

Clinical Disorders of Iron Metabolism

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Preface

There are few things more satisfying to the physician than to attend a chronically ill patient, to administer a simple, safe medication, and to observe complete recovery within a few days or weeks. When such a patient has been seen by many other physicians during the long years of illness, has been subjected to ineffective treatments, or has been told that the symptoms are of emotional origin, the physician who administers a specific curative remedy may feel justifiably proud. The physician in practice can frequently have this experience in the diagnosis and management of iron-deficiency anemia, since this is probably the most common of all organic disease, next to dental caries. A much rarer disorder of iron balance also provides the opportunity for satisfactory clinical experiences. Where else can the physician "cure" diabetes mellitus, but in the management of the patient with hemochromatosis? Hemochromatosis provides an unparalleled opportunity for practice of preventive medicine at its best.

Iron also has its strong attraction for the basic scientist. Here is an element which is easily measured either chemically or by the use of two readily available isotopes. It is a compound which forms esthetically pleasing pigments both in the living organism and in the test tube. In the electron microscope, where the world of chemistry and morphology meet, iron has uniquely beautiful properties. It is small wonder that scientists of all inclinations, among them biochemists, clinicians, physiologists, botanists, and geneticists, have been fascinated by the search for knowledge about iron.

It is our purpose to bring together in these pages some of this information for the student, the resident, and the practicing physician. This book is documented extensively. Those who wish to examine the evidence for themselves will be able to find it. We hope that in this way it will also be of some value to those actively engaged in research in this interesting field; however, we do not presume to regard it as all-inclusive.

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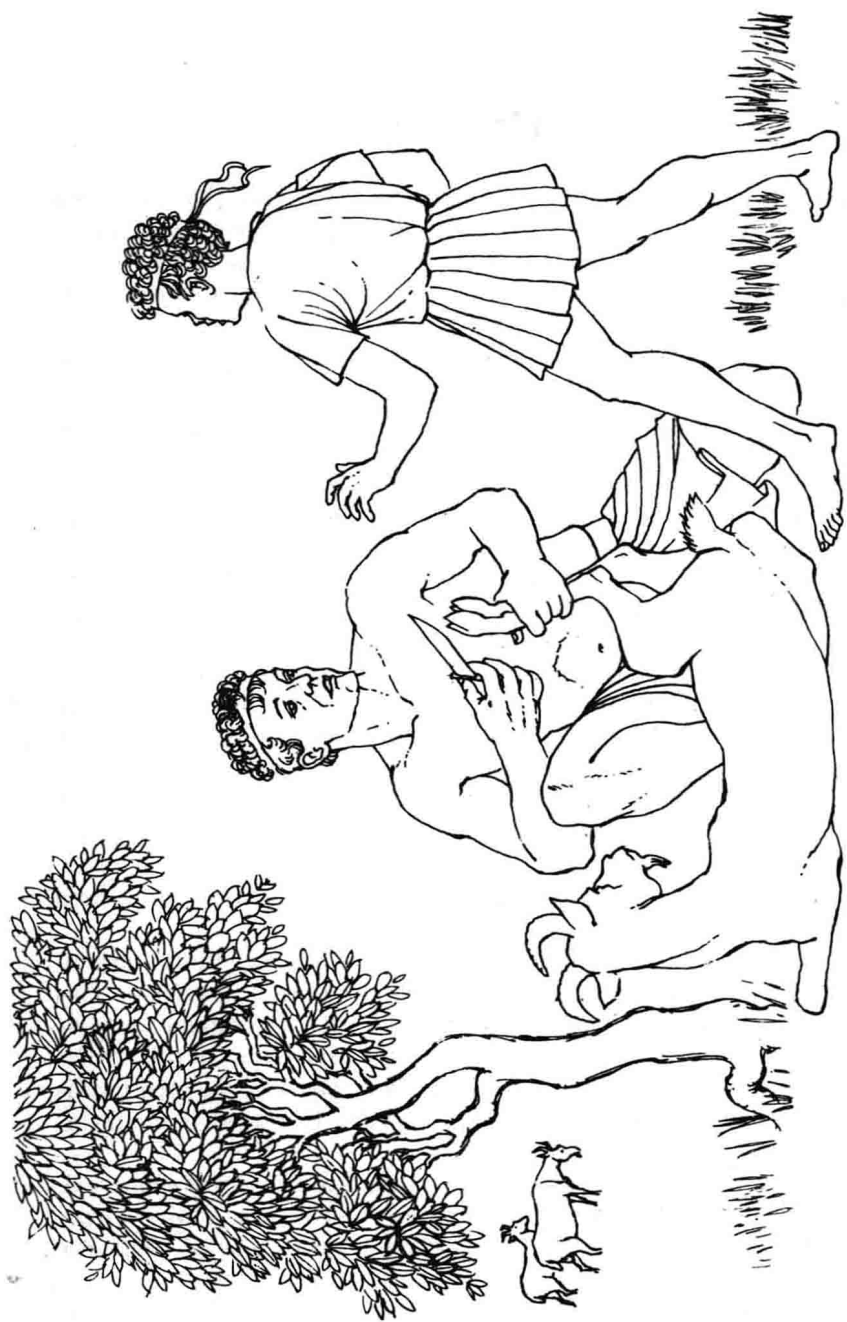


