the sixteenth to the nineteenth centuries. In addition, French, German and English physicians have published several clinical accounts of chlorosis in the literature.

Chlorosis was regarded as anemia of adolescent girls without definite etiology, which commonly occurred in the pauper inhabitants' living under poor hygienic conditions but not completely sparing their counterparts [7]. Sometimes, chlorosis was not even considered a separate disease; rather, it was applied as a label to different degenerative or debilitating diseases such as phthisis [4]. But the clinical accounts and descriptions were consistent having enough diagnostic features to distinguish chlorosis from other common enervating disorders at least up to mid of nineteenth century [1]. Different physicians provided multiple explanations for the cause of chlorosis but there was no general consensus on the etiology of the disease until the development of hematology and the usage of iron therapy [8]. Hence, in this paper we have analyzed how the role of iron therapy in adequate doses and development of hematology helped to re-conceptualize the disease chlorosis to hypochromic anemia among young women.

## History of Chlorosis

Dr. Johannes. Lange, a well-known German physician (1485-1566), was the first to describe a malady that may be recognized as hypochromic anemia during the mid of the sixteenth century (1554) [9]. Dr. Lange gave a description of a girl as "weak and her face which in the last years was distinguished by rosiness of cheeks and redness of lips, is somehow as if exsanguinated, sadly paled, the heart trembles with every movement of her body and she is seized with dyspnea in dancing and climbing the stairs. Her stomach loathes food, particularly meat" [10]. After his clinical assessment, Dr. Lange labeled the disease as "morbus virgineus" as it was commonly prevalent among the virgins [10]. The green color is the best-known sign of chlorosis, but in 1554, Dr. Lange in his original description neither used the term chlorosis, nor did he make any reference to green color in his description [10]. Dr. Lange thought that this disease occurred as a result of menstrual blood retention that causes sexual frustration. Therefore, he generally recommended that these young women should get married or live with men and copulate to conceive for better recovery [10]. In more contemporary terms, Dr. Lange considered the condition as psychosomatic due to reduced sexuality, which was thus solved by marriage [11]. This notion of "morbus virgineus" persisted in some form until the late 19th century [2].

In the seventeenth century, English Physician Dr. Thomas. Sydenham (1624-1689) classified green sickness as a type of hysterical disease [12,13]. The word "hysteria" is derived from the Greek *hysteron* meaning uterus [14]. The "hysteria" was considered a mental disease like mania, epilepsy, melancholy, paranoia, and Dr. Sydenham be-

lieved this disease to occur as a consequence of the uterus drifting in the body of a young girl [11]. He also thought that this hysterical disease was not only limited to adolescent girls, but also found in slim and weak women [13]. Dr. Sydenham also indicated that this condition is due to weak blood causing a dull color, trembling of the heart, and sometimes confusion of the spirits in severe cases [13].

Dr. Sydenham's pronounced contribution in this field was the advocacy of iron as a therapy for chlorosis. He proposed that "the sick must drink some mineral water impregnated with the iron mine" [13]. Although in the 1600s, it was not yet discovered that iron is an imperative component of blood, but in ancient Greco-Roman medicine, iron was considered as a sign of strength impregnated with force by the god Mars [15]. This may have been the rationale for Sydenham's promoting iron as a therapy to revive the devitalized blood and to provide strength to shattered spirits [15]. Thus, it was the period in medicine that drug's efficacy was established before discovering its mechanism of action.

## Etiology of Chlorosis with Different Explanations

There were numerous diverse views and beliefs regarding the etiology of chlorosis [16]. Initially, this disease was attributed to sexual frustration or love-sickness [17]. This view was generally held until the end of the eighteenth and beginning of the nineteenth century when a combination of environmental, organic, and psychogenic factors was recognized as the reason for chlorosis. A well-known French pediatrician, Dr. J. Parrot, believed that the disease results from physiological changes occurring in the bodies of adolescent girls at puberty [2]. He further explained that maturation of the nervous system causes different symptoms at the time of puberty. This maturation, in turn, stimulates the cardiovascular system to cause palpitations, the respiratory system to cause shortness of breath or dyspnea and the gastrointestinal system to cause epigastric pain, indigestion, and constipation [2]. Thus, Dr. J. Parrot considered chlorosis as a neuropathological disease resulting from nervous weakness and the greater sensitivity of females as compared to males [2].

