

3-1958

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Recommended Citation

Watson, John H. L. (1958) "Electron Microscopy, Iron Crystals and Medicine," *Henry Ford Hospital Medical Bulletin* : Vol. 6 : No. 1 , 111-119.

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ELECTRON MICROSCOPY, IRON CRYSTALS AND MEDICINE

JOHN H. L. WATSON

In electron microscopy one deals with objects and structures which have infinitely small dimensions, but which must be comprehended with a finite human mind. It is difficult for most of us to conceive of the ultimate "small" or the ultimate "big", and yet we use terms like "atomic" or "nuclear" quite freely. No one has ever really measured the diameter of an atom but only its mean free path. The atom is a nervous part of creation, it cannot stand still long enough to be measured. Still, we say that the diameter of an iron atom is 1.26 angstrom units†, meaning that it is most probable that the influence of the iron atom will be felt, more or less over this distance. In electron microscopy too we deal with such linear units approaching atomic dimensions.

For example in the discussion to follow, iron crystals will be considered which are anywhere from 100 to 5000 angstrom units thick and may be from 100 A.U. to many microns long. A single 30 micron side cube of cement dust could hold a billion of the iron crystals. Now, there are two classes of people who deal in billions easily; those who handle our national budget, and astronomers, but it is difficult for the average person to visualize a billion without certain mental stimulation. For example, if one billion seconds were counted using a clock, it would take 32 years to count a billion seconds, counting day and night without stopping, (with the standard 8 hour day the job could not be completed in a human life time); or if one stacked one dollar bill upon another (regardless of inflation), a billion-dollar pile would be 57 miles high (each bill being about 0.0036 inches thick). So a billion is a rather large number and should be treated with respect both to its own significance and the advantages to be gained in biology, medicine, magnetics and metallurgy by the use of single iron crystals as fine as tobacco smoke.

Many important basic contributions from electron microscopy have emanated from Institute projects. It is not possible nor intended to describe all of these here but a representative subject has been chosen which has certain novelty and is as yet not completely reported elsewhere. The discussion will center about what the electron microscope and related techniques have told us about the structure and properties of colloidal crystals of alpha iron. This is a fairly recent, in-progress emphasis which, because of its effects on the study of fine particle magnetics and because of the potential of its medical uses, may represent a considerable contribution to both physics and biophysics.

STRUCTURE. Electron microscopic studies of certain colloidal alpha iron crystals made in an electrolytic process were undertaken because of a long standing, laboratory interest in colloidal crystals and because of important inherent medical applications. Before the medical uses could be realized, certain basic properties of, and phenomena

†One centimeter = 10^4 microns (u) = 10^8 angstrom units (A.U.).

related to, the tiny crystals had to be known and determinable in advance.

Many of the solid state properties of the material have now been established and a new tool for medical research and application is available. Although iron itself is allotropic, these crystalline particles are always *alpha* iron (96) which has a body centered cubic structure. The process of manufacture is controllable and continuous and reproducible as far as size and shape of the colloidal crystals are concerned. It has been shown that their size and shape are not only functions of the conditions of formation but of the inherent crystalline properties as well. In turn, unique physical properties and consequent applications of the crystals are a result of morphology, size and other properties. There are several crystal types, notated for convenience as, *discrete particles*, *needles*, *nodular rods* and *weak* or *strong dendrites*. From these investigations all appear to be single crystals, and the genesis of each is a dendritic growth. The single difference between the particle types seems to lie in the extent and quality of this dendritic growth.

Because of the intrinsic dendritic nature of these iron particles, any complete understanding of their magnetic (145) or metallurgical properties (161) or of their medical uses will depend to some extent upon knowledge of their dendritic structure *per se*. This work represents one of the extremely few attempts to study the fine structure of submicroscopical dendrites by any method.

With techniques of electron stereo-microscopy* applied to partially etched, carbon mounted particulates (152) it has been possible to define the structures fairly completely, down to 50 and 100 A.U. The ultimate crystallites (*discrete particles*) of which the dendrite is composed appeared to be single 100 to 500 A.U. rhombic dodecahedrons as represented in Fig. 1. A monolithic linear arrangement of these, attached corner-to-corner along the cubic diagonals with the *111* planes perpendicular to the direction of dendritic growth comprises what is referred to as a *needle*. Whenever crystallites develop, in a similar fashion at periodic nodes along the sides of such a needle, a *nodular rod* is formed. Further development of the main stem and the side arms produces a *weak* or a *strong dendrite* depending on the extent of the growth.