FIGURE 1-I. When Iphyclus was a child he was in the field with his royal sire while the latter was gelding rams.

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CHAPTER I

History of Iron in Medicine

CURING A ROYAL AFFLICTION

IT IS CLEAR THAT IRON was well-known in the major civilizations of the Mediterranean area and Asia, and was used both ceremonially and in implements from the beginning of recorded history.

There is little doubt that iron was used therapeutically in the Mediterranean area as early as 1500 B.C. Some of the evidence of this early usage is to be found in surviving manuscripts; some of the early references are entirely legendary. An interesting example of the latter is the symbolic, little known, legend of Iphyclus,¹ a legend which foretold the medicinal usage of iron for the ensuing two thousand years. The setting was in Thessaly, a province of Greece, not long after the Dorian invasion in 1200 B.C.

In the nascent and primitive culture of ancient Greece, remarkable powers of divination and supernatural knowledge were often attributed to animals. One who could converse with animals and find their secrets was able to command much prestige and power. Such a one was Melampus, a seer-physician, who was believed to have learned this skill from serpents which had licked his ears when he was an infant. One day, Melampus was taken captive while trying to steal a pair of oxen belonging to Prince Iphyclus. The prince had been unable to beget a child, and, learning of the prisoner's supernatural powers, he consulted with Melampus for treatment. From a vulture, Melampus learned that when Iphyclus was a child he was in the field with his royal sire while the latter was gelding rams. His father frightened Iphyclus with the blood-smeared blade, and the boy ran away. The father then stuck the blade into a sacred oak-tree, where it remained. In passing years, the knife became completely buried within the substance of the tree. The remedy was to recover the weapon from the tree, to scrape the rust from the blade into wine and administer this to Iphyclus. After ten days of this treatment Iphyclus regained his fertility.

Iphyclus' problem, reinterpreted in the light of modern psychological concepts, seems clearly to have been one of castration anxiety; and the role of rust in wine a placebo effect. The legend is probably the earliest reference to the castration complex. Nevertheless, the spectacular success of this therapy may have helped to establish the widespread use of

iron salts in spirited beverages, elixirs and tonics, popular in the ancient world as in the modern.

THE METAL OF HEAVEN

The earliest documented therapeutic applications of iron come to us from the valley of the Nile and from Mesopotamia. Both the Egyptians and Sumerians ascribed a celestial origin to iron—"the metal of heaven." Iron preparations enjoyed some therapeutic use in these countries at a very early period. The Ebers Papyrus,² dating from about 1500 B.C., is a compendium of prescriptions, two of which represent the earliest recorded therapeutic applications of iron. One was for alopecia:

"O shining One, thou who hoverest above!

