IRON

IN CLINICAL MEDICINE

EDITED BY

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FOREWORD

Iron is one of the most plentiful and most ubiquitous of the elements. Although it is present in living organisms in only minute amounts, iron plays a biological role of tremendous importance. Mammalian life could not exist without the vital iron-containing compounds essential for oxygen transport and oxidative tissue processes. In clinical medicine iron plays an extremely important role, since disturbances in iron metabolism are responsible for some of the most prevalent of human diseases.

Ancient Egyptian, Hindu, and Greek physicians recognized the medicinal value of iron compounds in the treatment of "weakness," and Sydenham in 1681 recommended iron in the treatment of chlorosis, but only within the past thirty years have major advances been made in our understanding of the metabolism of iron. Much of this knowledge has been gained since the introduction of radioiron tracer methods of investigation in 1939. These methods have provided definitive information on the absorption and excretion of iron, the pathways that it follows in the body, and the dynamic aspects of its metabolic activity. Studies of iron metabolism have also yielded important information concerning the physiology and pathology of the bone marrow, of erythrocytes, of the reticuloendothelial system, and of tissue enzymes.

Clinical application of studies of iron metabolism have provided valuable diagnostic methods, have explained the pathogenesis of certain diseases, and have improved means of therapy.

Demonstration of the relatively great difficulty with which iron compounds are usually absorbed by the human has helped to explain the high incidence of iron deficiency and iron-deficiency anemia—probably the most common deficiency afflicting the human race. The ability to modify the absorption of iron from the enteric canal in accordance with the body's need is a unique and, as yet, not satisfactorily explained example of conditioned selective absorption. This selectivity is of fundamental importance as a homeostatic mechanism, because the human organism has an extremely limited capacity to excrete iron; and if iron were readily absorbed, it would accumulate in the body tissues and produce hemosiderosis, and perhaps even tissue fibrosis and hemochromatosis. The bypassing of this homeostatic mechanism by the parenteral administration of iron compounds is now a relatively easy procedure, and one that should be used with caution, since, undoubtedly, it is unwise to burden the tissue with an overabundance of iron.

The passage of iron through the plasma iron pool to the bone marrow and into hemoglobin and erythrocytes, and its eventual release from the red cell hemoglobin by the processes of the reticuloendothelial system and its return to the plasma iron pool, can now be readily traced and measured in the undisturbed human organism. These studies have changed our concepts of the pathogenesis of certain types of anemia, and have explained the influence of disease processes on the hematopoietic system. Further understanding of these processes will improve our ability to prevent or counteract these diseases and, in addition, will contribute to our understanding of the fundamental effects of disease on the host organism.

The study of metabolism of myoglobin, cytochrome C, catalase, ferritin, hemosiderin, and other iron-containing tissue compounds is of tremendous importance. How the metabolism of these compounds may be modified by normal and disease states is a new, relatively unexplored, and potentially very fruitful area for investigation. The methods for conducting this research are available. Only the interest and the endeavor of the investigator are required.

The studies reported in this volume are the most recent and most significant contributions to our knowledge of iron metabolism. Among the contributors are scientists of world-wide renown, and their reports will be of great importance and interest, both to medical practitioners and to other investigators. This presentation of the results of the past twenty years of research on iron metabolism is most timely!

JOSEPH F. ROSS, M.D.

PREFACE TO THE SYMPOSIUM

This symposium on Iron in Clinical Medicine was held at the University of California School of Medicine in San Francisco on January 28 and 29, 1957, under the joint auspices of the University of California Medical Extension and the Children's Hospital of San Francisco. The expenses were defrayed, in part, by a grant from Lakeside Laboratories, Inc., Milwaukee, Wisconsin.

Participants were chosen because of their contributions to different phases of iron metabolism. An attempt was made to represent as many medical institutions as possible. The individual papers are reproduced here essentially as given; occasional editorial alterations were made to facilitate the transition from the individual presentations to publication in book form. The discussion part was tape recorded during the symposium; for the sake of clarity the order of questions and answers was altered and the material grouped under two headings: "Parenteral Iron Therapy" and "Various Problems in Iron Metabolism."

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John B. deC. M. Saunders, M.D.

IRON AND THE DEVELOPMENT OF MEDICINE

The use of iron and its compounds in medical therapy reflects, in miniature, changing points of view in medical theory and philosophy that have occurred through the ages. To follow the rationale of the therapeutic use of iron is to provide an epitome of medical history in itself.

