

# CLINICAL DISORDERS OF IRON METABOLISM

*Second Edition, Revised and Expanded*

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VIRGIL F. FAIRBANKS • JOHN L. FAHEY  
ERNEST BEUTLER

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# CLINICAL DISORDERS OF IRON METABOLISM

*Second Edition*

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## PREFACE

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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 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 have this experience frequently in the diagnosis and management of iron-deficiency anemia because this is undoubtedly the most common chronic organic disease, after dental caries. A much rarer disorder of iron balance also provides the opportunity for satisfactory clinical experiences. When 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 is a source of fascination for the basic scientist. Here is an element which is easily measured either chemically or by the use of two readily available radioisotopes. Iron or iron-protein complexes also can be studied magnetometrically or by electrophoretic, immunologic, or chromatographic techniques. Iron complexes form beautifully colored and fluorescent pigments both in the living organism and in the test tube. Some iron compounds such as ferritin are easily precipitable as many-faceted crystals. Under the electron microscope, where the worlds of chemistry and morphology meet, iron has uniquely beautiful prop-

erties. For the biologist interested in the origin and evolution of life, studies of ferredoxin, the cytochromes, and myoglobin and hemoglobin have been particularly rewarding. 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.

The remarkably large number of outstanding contributions to this field since the first edition was published in 1963 has necessitated considerable revision of most of the pages of *Clinical Disorders of Iron Metabolism*. An indication of the growth of the literature in this field is the fact that of more than 1,700 articles cited in the bibliography approximately 40 percent were published in the 8 years intervening between this edition and the earlier edition of this book. We have attempted to give a balanced account of the subject, but with a strong clinical orientation. We hope that physicians will find the text both informative and utilitarian. We hope as well that those actively engaged in research in this field will find the documentation of this book of use as a guide to the literature on iron for the years prior to 1970. On the other hand, we do not presume to imply that the references cited are all-inclusive.

We acknowledge with deep gratitude the enduring support, assistance, and patience of many people, particularly of our families, our secretaries, our library and editorial staffs, and of Drs. Bernard K. Forscher, William P. Baldus, E. J. Walter Bowie, Paul Didisheim, Joseph M. Kiely, Jorge E. Maldonado, Lucian A. Smith, and Donald A. Wolochow.

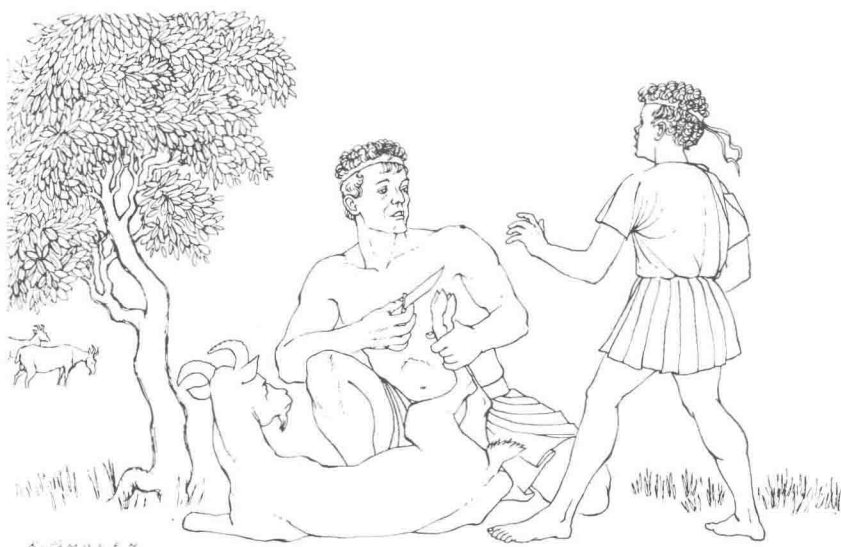


FIG. 1. 1. When Iphycus was a child he was in the field with his royal sire while the latter was gelding rams.

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## HISTORY OF IRON IN MEDICINE

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### CURING A ROYAL AFFLICTION

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 and some of the early references are entirely legendary. An interesting example of the latter is the little-known legend of Iphycus<sup>1</sup>— a story rich in symbolism, which foretold a major empirical medicinal use of iron for the ensuing 2,000 years.