It has been observed that three secondaries form at any node along the primary. These have 120 degrees of angle between them and each slants at about 60 degrees toward the direction of primary growth. Where tertiary arms occur they follow the same habit. The dendrite as a whole is itself a single crystal of alpha iron with certain preferred directions iron-filled. A further development, called a *filled-in dendrite*, occurs when conditions are such that the branches and crystallites "coalesce" in extended development. The weak dendrites are formed under conditions where some secondaries are aborted or lack uniformity of length and distribution along their primary. Fig. 2 is a typical electron micrograph from which these observations were drawn. This is a partially etched, carbon replica of a field of strong dendrites. Unetched, all branches were opaque, and overlapping themselves or the primary, one set always went undetected by other mounting methods. The dendrite at *A* is lying

*John H. L. Watson. *Can. J. Res.*, 21, 89 (1943).

with two sets of transparent etched secondaries slanting down into the plane away from the viewer. The relatively unetched opaque series of triangulations along the primary represents a third set of secondary branches growing toward the viewer from the plane. At *B* and *C* are other dendrites oriented differently with one transparent set parallel to the plane, and a second set slanting down into it. An opaque third set, superimposed on these, slants upward toward the viewer.

A corner-to-corner (along the diagonals) development of the arms has been indicated by direct observation in many of the better resolved micrographs. In addition such growth is inferred from the observation of a 60 degree angle between secondaries and primary, as well as from the identification of sets of three secondaries with 120 degrees between them. Briefly, from electron microscopic studies a dendrite model has been established† which satisfies not only all of the microscopy observations but fulfills certain concepts concerning the crystallization of body centered metals as well. Although the dendrites tend to assume their most stable positions, Fig. 2, and do not easily demonstrate their three secondaries, micrographs of "end-on" dendrites, Fig. 3, are obtained occasionally.

An additional particulate crystal form is referred to as a *platelet* and has often been seen in these samples, Fig. 4. Many of these colloidal platelets are dendritic in two dimensions. By selected area electron diffraction these crystals demonstrate the Kikuchi N pattern with Kikuchi lines for platelets 80 A.U. or less thick and are also identified as alpha iron, Fig. 5.

MAGNETIC PROPERTIES. The magnetic properties of colloidal iron crystals, particularly in this era of the magnetic tape, the powerful miniature magnets, the transistors, and the printed circuit, are of immense importance. It has been essential to correlate shape, structure and size of these colloidal alpha iron crystals with their magnetic properties. From statistical areal analysis performed upon electron micrographs, it has been possible to conclude (a) that nodular rods and needles, Fig. 6, are those particles which contribute to the higher coercive force and that the other particulate types tend to lower it, and (b) that in some manner, as yet undetermined, the coercive force is improved as the particle dimensions are reduced to some optimum size.

Experimental evidence has shown that these crystals have coercive force of unusual magnitude. The electron microscope was able to explain the enhanced coercive force by reasons inherent in the size, shape and structure of the particles, chiefly their shape anisotropy and their monolithicity.

The processes of alignment associated with these particles has been studied by a unique method which involves suspending them in capsules of n-butyl methacrylate monomer within the region of a magnetic field. Under these circumstances the particles, affected by the field, attempted to align themselves in preferred directions

†This model was first discussed before the American Crystallographic Association June 11, 1956 at French Lick, Indiana in the paper "The Ultrafine Structure of Elongated, Magnetic Single-Domains and of Dendrites of Alpha Iron". John H. L. Watson, Michael W. Freeman, and Nicholas N. Solimene.

against the mechanical forces of the liquid. Although certain evidences of orientation and alignment were seen, especially in the macroscopic, in the microscopic they were observed to form closed networks quickly in order to minimize their magnetostatic energies. The result was that at fields as high as 25,000 gauss, while the iron particulates appeared to the eye to be aligned by the field, in the electron microscope very little alignment of the individual microscopic crystals had actually occurred. This in itself was an important negative observation which indicated that improved, different methods of alignment would be needed.

In order to make these observations the capsule of monomer-suspended iron crystals was polymerized by an appropriate means (159) to a solid block and this block was ultrathin sectioned for electron microscopy. The sections were cut at known directions to the direction of the field. This work is still continuing with improved technique and with higher magnetic fields. As a result of the work to date with low iron concentrations and relatively low fields a general "streaming" of the single crystalline rods and needles in the direction of the field has been observed. Micrographs have shown a tendency for the rods to attach end-to-end in a chain-like arrangement in a straight line or often in circles as the particles have sought to minimize their energies. Palisade configurations were sometimes seen but these were usually artifacts introduced by fortuitous cutting of a dendritic particle along and close to a primary stem.