Long before the true Iron Age, which began around 1000 B.C., the element was known and used in medicine in its naturally occurring forms. First of all, there was meteoric iron, which was recognized as being of celestial origin and, of course, emphasized the supernatural and superstitious side of medicine; second, there were many oxides and carbonates, such as hematites, ochers, and siderites. Among the ancient Egyptians, it was known, for example, as "black copper from heaven," and the Sumerians called it "heaven metal." A belief in the divine properties of this metal gave rise to legends such as that of Apollodorus of Iphyclus, one of the Argonauts, who is said to have been cured by Melampus of his sexual impotence; from its fancied relationship to the planet Mars (*Crocus martis*) arose the concept of the Telephian wound, the wound that could be healed only by the metal of the weapon inflicting it.

This superstitious use of iron became a part of the tradition of medicine, so that we find the same prescriptions advocated by Melampus still used as late as the time of Sydenham in the seventeenth century.

On the other hand, the naturally occurring iron carbonates and oxides, such as magnetite, the sesquioxide, of the *Ebers Papyrus,* were used quite rationally according to a very astonishing Egyptian theory of disease, known as the *wḫdw* theory, which claimed that the corruption of food residues was responsible for illness. This theory was adopted by the most ancient of the Greek schools, that at Cnidos, to become incorporated in modified form in the Corpus Hippocraticum and with it the use of iron as an internal remedy, together with the knowledge of its value as a styptic.

In the classical period there was no such thing as a clinical entity as we know it. There was only disease, and in the singular, and all illnesses were regarded as different and varying manifestations of the same thing. In early times, the symptom was the disease. This is very evident in the so-called humoral doctrine, in which all therapy is directed toward the restoration of the balance of the mixture, or *crasis,* of the humors. Iron thus plays its "elemental" role in therapy. Nonetheless, and in spite of theory, Dioscorides, Galen, and the copyists Celsus and Aetius advocated the use of iron in cases of splenic enlargement, dysenteries, and menorrhagia, all of which suggests an early recognition of the value of iron for the treatment of the secondary anemias. Thus it was that the medical use of iron became established in the Western tradition.

Although iron in its metallic form continued to have its advocates who perpetuated superstitious beliefs, Peter Mattioli in his commentary on the works of Dioscorides informs us that it was Avicenna, the Prince of Physicians, who recognized that the metal possessed no therapeutic values unless converted into a salt. The dispute on the value of the soluble over the insoluble form of iron continued for many centuries. Avicenna recommended the acetate, and gave a method for the digestion of the metal that was long accepted as a standard. He warned of the gastrointestinal disturbances from excessive and prolonged dosage. To him we are also indebted for the clinical description of chlorosis and its treatment, a description that, although less poetic, is technically far superior to that of the Roman poet Ovid. Avicenna marks the beginning of a highly empirical phase in the long history of the metal.

Pliny, the old gossip, perpetuated the ancient belief in the use or value of iron for sexual impotence—a belief that was carried forward by many of the Arabians, such as Rhazes, Albucasis, and Serapion, in the medical literature of medieval Europe and of the Renaissance.

A new field of medicine was opened during the Renaissance with the development of iatrochemistry by Paracelsus. The stimulus for a new use of iron came with the development of a new technology for the manufacture of the heavy mineral acids to recover the precious metals from the impoverished ores left in the mines of Switzerland. Paracelsus, who came from a family of Swiss miners, was familiar with the new process of acid digestion, and blended the newer techniques with the older distillation methods of the alchemists. Unfortunately, Paracelsus became preoccupied with the distillate rather than the residues of acid digestion, which contained the iron and many other substances, and "he threw the baby out with the bathwater." His theories ran far ahead of practical understanding, and his metallic "quintessences," regarded as possessing "great virtues of human infirmities," were of no value and his analyses largely symbolic imaginings. Nonetheless, the Paracelsian movement gave a chemical direction to investigation. The new direction led to the most extraordinary, premature discovery in the history of biochemistry. The Paracelsians, Lémery and Geoffroy, in 1713 established the presence of iron in the ash of blood. This discovery has been ascribed to Menghini in 1746, but actually he seems to have popularized the work of Lémery. Menghini, however, made a very important contribution by showing that the iron in the blood could be increased by feeding animals on iron-containing food, an observation confirmed by Rouelle and Bacquet in 1747, by Von Forke in 1779, by Lichtenstein in 1899, and by George Whipple in this century.

Lémery's discovery, rather than Friedrich Wöhler's synthesis of urea in 1828, really marked the beginning of modern biochemistry, but it must be called premature since he was still under the influence of the Paracelsian theory, believing that iron was composed of an earth, a salt, and sulfur in unstable combination.

The idea that iron was contained in the blood had long been hinted at and was based on reasoning by analogy, or the relationship of "similars"—from the primitive belief that since both blood and rust are red in color, so iron must exist in the blood itself. Although a very simple type of reasoning, it has curiously enough, despite later views on the validity of the scientific method, been one of the most potent and productive methods in the history of science. Both Sydenham and Willis expressed the belief that iron could impart its color to the blood.