The setting of the Iphycus legend was Thessaly, a province of Greece, not long after the Dorian invasion in 1200 B.C. In the primitive culture of prehistoric Greece, remarkable powers of divination and supernatural knowledge were often attributed to animals. One who could converse with animals and learn their secrets was able to command much prestige and power. Such a one was Melampus, a seer-physician, who was believed to have learned his 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 drove the blade into an oak tree, where it remained. In passing years, the knife became completely buried within the substance of the tree. The remedy was for the prince to cut down the old oak tree, recover the knife, scrape rust from the blade into wine, and drink the iron-fortified liquor. Soon the queen conceived, and the royal succession was ensured.

A modern interpretation of this legend might be that Iphyclus suffered castration anxiety. The oak represented, perhaps, the lingering menace of paternal authority. The role of rust in wine was, we should say, a spectacular placebo effect. The legend seems to be the earliest reference in Western literature not only to the castration complex but also to the systemic use of iron medicinally.

#### THE METAL OF HEAVEN

In ancient civilizations of the Eastern Mediterranean area, a celestial origin was ascribed to iron, perhaps in recognition of the high iron content of meteorites. The "metal of heaven" was used therapeutically both in Egypt and in Mesopotamia. The oldest surviving manuscript of mankind, the *Ebers Papyrus*,<sup>2</sup> is an Egyptian pharmacopea dating from about 1500 B.C. Two of the remedies described in the *Ebers Papyrus* contained iron. These are the earliest prescriptions for iron which have been preserved in written form. One prescription was for relief of baldness:

"O shining One, thou who hoverest above!  
 O Xare! O disc 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.<sup>3</sup> For photophobia, Babylonian physicians applied a paste containing iron ore mixed in the perinephric fat of a black ox.<sup>4</sup>

Although medicine in the Indian subcontinent 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 iron:<sup>5</sup>

"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 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 more than 50 biblical references. Yet neither in the Bible nor in the Talmud is a medicinal use suggested for iron.

#### "GREAT EFFECTES AND MARVELLOUS WORKES"

Greco-Roman medicine was represented in several divergent theories on disease, 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. Yet iron compounds enjoyed considerable popularity among medical practitioners of this age. The effects of iron salts on the gastrointestinal

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\*The humors Vayu, Kapham, and Pittam may also be translated as wind, phlegm, and bile, respectively. The interpretations indicated in parentheses are those of Bishagratna<sup>6</sup> in his scholarly translation and commentaries on Susruta's *samhitas* and may only represent an attempt to recast Susruta's ideas in more modern terms.

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.

During the first century of our era, a prodigious encyclopedia was compiled by Caius Plinius Secundus ("Pliny the Elder") who collated his study of the 2,000 books then accessible to him into 37 volumes containing 20,000 subject reviews. In the 34th volume he wrote extensively of iron. We quote from the handsome Philemon Holland translation<sup>6</sup> of 1601:

It remaineth now to discourse of . . . yron, a metall which wee may well say is both the best and the worst . . . in the world: For with the help of yron we breake up and ear the ground, we plant and plot our groves, we set our hortyards . . . by meanes of yron and steele we build houses, hew quarries . . . yea and in one word, we use it to all other necessarie uses of this life. Contrariwise, the same yron serveth for warres, murders, and robberies . . . this I take to bee the wickedest invention that ever was devised by the head of man . . . whereby it is evident, that the mischeefe proceeding from yron, is not to be imputed to the nature of it, but to the unhappie wit of man.

As touching the use of yron and steele, in Physicke, it serveth otherwise than for to launce, cut, and dismember withall: for take a knife or dagger and make an imaginarie circle two or three times with the point thereof, upon a young child or an elder bodie . . . it is a singular preservative against all poysons, sorceries, or enchantments. Also to take any yron naile out of the coffin or sepulchre wherein man or woman lieth buried, and to sticke the same fast to the lintle or side post of a dore . . . leading into the house . . . where any dooth lie who is haunted with spirits in the night, he or she shall be delivered and secured from such phantasticall illusions. Moreover, it is said, that if one be lightly pricked with . . . sword or dagger which hath been the death of a man, it is an excellent remedie against the paines of sides or breast, which come with suddaine prickes and stitches. An actual cauterie of yron red hot, cureth many diseases, and especially the biting of a mad dog; in which case it is so effectually that if . . . the patient be fallen into an Hydrophobie . . . the partie shall find help presently.