The method is being further developed to provide a means of obtaining statistically quantitative estimates of the packing fraction for correlation with magnetic measurements on identical specimens, and to give direct observation for the first time of some of the theoretical aspects of fine particle magnetics, particularly shape anisotropy.

OTHER PHYSICAL PROPERTIES. The electron microscope studies were instrumental in explaining other properties of these crystals. The fine particle sizes and interstices in the microstructures explain the high specific surface of about 20 m²/g. The minute nature of the crystallites also accounts at least partly for their extremely high surface energy. As a corollary to the highly crystalline nature of the particles, the high incidence of available crystal corners and edges, and the nature of the dendritic growth itself, in addition to surface energy there are "built in" strain energies due to lattice deformations. These characteristics impart such high energies that each crystal reacts chemically rather than as a particle of the element whose name it bears. The high energy associated with the monolithic, crystalline particles makes them extremely active physio-chemically so that they react readily and molecularly with metals, plastics and biochemical compounds to form new materials of unexpected physical properties.

MEDICAL APPLICATIONS. In addition to its fundamental interests in the electron microscopy of colloidal crystal systems, the Department of Physics has been interested in the alpha iron crystals because of projected medical investigations, suggested for them first by Michael W. Freeman. Armed with pertinent data* on their physical,

*The solid state properties of the material have been established and reported before several scientific groups for their criticism and study. The investigations have been reported before two conferences on Magnetism sponsored by the American Institute of Electrical Engineers, before the American Crystallographic Association, the Electron Microscope Society of America, and the Metal Powder Association.

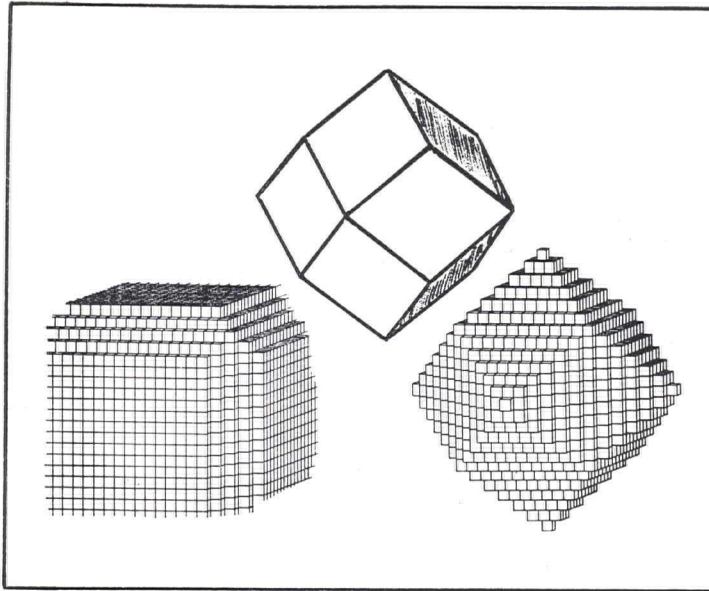


Figure 1

Drawings to demonstrate how a rhombic dodecahedron may be developed from the cube by regularly removing rows of cubelets. *A* shows the cube with rows of component cubelets being removed to develop the planes parallel to the faces of the dodecahedron. *B* shows the completed dodecahedron. *C* is a planar representation of *B*.