On the other hand, a German physician, Dr. Andrew Clerk believed that chlorotic girls are constipated, which causes retention of noxious substances (ptomaines) created by retained stools, which are absorbed into the blood (Figure 1) [18]. This in turn breaks down red blood cells thus causing alterations in the blood [18]. In contrast, Dr. Von Noorden, an influential German clinician well known for metabolic disease research, had a different belief regarding the etiology of chlorosis. According to Dr. Noorden, chlorosis is caused by the weakness of the blood-forming organs, resulting from a loss of chemical and physiological stimuli originating in the female genitals [2]. Based on this explanation for the disease, Dr. Noorden proposed arsenic, iron, and hydrotherapy as different modes of treatment to recuperate the blood-forming organs [2].



Figure 1



On the contrary, Dr. William Osler, a well-known Canadian physician, attributed this disease to poor environment and lifestyle of the young girls [19]. He believed that young girls might present with emotional and nervous disturbances, but he did not consider this disease resulting from nervous or psychiatric disorders [19]. According to Dr. Osler “chlorosis is most common among ill-fed, overworked girls of large towns who are confined all day in closed, badly lit rooms. Cases are frequent, however, under the most favorable conditions of life. Lack of proper exercise and fresh air and improper food are important factors” [19].

### Role of Epidemiology: Evidence Regarding Burden of Chlorosis

Overall, there is a dearth of statistical or epidemiological evidence about the prevalence of chlorosis. The existing literature shows that the cases of chlorosis were reported from London, Italy, Spain, Europe, and the United States of America [16]. Since it was the pre-epidemiology era, no population-based studies were conducted or reported in the literature [20]. Hence, the most important evidence on the burden of chlorosis only comes from the records of the hospitals and

dispensaries [4]. The hospital-based data reveals that chlorosis was common among the indigents during the latter half of the eighteenth and throughout the nineteenth centuries. For instance, dispensary records, which are particularly considered valuable sources on the morbidity patterns during the initial industrial revolution, come from the Finsbury Dispensary in London for the year 1800 as shown in (Table I) [4].

The dispensary record of one month indicates that amenorrhea and chlorosis were more prevalent conditions as compared to other diseases. Furthermore, in the 12 monthly reports for 1800, out of 3001 admissions at the Finsbury Dispensary, 184 (6.1 %) patients were admitted with chlorosis, which was found to be the third or fourth most common disorder [4]. The evidence regarding incidence is further summarized in (Table II, III) which shows that disease was more common across London and in different provinces during late 18th and early 19th centuries [4]. In addition to this, the records in hospitals were also maintained by age strata as shown in the (Table IV) which depicts that disease was more commonly found among 15 to 24 years’ older women as compared to extremes of the age strata [4].

Table I

**TABLE I—Monthly report of diseases<sup>11</sup> admitted under the care of the physicians of the Finsbury Dispensary, St John’s Square, Clerkenwell**

List of diseases etc from 20 March to 20 April 1800			
Continued fever	16	Nephralgia calculosa	1
Scarlet fever	2	Pleurodyne	3
Measles	1	Hydrops	4
Sore throat	4	Hymorrhis	3
Haemoptysis	4	Hysteria	3
Pulmonary complaints without fever	53	Paralysis	3
Phthisis pulmonalis	12	Apoplexy	1
Dysentery	3	Schrophula	2
Diarrhoea	4	Colica Pictonum	1
<i>Chlorosis and amenorrhoea</i>	29	Hypochondriasis	1
Leucorrhoea	7	Insanity	2
Menorrhagia	6	Hooping cough	4
Asthenia	10	Rheumatism	4
Dyspepsia	6	Febricula	4
Enterodynia	2	Febris mesenterica	3
Peritonitis	1	Verues	8
Constipation	1	Fever infantilis	6
Vertigo	2	Chronic cutaneous diseases	15
Cephalaea	5		

Table II

**TABLE II—Number of admissions to dispensaries for amenorrhea and chlorosis, menorrhagia, and all menstrual disorders, expressed as total numbers and as percentages of total medical admissions to the dispensaries**