O Xare! O oisc of the sun!

O protector of the divine Neb-Apt!

to be spoken over

Iron

Red Lead

Onions

Alabaster

Honey

make into one and give against."

The other prescription was for a paste to be applied for pterygium. It is interesting to note that the use of iron preparations for disorders of the eye persisted until relatively recent times. For photophobia, Babylonian physicians applied a paste containing iron ore mixed in the perinephric fat of a black ox.³ As late as the 10th Century A.D., Arabic physicians⁴ employed "blood ironstone" in the treatment of trachoma.

Although medicine in the Indian sub-continent concerned itself primarily with surgical procedures, Susruta, a contemporary of Buddha (circa 500 B.C.) may have been the first to recognize the systemic effects of iron⁵:

"Iron generates Vayu (nerve force), is cooling in its potency, allays thirst, and subdues the deranged Pittam (energy or heat) and Kapham (lymph)".*

It would be asking much of credulity to suppose that Susruta had found the element to be of therapeutic value in anemic states. However, this possibility is suggested in that he believed an excess of "Kapham" to give rise to "whiteness and coldness of the body, and heaviness of the

* The humors Vayu, Kapham, and Pittam may also be translated as wind, phlegm, and bile, respectively. However, the interpretations indicated in parenthesis are those of Bhisagratna in his scholarly translation and commentaries on Susruta's *samhitas*.

limbs," and that an excess of "Pittam" resulted in "sallow complexion, diminution in strength, and fits of fainting." Since it is believed that the subsequent development of Greek medicine owed much to the doctrine of the humors and of therapeutic principles elaborated by Susruta and other Indian physicians, such observations may have had appreciable influence on the practice of medicine in archaic civilizations.

The ancient Hebrews were well acquainted with the properties of the metal, as attested by fifty-odd biblical references. Yet neither in the Bible nor in the Talmud is a medicinal use suggested for iron.

"GREAT EFFECTES AND MARVELLOUS WORKES"

Helleno-Roman medicine was represented in several divergent theories on diseases, of which the best known is the humoral theory. According to this theory disease was a state of imbalance in the four humors, and therapy was directed toward restoring the proper balance. Consequently hygienic measures played a prominent role in treatment. And yet, iron compounds enjoyed considerable popularity among medical practitioners of this age. The effects of iron salts on the gastrointestinal tract were recognized in the Hippocratic writings. Hippocrates is also believed to have been the first to employ iron salts as styptics, a usage perpetuated today in the form of Monsel's solution.* Among the Greeks, iron was applied in the healing of battle wounds, for it was believed that they could be most quickly healed by the touch of the weapon which caused the wounds.

We are indebted to Nicholas Monarde,⁷ a 16th Century physician of Seville, for an interesting review (in *Joyfull Newes out of the New Founde Worlde*) of the medicinal uses of iron in the Roman empire:

"The iron and steele do serve in medicine with great effectes and marvellous workes, by curing and healing divers diseases, and so Plinie in his booke of the natural historie, treeting of this matter of iron, after he wrote great things of it, as well in that which doth profit in the service of man, as other curious thinges, hee treateth of the vertues and woorkes which it doth in medicine, shewing first the qualities of it, saying: The yron hath vertue to drie up, to retayne and to holde faste; it is good for such as dooe lacke their haire, that it may growe, beeing prepared and mingled with some licour prepared and made for the same purpose, it taketh away the roughnesse of the cheekes, mingled with vinegar; and being made in an oyntment with oyle of Myrtilles and waxe, it taketh away the blisters of all the bodie; the pouder of it mingled with vineger, doeth heale the disease called Saint Anthonies fire, as also al manner of skabbes: it healeth the little sores between the nailes and the finger, the pouders thereof being ap-