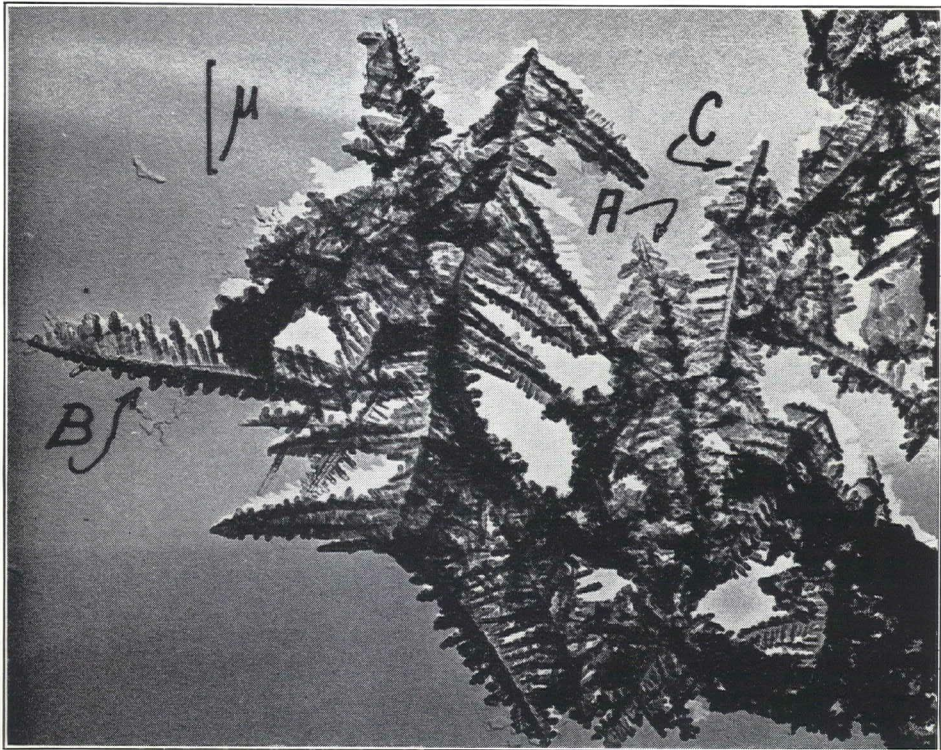


Figure 2

Electron micrograph, X15,000 of a carbon replica of strong alpha iron dendrites, partially etched with HCL. Note: in all micrographs the line represents a micron.

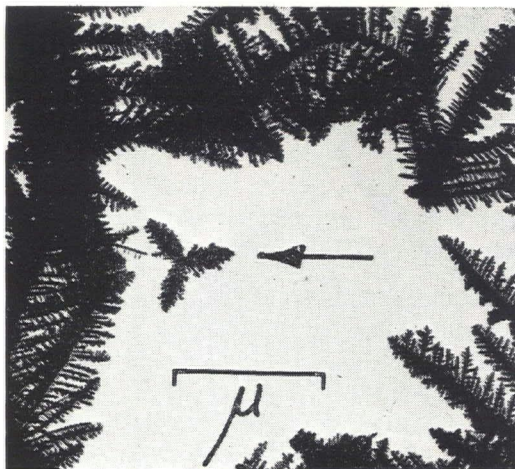


Figure 3
Electron micrograph, X20,000, of strong dendrites of alpha iron, showing at the arrow an example of a dendrite oriented 'end-on' so that three secondary branches at 120° can be seen.

Figure 4
Electron micrograph X10,000 of platelet crystals of alpha iron.

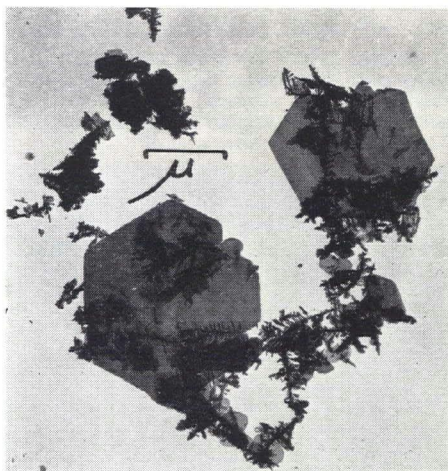


Figure 5
Selected area electron diffraction pattern of a single platelet crystal of alpha iron.



Figure 6
Electron micrograph, X19,000, of nodular rods and needles of alpha iron.