As touching the vertues thereof, . . . it recovereth the haire . . . many use it for the roughnesse about the eyelids: the pimples also breaking forth over all the bodie. For shingles and St. Anthonies fire, it is singular good. Likewise it killeth scabs, and healeth whitflawes of the fingers. . . . The same if conveyed up in wooll after the manner of a pessarie into

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\*Ferric subsulfate.

the naturall parts of a woman, stayeth the immoderate flux both of whites and reds. The rust of yron tempered in wine . . . is good for a green wound: put thereto vinegre, and then it helpeth the piles and swelling biggs of the fundament. . . . But marke this one thing: yron being that which woundeth most and sheddeth bloud, yet the scales that come from it staunch the same. Reduced into a fine pouder, and gently strowed upon the eyelids, they are good for the accidents thereto belonging.

A more extensive and up-to-date review of the medicinal uses of iron in the Roman Empire was provided by Dr. Nicholas Monardes,<sup>7</sup> a 16th century physician of Seville, who wrote in *Joyfull Newes Out of the Newe Founde Worlde*:

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, treading 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 Myrtiles and waxe, it taketh away the blisters of all the bodie; the pouder of it mingled with vinegar, 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 applied 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 applyed thereunto after the manner of a Tent in the lower partes: the pouder being mingled with mirrhe and put to the sores or wounds new hurt, doeth soder them and heale them: and beeing mingled with Vinegar 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.

It is remarkable that ancient physicians correctly guessed that iron is the source of the color of blood. So far as can be established, this clairvoyance was based entirely on a similarity in color between blood, and perhaps blood-stains, on the one hand, and iron ores (hematite) and rust on the other. Arabic physicians<sup>8</sup> who used "blood iron stone" (probably hematite) for treatment of trachoma in the 10th century A.D. drew the same analogy, although the validity of the relationship was not to be established for many centuries.

Let us return to the account by Monardes:

It is given to be 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 fluxe. And in the tenth of the simple medicine, he commaundeth that milke be given wherein peeces of yron have been quenched, and saith that such kinde of milke dooeth good unto them which have the bloody fluxe.

Dioscorides in the chapter where he treateth of the rust of yron, saith, 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 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 Monardes for the Roman era may be summarized as follows:

|                           |                       |
|---------------------------|-----------------------|
| alopecia                  | diarrhea of all sorts |
| acne                      | perianal fistulas     |
| dermatitides of all sorts | excessive lacrimation |
| erysipelas                | vomiting              |
| paronychia                | weakness              |
| vaginal discharges        | edema                 |
| wounds                    | fever                 |
| hemorrhoids               | cystitis              |
| gout                      |                       |
| pulmonary diseases        |                       |

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\*Opilations: probably means ablution—that is, purification.



Every age, it seems, has its panaceas. One may wonder whether iron might have attained so huge a reputation because of its very salutary effect upon the anemias which accompanied intestinal parasitism and amebiasis (no doubt largely responsible for the "bloody fluxe") as well as that commonly occurring as a result of "the fluxe of women."

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.

From Pliny to ibn-Sina (Avicenna) is a span of nearly 1000 years. Ibn-Sina systematically catalogued all that was known in the 10th century of anatomy, physiology, and pharmacology in his massive *Canon of Medicine*, a treatise which would be the authoritative medical encyclopedia for several centuries. An adequate translation of *The Canon* into English seems not yet to have been made. In the Latin text,<sup>8</sup> published in Louvain in 1658, there are detailed descriptions titled "Ferrum" and "Haematitis lapis" (blood stone). The former reads, in part:

*IRON.* It is known to everybody. There are, however, three forms . . . iron ore, rust, and steel. *Effect and properties:* Iron rust . . . has an astringent and corrosive quality. Its slag is . . . a potent desiccant. *Cosmetics:* The rust of iron should be put on paronychia with wine. *Tumors and tubercles:* Apply the same with wine to erysipelas and pustules. *Application for joints:* The same applied with wine to podagra (gout) will be of help. *The parts of the head.* Mix with vinegar; and vinegar which is fortified with iron rust may be used to heal draining ears. *The parts of the eye.* It [iron rust] is useful for scabby eyelids and pterygium. *Digestive parts:* Wine, also water, in which iron has been quenched, will help the spleen, weak stomach, and the debilitated. *Excretory parts:* Fine scales [of iron] draw off water, but they are less efficacious than are scales of brass. Iron has a styptic property by which the flow of women can be made to subside. It dries up hemorrhoids. Wine, in which iron has been quenched, restrains chronic abdominal discharges; it is good for loose stools; it improves incontinence of urine; it restrains menstrual flow; it restores sexual potency and strength to men.

Ibn-Sina's *Canon of Medicine* was based on Greco-Roman medicine. One senses an echo of the legend of Iphycus in the last sentence of this excerpt.