* Ferric subsulfate

pled thereunto with a linen cloath. It healeth also the flux of women of what sorte soever it be, being put thereunto with wooll or with cotten wool, and also if they be applied thereunto after the maner of a Tent in the lower partes: the powder being mingled with mirrhe and put to the sores or wounds new hurt, doeth soder them and heale them: and beeing mingled with Vineger and put upon the piles, it dissolveth them. It is a great remedie for such as are gowtie, being applied with thinges made for the purpose upon the grief: it stencheth the blood of such as are wounded, which is for the most part made of Iron."

Here there seems to have been some connection drawn between iron and blood, presumably based on a similarity in the color of blood and iron oxides. This association recurred the early accounts of iron (cf. the use of "blood iron stone" for trachoma in the Arabian World of the 10th Century A.D.), although its essential validity remained unconfirmed for 1500 years. Monarde continues to recount the virtues of this wondrous element:

"It is given to bee drunke to such as are diseased of the lungs, for it consumeth the disease, and healeth him that is sicke, it stayeth any manner of fluxe and the Piles, and doeth remedie the sores of them. It healeth sore cheekes, casting the pouders upon them it is a great remedy and worthy of estimation. He that doeth cause it to be made and doeth put it upon a Plaister called Higre, the which doth profite to take away and make cleane the soares, and to take away the Fistula and to eate away the Braunches, and too cause that the sores bee filled with fleshe: all this is of Plinie in the Chapter of Iron. Galen . . . declareth much the necessitie of Iron, for the life of mankinde and for the service of man, and dooeth account it for a most excellent remedy, for to dry up the moystures and teares of the eyes. In that of continuall dissolution, hee sayth: that peeces of burning yron cast into milke, by taking away the waterishness which the milke hath, is good for over much stooles, and especially for the bloodie flux. And in the tenth of the simple medicine, he commaundeth that milke be given wherein peeces of yron have bene quenched, and saith that such kinde of milke dooeth good unto them which have the bloody flux.

Dioscorides in the chapter where he treateth of the rust of yron, saieth, that the water or the wine, that hath quenched a peece of burning Iron, is good for them that have the fluxe of the stomach, and the bloody fluxe, it dissolveth the hardnesse of the lungs, and serveth in cholerike stooles, and in the loosenesse of the stomacke. Aecio, treating of certaine rowles which are verie excellent for the opilations* of the inner partes, sayeth, that it is a moste convenient remedie for the Lunges, and inner partes of the Bodye, that the water that hath quenched whotte Iron bee taken for a long time: but such as have a whotte disease, must use of the water, and such as are colde if they be weake, of wine that hath quenched yron. Scribonio, an auncient Phisition sayth, that the water which hath quenched whot steele is a great remedie for such as are

* Opilations: probably means ablution, e.g., purification

swollen, and for such as have sores and griefs of the bladder, chiefly if they use it continually."

The therapeutic indications for iron detailed by Monarde for the Roman era may be summarized as follows:

- alopecia
- acne
- vesicular, bullous and crusting eruptions
- erysipelas
- paronychia
- vaginal discharges
- wounds
- hemorrhoids
- gout
- tuberculosis (probable)
- diarrhea
- peri-anal fistulas
- excessive lacrimation
- amebiasis (probably accounting for "bloody fluxe")
- vomiting
- weakness
- edema
- fevers
- cystitis

Every age, it seems, has its panaceas. It is likely that iron attained its reputation, at least in part, by a salutary effect upon iron deficiency anemia accompanying the "bloodey flix" and "the flux of women." In an age which employed a myriad of pharmacologically inert or noxious agents, such remedies as were occasionally beneficial were applied with such therapeutic zeal as would make even a modern blush.