Date	Dispensary	Admissions for amenorrhea and chlorosis		Admissions for menorrhagia		Admissions for all menstrual disorders		Total medical admissions to the dispensary
		No	%	No	%	No	%	
<i>London</i>								
1774	General Dispensary <sup>17</sup>	29	1.7	22	1.3	51	3.1	1662
1775-6	The Westminster General <sup>18</sup>	12	0.9	20	1.5	32	2.4	1320
1800	Finsbury Dispensary <sup>19</sup>	128	4.6	74	2.7	202	7.3	2771
1811	Western Dispensary <sup>10</sup>	36	2.8	4	0.3	42	3.3	1283
1801	Public Dispensary <sup>11</sup>	78	2.2	38	1.1	116	3.3	3508
<i>Provincial</i>								
1804	Liverpool Dispensary <sup>12</sup>	208	2.0	97	0.9	315	2.9	10350
1801	Bath City Dispensary <sup>13</sup>	19	1.5	14	1.1	33	2.6	1222
1808	Plymouth Dispensary <sup>14</sup>	134	3.3	55	1.4	194	4.8	4010
1808	Norwich Dispensary <sup>15</sup>	18	2.9	10	1.6	29	4.7	611
1818	Combined Dublin Dispensaries <sup>16</sup>	285	1.6	165	0.9	450	2.6	17269



Table III

**TABLE III—Number of admissions to the outpatient departments of various hospitals for amenorrhea and chlorosis, menorrhagia, and all menstrual disorders, expressed as total numbers and as percentages of all admissions**

Date	Hospital	Admissions for amenorrhea and chlorosis		Admissions for menorrhagia		Admissions for all menstrual disorders		Total admissions
		No	%	No	%	No	%	
1799	Westminster Hospital <sup>17*</sup>	51	4.4	12	1.0	63	5.5	1153
1760	Bristol Infirmary	63	4.2	14	0.9	77	5.1	1165
1800		40	5.1	10	1.3	50	6.4	783
1820		11	1.4	5	0.6	16	2.1	800
1840		35	3.2	3	0.3	38	3.5	1104
1806	Nottingham General <sup>18*</sup>	60	3.9	10	0.7	70	4.6	1522
1837	Radcliffe Infirmary Oxford	10	5	No record		15	7.5	200

Sources: Records of Bristol Royal Infirmary, Bristol Records Office, The Council House, Bristol. Records of the Radcliffe Infirmary, Archives: Oxfordshire Area Health Authority (Teaching), Oxford. \*Inpatient admissions are included.

Table IV

**TABLE IV—Age-incidence of cases of chlorosis and amenorrhea and of cases of menorrhagia at outpatients department at Bristol Royal Infirmary**

	Age groups					Total
	10-14	15-24	25-34	35-44	45-54	
<b>Amenorrhea and chlorosis</b>						
1760	1	35	22	4	1	63
1800	1	33	6			40
1840	1	26	7	1		35
<b>Menorrhagia</b>						
1760		1	5	6	2	14
1800			3	4	3	10
1840			2	1		3

Source: Outpatient registers, Bristol Royal Infirmary, Bristol Records Office, The Council House, Bristol.

Moreover, the existing literature indicates that different physicians have counted and reviewed cases of chlorosis, who either visited outpatient departments or were admitted in the hospitals. For example, in 1836, Dr. Samuel Ashwell described fifteen cases of chlorosis characterized by anemia in young girls, along with menstrual irregularity and other gastrointestinal or pulmonary disorders [21]. He also mentioned that these chlorotic cases are characterized by reduced appetite and inadequate diet [22]. Similarly, Dr. Noorden, after reviewing 217 cases in 1905, mentioned that a substantial number of chlorotic cases arise in the same family. Dr. Noorden also highlighted that in addition to symptoms resembling anemia, a considerable number of young women present with loss of appetite, epigastric pain, vomiting, and constipation [17].

Furthermore, in 1923, Dr. Campbell reviewed the symptomatology of 104 cases that visited in London between 1888 and 1922 [23]. His description of the disease matched Dr. Noorden's narratives, but he also pointed out that a considerable number of cases had low gastric acidity with symptoms persisting for many years [23].

## Role of Iron in Re-conceptualizing Chlorosis to Iron Deficiency Anemia: A Paradigm Shift

Iron was prescribed for almost three centuries for chlorosis indicating that its therapeutic use is far older than the rational explanation of its mode of action, and beliefs regarding its worth have transformed

significantly with the passage of time [9]. Only recently clinicians have come to know about the effective preparations and ways of administering iron in adequate dosages [24].

Physicians have used iron salts for different purposes since the time of Hippocrates [9]. The main tribute for introducing iron to treat chlorosis can be contributed to Dr. Thomas Sydenham, who did not know the mode of action [25]. The applications of iron in the earlier years were more often symbolic, with the notion that iron was suggestive of strength and power [25]. Thus, for around next 150 years' iron continued to be used for the treatment of chlorosis but with variable results and without a suitable mechanism of action [9,26].