No clear idea of the clinical or nosological entity existed before the seventeenth century. Medical historians, especially those of the nineteenth and early twentieth centuries, have been remiss in forming their own nosological beliefs along those of the ancients. The establishment of the clinical entity had to await the time of Sydenham (1661). Sydenham's attempts to classify diseases—based on the belief that a disease ran a regular course with a natural history of its own—led to the idea that each disease was a definite species that could be described as a botanist describes a plant. Observation and experience were the tools of the English Hippocrates. Although Lange (1554) gave a recognizable account of chlorosis, it is in Sydenham that we find a brilliant description of chlorosis and the clinical recognition of the fact that improvement of the blood picture following the administration of iron can be observed in the increase in the redness of the cheeks and gums. Sydenham prescribed iron as a tonic in various conditions, including, curiously enough, sexual impotence, and his recipe was very similar to that used by Melampus of legendary times.

Following Sydenham there appeared a whole series of new clinical descriptions, of which one of the most accurate and complete was the *Dissertatio* (1731) of Francis Hoffman, but he was overenamored with the iatrophysical school of medicine and the humoral doctrine.

The battle of iron dosage opened in the eighteenth century with Pierre Pomet, druggist to Louis XIV, who wrote on the use of iron in 1720. William Cullen, the Scotch physician, emphasized in his teaching that the good effects achieved in the treatment of chlorosis were often missed by too small a dosage of iron, and his influence resulted in the immortal Blaud's pill, in 1832.

The clinical value of iron had been long established, but views on its action were empty theory until well into the nineteenth century. Explanations had to await a fuller development of the experimental method. Nothing substantial was possible without the achromatic compound microscope and the cellular theory (Matthias Schleiden and Theodor Schwann), in 1839, to be followed by the investigations in cellular pathology initiated by John Goodsir and developed by Rudolf Virchow. Virchow's study (1872) was a notable contribution to the understanding of the pathology of chlorosis. This understanding was extended by Zaleski's (1886) demonstration of the presence of iron-bearing bodies in the tissues, a finding confirmed and elaborated on by Alexander Spitzer.

The understanding of the interchange of iron in food with iron in the body and many other important contributions, such as the explanation of the passage of iron from the mucous membrane of the alimentary tract and of spleen and liver storage indicate that new methods and superior tools are of singular importance in developing scientific knowledge.

The whole history of iron, then, is one which demonstrates the important fact that medicine, although both an art and a science, is largely dependent for its progress on methods. Initially, methods were too speculative, but eventually they became more scientific. And new understanding came most swiftly when hypothesis, clinical interpretation, and the experimental method advanced hand in hand.

Finally, let me remind you that it is very appropriate that this symposium should be held on this particular campus and in this particular room. Here, on this campus, George Whipple began his epoch-making experiments on iron metabolism and here, in this room, he spoke many times on his concepts of iron and on his ideas of therapy for which he received the Nobel prize.

Carl V. Moore, M.D.

AN OUTLINE OF IRON METABOLISM

Iron, as an essential component of hemoglobin, myoglobin, the cytochromes, and other enzyme systems, is required for the important physiologic functions of oxygen transport and cellular respiration. The body of a normal, adult human contains approximately 3–5 gm. of iron. Roughly 55 per cent of this total is present in the circulating hemoglobin, approximately 10–20 per cent in myoglobin, and a small amount in cells in the form of respiratory enzymes. The remainder is stored chiefly in the liver, spleen, kidney, and bone marrow.

Ingested iron must be reduced to the ferrous form in the stomach and intestine before it can be absorbed [1, 2].* Iron can be absorbed from the stomach, but normally the amount absorbed this way is probably small (fig. 1). Absorption is probably greatest in the upper part of the small intestine and progressively less in the more distal segments of the gastrointestinal tract. The reason for this diminishing gradient has never been adequately explained. It may be that the ileum, for instance, is not so efficient as the duodenum in absorbing iron, but the difference could be due solely to the fact that insoluble, complex salts of iron are formed by the time the iron reaches the ileum.

Patients with iron deficiency absorb iron more efficiently than do normal persons [3, 4]. The intestinal mucosa serves to some extent, therefore, as a regulator of iron metabolism, but the mechanisms responsible are incompletely understood. The formation of ferritin within mucosal cells may be part, but only part, of the story. Recent evidence indicates that absorption may also be greater than normal whenever erythropoiesis is stimulated [5, 6]. When iron passes into the plasma, it

* For bibliographical references, see pp. 142–143.