With the fall of the Roman Empire, the vestiges of Roman civilization and Greek and Roman medical practice were swept away. It was during this medieval period, when intellectual darkness blanketed the northern Mediterranean littoral, that the Arabic civilization came into blossom. This culture took inspiration from Greek and Roman sources. The Saracens translated and preserved the medical knowledge of the ancients and added the benefit of their own experiences. Even today, much of the writings of Greek and Roman physicians are available only in Arabic. However, in contrast to the prodigious Arabic contributions to mathematics and physical sciences, there seems to have been little advance in medical science from that known to Galen and his contemporaries. Avicenna⁸ concisely summarized the medicinal effects of iron as understood to the 10th Century physician:

"Thus, ferruginous waters impart strength to the internal organs, prevent stomach trouble, and stimulate the appetite. They resolve the spleen and are beneficial to those who cannot cohabit properly."

At such centers of learning as Cordova and the University at Salerno, the medical knowledge of Greeks, Romans, and Arabs was passed to a re-awakening Europe. Still, despite many centuries of experience with various iron concoctions and tonics, there seems to have been no further progress toward elucidating the physiological and pharmacological properties of the element.

THE TREATMENT OF IRON POISONING

In 14th Century Italy, interest in the toxicology of iron antedated the Borgias⁹:

"He to whom shall have been given the rust of iron or the dross of it, shall be dried up as to his joints and his belly shall adhere to his loins...his cure is to moisten all of his body with a bath in which turtles are boiled...he is to eat of new butter and fatty soup, and the bezoar (antidote) of it is powdered magnetic stone...."

"He to whom has been given the magnetic stone...will become lunatic, melancholy, or furiously mad. Now the treatment is...fragments of emeralds and gold filings...with wine, and he is to be clystered* with the milk of ewes and oil of sweet almonds."

In the modern era, iron poisoning continues to be a dire and all-too-common experience in the pediatric age group. However, concepts have changed appreciably since the 14th Century, and these will be elaborated upon in a subsequent chapter.

THE SICKNESS OF VIRGINS

Following the Renaissance, iron as "crocus martis" or "saffron of Mars"† continued to be extensively employed by European physicians in the empirical treatment of a variety of disorders. In the 17th Century there appeared a new and ultimately rational role for iron as specific therapy for a single disease: chlorosis. Indeed, chlorosis was to become the central issue of iron therapy for the ensuing two hundred years. In view of the importance of this association, a digression should be made

* Clyster: enema

† Also "Martian Flowers." These designations for iron-containing tonics date back to the Helleno-Roman period, when iron was regarded as a gift of the god of war. Alchemists designated iron as Mars, and late Renaissance apothecaries perpetuated the terminology.

at this point, to look back again through time and consider early allusions to this peculiar affliction of young women.

The Ebers Papyrus contains the earliest reference to what may have been iron deficiency anemia. Although only fragments of this ancient treatise are available in English, it is understood² that the original described a "deadly AAA disease," characterized by chest pain, dyspnea, palpitation, and edema, and caused by worms. The condition was recognized in both sexes. There is some question whether the AAA disease was ankylostomiasis or schistosomiasis. It is maintained by some authorities¹⁰ that the ancient scribe had recorded the symptomatology of advanced iron deficiency anemia occurring in hookworm disease.

In the Hippocratic Collection⁶ is found the next comment on a condition which we might now attribute to iron deficiency anemia, and there is noted as well the symptom known as pica:

"Such women as cannot conceive, but appear green, without fever, and the viscera are not in fault; these will say that the head is pained and that the menstrual discharge is vitiated and scanty.

"Both men and women who have long had a bad color, but not in the form of jaundice . . . eat stones and earth and have piles. Those who have green color, without decided jaundice, are affected in like manner."