It was the French physician, Dr. Pierre Blaud, who first featured the specific action of iron to treat chlorosis and recommended appropriate doses of iron therapy [27]. Dr. Pierre Blaud introduced pills having a mixture of ferrous sulfate and potassium carbonate [28]. During the 1830s, Dr. Blaud prescribed iron in proper dosages even before the estimation of hemoglobin or red blood count [9]. Dr. Blaud thought that chlorosis was due to the defective formation of blood, which makes blood an imperfect fluid [9]. He further elaborated that chlorotic girls lose the coloring matter in the blood, which is required for stimulating and maintaining the regular functions of the body [9]. He also explained that iron medications help blood to restore the most important principle (its coloring substance), which is lost during menstruation [9].





Dr. Blaud suggested the use of a combination of iron sulfate with potassium carbonate because he believed that potassium carbonate increased the absorption of iron (Figure 2) [29]. Dr. Blaud initially provided treatment to thirty patients, who were cured and recovered from chlorosis within ten to thirty-two days [9]. Dr. Blaud mentioned, however, that iron was used by many physicians in the past but pre-

vious failures were due to the use of small and inadequate iron doses [9]. Thus, Dr. Blaud emphasized that his promising results were due to the use of the iron preparation he suggested and the large doses of iron he prescribed. For instance, his way of prescribing iron in proper and correct doses is given in the Figure 2 [9].

This prescription gives the equivalent of 5 grains (0.3 Gm.) of ferrous sulfate, or approximately 2 grains (0.1 Gm.) of ferrous carbonate, in each pill.

The method of administration suggested was:

1, 2, 3 day	one pill before breakfast and at bedtime.
4, 5, 6 day	one pill three times a day
7, 8, 9 day	two pills in the morning and evening
10, 11, 12 day	two pills three times a day
13, 14, 15 day	three pills twice a day
16 and follow- ing days	four pills three times a day

Figure 2

Dr. Blaud suggested that the success of his prescription was due to the finely divided state of the ferrous salts and the addition of potassium carbonate [28]. Moreover, he emphasized the two important principles of iron therapy, the use of ferrous salt, which is easily absorbed as compared to ferric salts and large doses of iron [30]. For several years physicians followed Dr. Blaud's important principles of iron therapy. In fact, the most recent development in iron therapy was also based on the greater strength of ferrous salts and adequate doses of iron [24].

### Role of Hematology in Re-Conceptualizing Disease to Iron Deficiency Anemia: A Paradigm Shift

During the mid of 19th century (1852), the first red cell count was made. This was followed by the invention of the first haemoglobinometer in 1876, which resulted in the inception of clinical hematology [31]. Although propositions that the blood might be altered in chlorosis were made as early as 1830, the theory of anemia was only accepted around forty or fifty years later [4]. E. Lloyd Jones, a pathology instructor at Cambridge and a research scholar for the British Medical Association, proposed an explanation of the causes of chlorosis that reflected new research techniques and insights from the science of hematology [32]. Jones argued that chlorosis was best understood in relation to the blood changes, mainly a drop in specific blood gravity among young females at puberty [32].

Jones highlighted that there is a significant drop in the specific gravity of blood among chlorotic young females at the age of puberty as compared to males [32]. Jones further explained this gender disparity in the drop of blood gravity by using the centrifugal method (revolving tubes of blood at a speed of 1,000 rpm) [32]. He found a reduction

in the amount of hemoglobin, a less number of red blood cells, and an increase in the proportion of serum to red blood cells in chlorotic girls as compared to males [32].

In 1890s, Dr. Ralph Stockman, physician and lecturer in Edinburgh, wrote/discovered that inorganic iron was utilized to synthesize hemoglobin [8]. He further explained that scientists seeking to cure disease through other methods did not realize that the absence of a small element such as iron could be a cause of disease [8]. Dr. Stockman analyzed the food consumed by chlorotic patients and based on his analyses of iron in different food articles, he found that diet of chlorotic patients contained significantly fewer levels of iron as compared to healthy subjects [8]. More specifically, he demonstrated that the dietary intake of iron of chlorotic patients had 1.3-3.0mg of iron per day as compared to 6-11mg of iron found in the diets of healthy subjects [8]. He further explained that onset of menstruation, while the body is actively growing, makes a great demand on the blood [33]. He took advantage of clinical hematology and described that during a menstrual period in a chlorotic girl, the red blood cells fell as much as 10 to 20 percent of their total number. For example, in five days he found that they fell from 4,432,000 to 3,764,000 per cubic millimeter [8].