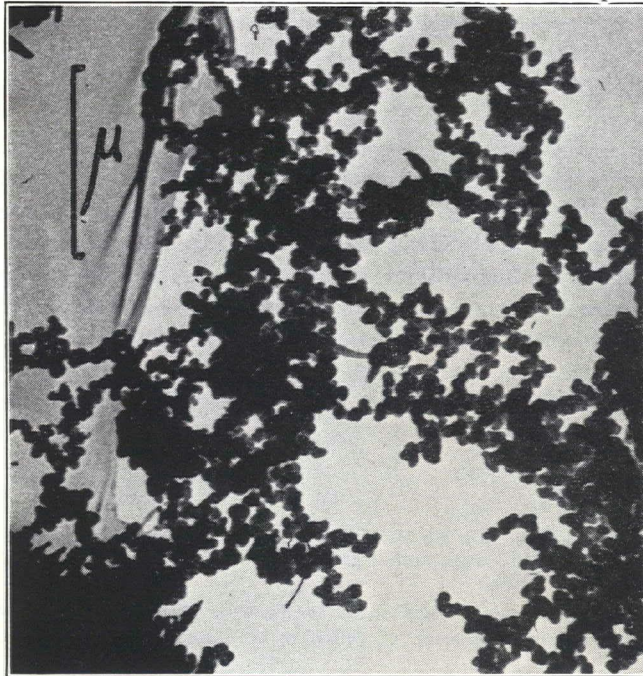


Figure 7
Electron micrograph X25,000 of chains of discrete particles of alpha iron. Average diameter of the sample 400 A.U.

magnetic and other properties one can evaluate the potential uses of the crystals for the medical field.

An immediate consideration is the employment of this knowledge in the treatment of cancer and in basic biochemical problems. A first emphasis is to develop a new method for the treatment of tumors with radioactive, magnetic iron[†] crystals concentrated in situ by external magnetic fields as prescribed. Many tumors are known to maintain a highly vascular functional system to sustain a preferred nutritional status with respect to surrounding healthy tissue. Such tumors with good vascularity would be chosen for treatment at the outset. Electron microscope studies have shown that the crystals are producible with diameters as low as 400 and 200 A.U., Fig. 7, and with a variety of shapes, while still keeping them well within the limits necessary for circulation in the finest capillaries. It is known that the finest capillaries in the lungs, for example, are about 5 μ in diameter. The volume of an average red blood cell would be equivalent to about 11 million individual 200 A.U. particles. If the iron crystals were made radioactive and still retained their ferromagnetic properties they could be used for radiation therapy of cancer tumors through the route of the circulatory system. Introduced into this system it is conceivable that their concentration, intensity, and exact localization could be controlled by external magnetic fields to pin-point radiation at the site of a neoplastic lesion with little or no destruction of healthy tissue. As a preliminary effort in this work electron microscopy of ultra-thin sections would be used along with histo-biochemical methods to determine the ultimate fate of the iron crystals. It is possible that by use of crystals of appropriate shape and size, radiation could be delivered to specific locations in the reticular endothelial systems, which are known to retain particles in specific ranges of size and shape* preferentially.

There will be many preliminary investigative steps in the program, each of which may, in its own development, contribute worthily to the sum of basic scientific knowledge. Among these will be problems related to proper preparation and introduction of the iron. The whole effect of radiation from the radioactive iron crystals upon various facets of the human body, especially on the reticular endothelial systems will have to be studied. A fascinating side of the physical problem will be the whole question of concentration of ferromagnetic particles in a living organism by external magnetic fields. It may be necessary to coat individual particles either to prevent physiological reactions with them, or to filter their radiation, the while maintaining their ferromagnetic properties.

[†]The two radioactive isotopes of iron are Fe55 with a half life of 2.9 years, a gamma emitter only; and Fe59 with a half life of 46.3 days, both a gamma and beta ray emitter. The Fe55 is present in twice the abundance of the Fe59.

*"Effet de l'injection de saccharate d'oxyde de fer sur l'activite phagocytaire du systeme reticulo — endothelial chez le Rat". B. Benacerraf, C. Stiffel et G. Biozzi, *C. R. Seances Soc. Biol.*, 150, 1161 (1956).

"Observations on the Reticulo — Endothelial Elements of the Liver and Spleen of the Rat Following Injections of Gelatin — Stabilized Gold Colloid". Arlene R. Seaman and Irwin M. Murray. *Acta haemat.* 17, 49 (1956).

The high physio-chemical activity of the particles is indicative of other biological applications. For example it is proposed to observe the effects of the iron crystals, in radioactive or non-radioactive form, in the study and treatment of leukemias. If a physiological preference can be demonstrated for hemoglobin or some enzymatic activity, the crystals may be used to reinstate normal hemopoiesis*. Throughout all such studies a research by-product would continue to concern basic physiological phenomena not identified clearly heretofor.

The above sets forth some of the final objectives inherent in the medical uses of the submicron iron crystals and indicates the minimum essential preliminary steps.

*"Intramuscularly Administered Iron in the Treatment of Iron-Deficiency Anemia". Albert B. Hagedorn, *J.A.M.A.*, 164, 1642 (1957).



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