It has been held that "Hippocrates" advocated venesection for this condition, although such is not indicated in the English translation. However, this appears to have been the practice of his successors almost until the modern era⁸:

"Blood-letting is applicable . . . (in) women who fail to menstruate, but do not show the two colors indicative of a need of venesection because they are so dusky, or pale, or greenish."—AVICENNA

Although these ancient authorities had recognized bad color or green color in women with menstrual disorders, it remained for Johannes Lange,¹¹ in 1554, to give the first clear description of chlorosis:

"... Since you demand this opinion of the disease of the girl, and dependable advice concerning marriage, because of our old friendship, and at the same time you rightly ask with what kind of disease is she afflicted; since the qualities of her face, which in the past year 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 the arteries of her temples pulsate, and she is seized with dyspnoea in dancing or climbing the stairs, her stomach loathes food and particularly meat, and the legs, especially at the ankles, become edematous at night. From these accidents indeed, and from the pathognomonic signs of the disease, which betray the cause and nature of the disease,

point out its treatment, I marvel that old physicians do not know the cause and nature of the disease....

"... Nor has this disease a proper name, as much as it is peculiar to virgins, might indeed be called 'virgineus,' which is the custom of the matrons of Brabant to call white fever, or pale face and the fever of love; since every lover becomes pale, and this color is proper for a lover,* although a fever very rarely is present. But this disease frequently attacks virgins, when now mature they pass from youth to virility."

Not content with this elegant description of severe iron deficiency, Lange attempted to define the pathophysiology:

"For at this time, by nature, the menstrual blood flows from the liver to the small spaces and veins of the womb which when from the narrow mouths, which are not yet distended, also obstructed by thick and crude humors, and finally from the thickness of the blood, cannot escape: then carried backwards through the vena cava and the large arteries flows to the heart, liver, diaphragm and veins of the diaphragm: also a good part is distributed to the head, and grave accidents appear in the viscera, dyspnoea, a tremulous throbbing of the heart, inflation of the liver, nausea of the stomach, cardalgia; not rarely epilepsy with loss of senses, and delirium...."

The role of excessive blood loss seems to have been elusive. However, Lange observed that extended interruption of menses was curative, a curious observation which is inconsistent with modern concepts of the influence of pregnancy on anemia:

"I therefore say, I instruct virgins afflicted with this disease, that as soon as possible they live with men and copulate, if they conceive they recover."

Lange offered *morbus virgineo* (the sickness of virgins) as a title for this malady. Subsequently, the disease became widely recognized. Indeed, it reached almost epidemic proportions in Europe. As "the green-sickness" or "love-sickness," it caught the imagination of painter and poet. The features of chlorosis have been preserved in numerous canvases by painters of the Dutch school. Frequent allusions may be found in the writings of Shakespeare and his contemporaries:

"She never told her love
But let concealment, like a worm i' the bud
Feed upon her damask cheek; she pin'd in thought
And, with a green and yellow melancholy
She sat, like patience on a monument."

—SHAKESPEARE, *Twelfth Night*

* Cf. Ovid, "*Palleat omnis amans, hic est color aptus amanti.*" All who love are pale, this is the proper color of love.

Most contemporary medical authorities seemed to feel that chlorosis was much less common among country girls, perhaps reflecting different dietary or matrimonial practices:

"I married a wife of late,
The more's my unhappy fate:
I married her for love
As my fancy did me move,
And not for a worldly estate.

But oh! the green-sickness
Soon changed her likeness;
And all her beauty did fail.

But 'tis not so
With those that go
Thro' frost and snow
As all men know
And carry the milking pail."

—IZAAB WALTON, *The Compleat Angler*

BLOOD AND IRON

In 1681, Sydenham¹² expressed the majority opinion of medical authorities of his era, in regarding chlorosis and hysteria as one and the same disease, due to "the faulty disposition of the animal spirits." However, he is to be given credit for first recognizing the value of iron in chlorosis.

"The chief curative indication is the restoration of blood—the fount and source of the spirits. . . .

"With this view, I bleed. I then purge for three or four mornings running. Meanwhile, the patient is so far from improving that she gets worse. . . .