Dr. Stockman further highlighted that in chlorotic girls, the decreased red blood cell forming power was due to lack of iron and possibly also to a general impairment of nutritional activity [33]. He emphasized that as soon as iron is given under favorable hygienic conditions, new red blood cells are formed rapidly [33]. Furthermore, he explained that the healthy woman has sufficient reserves of iron in the liver and spleen, but in girls malnourished from any cause including hemorrhage, there is little or no iron in the body to draw on for the production of red cells thus resulting in anemia [8].



Dr. Stockman also gave a rationale for finding chlorosis more commonly in women as compared to men [8]. He suggested that women generally have about 10 % fewer red blood cells, 8 to 10 % less hemoglobin, and 4 or 5 % more water in the blood as compared to men [8]. Blood of females is, therefore, less able to resist any drain on it mainly during hemorrhage (menstruation). Therefore, it is particularly noticed immediately at puberty when there is greater drain that takes place in young women [8].

He further emphasized that in 63 cases of chlorosis treated in the hospital, the majority of the cases' red blood cells were lacking in hemoglobin and usually in number, but often many red blood cells were ill-formed and small [8]. Thus, the severity of the clinical symptoms depended primarily on the degree of reduction in hemoglobin [8]. He further explained that in healthy women, 100 cubic centimeters (c.cm) blood yield 21 to 24c.cm of oxygen, while in chlorotic women the same amount of blood gives only 10 to 15 c.cm of oxygen [8]. Thus, it is the deficiency of hemoglobin, combined with the resultant oxygen deficiency, which forms the clinical picture of chlorosis [8]. Hence, Dr. Stockman concluded that there are two main direct causes of chlorosis: blood loss and insufficient supply of iron by the food that increases demands for iron [8].

## Combined Role of Hematology and Iron Therapy

The role of iron therapy and development in hematology helped physicians in assessing hemoglobin levels and provide treatment based on the levels of hemoglobin rather than symptoms and gender [5]. For instance, Dr. J Patek gave a detailed account of four chlorotic patients (15 to 16-year-old girls) who were admitted in the hospital during 1930s [5]. He did a thorough analysis of these chlorotic girls by taking detailed history, measured their growth, examined their blood for hemoglobin and iron, stool for occult blood, and conducted a gastric analysis [5]. After taking detailed history and undertaking detailed analysis, Dr. Patek analyzed factors responsible for iron deficiency in these adolescent girls [5]. He found that these girls did not have enough iron in their diet. The total iron found in their diet was 5.4mg, which could only satisfy the maintenance needs of this patient but could not efficiently make up the hemoglobin deficit [5]. Furthermore, Dr. Patek found that mothers of these girls were iron deficient during their pregnancy; as a result, sufficient iron stores failed to transfer from mother to these girls, thus making them susceptible to iron deficiency anemia [5]. Moreover, Dr. Patek also highlighted that gastric analysis of these girls showed less acid in the stomach of these patients (adequate amount of acid is important for iron absorption) [5].

Dr. Patek treated these cases with adequate iron therapy and observed a prompt recovery in these girls. Specifically, he saw hemoglobin levels rise from 40 to 81 percent in two months [5]. With his analysis, Dr. Patek made the conclusion that chlorosis had not disappeared; rather, it was prevalent in the form of iron deficiency anemia [5]. He further said that chlorosis is the exaggeration of a normal tendency towards anemia in adolescent girls, created by the increased demand for iron made by growth and by menstrual blood loss [5].

Changes in diet and nutrition after 1900, along with an increased understanding of ovarian function and iron deficiency anemia, provide some explanation of the disease's reconceptualization to iron deficiency anemia by 1930 [6]. Although now generally rare in the population, recently, a 9-year-old Filipino decent girl was diagnosed with symptoms of chlorosis and severe deficiency of iron. The girl was successfully treated, and her symptoms disappeared with iron salt therapy [34].

## Conclusion

Chlorosis was an important subject of medical literature until the second to third decades of the twentieth century. Hematology and iron therapy has played an important role in re-conceptualizing dis-

ease from Chlorosis to iron deficiency anemia. In addition, overall improvement in nutrition, the environment of the working class and intake of adequate diet have also contributed. This disease has not disappeared from the world; rather, it is prevalent as one of the most common types of anemia (i.e. iron deficiency anemia in the contemporary world affecting most of women of reproductive age, children and adults mainly in the developing countries).

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