"After these evacuations, I comfort the blood and the spirits belonging to it by giving a chalybeate* thirty days running. . . . To the worn-out and languid blood, it gives a spur or fillip, whereby the animal spirits, which before lay prostrate and sunken under their own weight, are raised and excited. Clear proof of this is found in the effects of steel upon chlorosis. The pulse gains strength and frequency, the surface warmth, the face (no longer pale and death-like) a fresh ruddy color. Here, however, I must remark that with weak and worn-out patients the bleeding and purging may be omitted, and the steel be begun with at once.

"Next to steel in substance, I prefer a syrup. This is made by steeping iron or steel filings in cold Rhenish wine. When the wine is sufficiently impregnated, strain the liquor; add sugar; and boil to the consistency of syrup."

Sydenham's observations, like those of his predecessors, were entirely empirical. However, until the early 20th Century, the history of iron became inextricably entwined with that of chlorosis.

* Chalybeate: containing or charged with iron.

It was not until the first part of the 18th Century that the ash of blood was shown by Lemery and Geoffroy^{13*} to contain iron. By the middle of the century, Menkhini^{14*} had demonstrated that the blood iron content could be elevated in experimental animals by placing them on iron-rich diets. The chemical rationale for iron therapy was provided by Födisch^{15*} in 1832, who demonstrated a reduction in blood iron content in chlorosis. However, even a year before this important discovery, Pierre Blaud¹⁶ had written:

"But in all these cases, it comes from a vicious sanguinification, the result of which is an imperfect fluid, where the serosity predominates, where the coloring principle is lacking and which is no longer adequate to excite suitably the organism and carry on the regular exercise of its function . . . the treatment is feruginous preparations, modifiers of the organism, which return to the blood the exciting principle which it has lost, that is to say the coloring substance. When one knows the importance of the blood and the role which it plays in the organic scene of life, when one knows that this fluid is the exciting agent of all our parts, and the prime mover of all their functions, one is little astonished at the trouble manifested when the conditions necessary to its influence no longer exist in its composition and that it lacks some one of the elements. Here the coloring matter is lacking. It is a clinical fact, which we know to be beyond doubt and it is this which gives birth to all the functional disorders. . . ."

Blaud reported the cure of thirty cases of chlorosis. His tablets contained ferrous sulfate and potassium carbonate, 320 mg. of each, to provide 64 mg. of elemental iron per tablet. He administered this in increasing dosage until his patient was receiving twelve tablets (770 mg. of elemental iron) daily.

Blaud recognized that in solution these salts would result in precipitation of the insoluble ferrous carbonate. However, he believed that a fine dispersion of the ferrous carbonate would be achieved in the gastrointestinal tract, and that potassium sulfate would enhance iron absorption by a direct action on the lymphatics and peristalsis of the intestine. We now know that this mixture results in less intestinal absorption than would be achieved with ferrous sulfate alone, and that the outstanding results achieved by Blaud were due to the large amount of iron administered. Indeed, the doses of iron given by Blaud are in excess of those generally advocated today. An additional factor was Blaud's use of the reduced form of iron: he seems to have been the first to employ a ferrous salt. Blaud's experience was soon amply confirmed by his contemporaries, and his pills became widely employed throughout the world as "the veritable pills of Dr. Blaud."

* These works are not available for examination in the original.

Felix von Niemeyer,¹⁷ in his influential textbook of 1872, expressed his opinion that one iron salt was probably as efficacious as another, but:

"For more than 20 years, I have used Blaud's pills almost exclusively in chlorosis, and have witnessed such brilliant results that I have never found any opportunity to experiment with other articles....

"The number of patients who have recovered in my practice through the employment of Blaud's pills after they have taken small doses of tincture of iron and wine of iron for years, without positive effect... is large enough to warrant the assertion that we shall cure chlorosis most speedily and surely by means of ferruginous preparations which can be tolerated in large doses, and of these Blaud's pills stand highest in the list."

Although iron became accepted as the standard treatment of chlorosis, the mechanism through which it exerted its beneficial effects remained in doubt. It would have seemed that absorption and incorporation into hemoglobin would be the simplest and most likely process. However, as Immerman,¹⁸ in 1875, observed in his extensive review of anemia:

"At this point, it should be remembered that the healthy organism derives its needed iron from iron-containing dietary articles, without the addition of medications, and that large doses of iron are actually taken up only in small part in the intestinal fluids, the preponderant portion being discharged with the stool as black iron sulfide. This makes a certain difficulty in the clarification of the mode of action of medicinal iron."

At the close of the 19th Century, other dissenting voices were heard, the most influential of which was that of Bunge, an outstanding physiological chemist. Bunge's views were based on the theory that synthetic processes were almost exclusively found in the plant kingdom¹⁹:

"As is well known, Liebig taught that syntheses occur only in plants; in animal bodies, on the other hand, only degradation (occurs). Admittedly, this doctrine was soon shaken by Wöhler's discovery of the synthesis of hippuric acid in the animal body. But hippuric acid is a relatively simple compound: it contains only nine carbon atoms per molecule compared to at least 700 in hemoglobin. Therefore, it is incomprehensible that it should be generally believed that this complicated compound arises in our bodies...."

Bunge proposed an ingenious theory of etiology of chlorosis: the pubertal female was thought to build up iron stores in liver and spleen in anticipation of future pregnancy, thus leaving little iron available for blood formation; and leading to the development of chlorosis. He emphatically denied the absorption of iron through the gastrointestinal tract, citing

numerous experiments as support for his argument. To Bunge it was inconceivable, for reasons indicated, that inorganic iron could be utilized by the body in synthesis of hemoglobin. Impaired absorption of organic iron compounds in chlorosis was attributed to a disorder of the nervous system, in which emotional disturbances affected the absorption or assimilation of the organic compounds, in some fashion. Therapy with inorganic iron, Bunge regarded as purely suggestive, without any physiological or pharmacological significance, and he ridiculed clinicians who thought otherwise¹⁹:

"It has been found that after the administration of Ferratin to anemic individuals there is an increase in the number of blood cells and the hemoglobin content of the blood. But a control series is lacking. . . . We must go still further in our scepticism; we must pose the question whether physicians would not be justified in attributing the successes of iron therapy to suggestion, and therefore discarding all iron preparations. Modern psychological research has taught us to suggest without administering poisons. . . . If a poison is to be used in such psychotherapy, it is better that one pick an unabsorbable poison. In that case one should stick with Bland's pills, or—better yet—bread pills. A good physician knows how to suggest without pills."

It is of particular interest that as early as 1885, it had become fashionable to ascribe poorly understood responses to psychologic effect. Bunge's call for the application of controlled series and rigorous scientific methods was sorely needed at a time of much confusion in the subject of iron therapy. However, in accepting uncritically, and without good experimental evidence, the theories of non-absorption and non-utilization of iron, and the theory of a placebo effect, he committed an error of the same type for which he condemned Bland, Niemeyer, and others. His views were widely accepted. He undoubtedly delayed the acquisition of knowledge in this disputed area and helped to turn back the treatment of chlorosis, by sixty years at least.

The most significant clinical contribution of this era was by Stockman in 1893.²⁰ He demonstrated in chlorotic women: an adequate hemoglobin response to parenterally administered iron citrate, and iron peptonate; an adequate response to oral ferrous sulfide; and that bismuth, arsenic, manganese, and hydrochloric acid administered orally were totally ineffective in cases which subsequently responded satisfactorily to reduced iron (i.e., powdered elemental iron), 500 mg. daily by mouth. Unfortunately, this important contribution seems to have gone largely unnoticed.

Stockman²¹ also assayed the iron content of a variety of diets. He found his own diet to contain 8.0 and 10.9 mg. on two separate days. The