# CASE STUDY - IRON DEFICIENCY

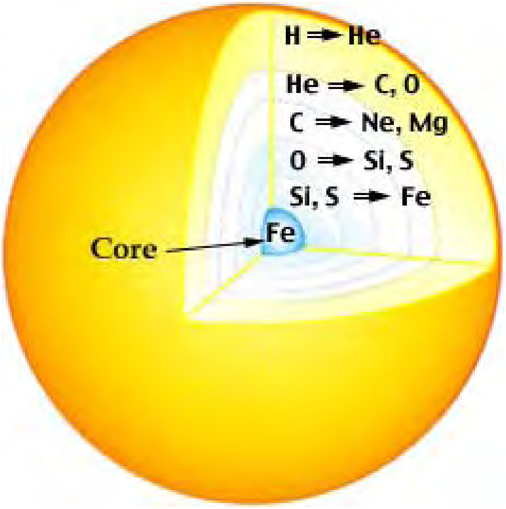
A 55 year-old woman presented to the emergency room with the chief complaints of exertional chest pain and dyspnea of one-week duration. EKG demonstrated sinus tachycardia with inferolateral ST depression suggestive of ischemia. The patient gave a history of hypertension and cigarette use. Family history was remarkable for her father having suffered his first MI at 45 years of age. With this information, the cardiology service was consulted to admit and evaluate the patient.

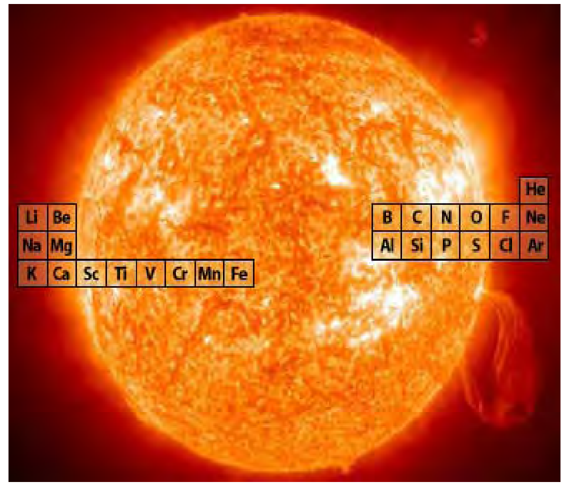
Physical examination was remarkable for a well-developed woman who was slightly pale and dyspneic. Blood pressure was 105/89, HR 120. No JVD was present. Lungs were clear. Cardiac examination revealed a 1/6 systolic murmur; no S3 or rub was appreciated. Abdomen was soft and non-tender with normal bowel sounds present. Lower extremities were not edematous.

Admission lab results included abnormally low hematocrit of 24% with MCV of 55. At this point, it was felt that severe anemia was likely responsible for the patient's symptoms. Consideration was given to transfusion and GI consultation was requested. However, the patient developed increasing symptoms of chest pressure and EKG abnormalities became more pronounced, so urgent cardiac angiography was performed: this revealed only minimal coronary atherosclerotic irregularities and normal LV systolic function. Subsequent lab results demonstrated Fe/TIBC of 20/250 (8% saturated): a diagnosis of iron-deficiency anemia was made.

Iron deficiency was an absolute state in the early universe. The large first generation stars whose remnants would later become our solar system shone brightly in a Milky Way galaxy that did not yet contain our Sun. As each of these stars matured, it consumed hydrogen and produced enough helium in the 10 million degree plasma fusion furnace of its stellar core that helium nuclei accumulated into a dense inner core. It was here that helium nuclei became concentrated and energetic enough (at 100 million degrees now) to collide and fuse into beryllium and then to fuse into carbon.

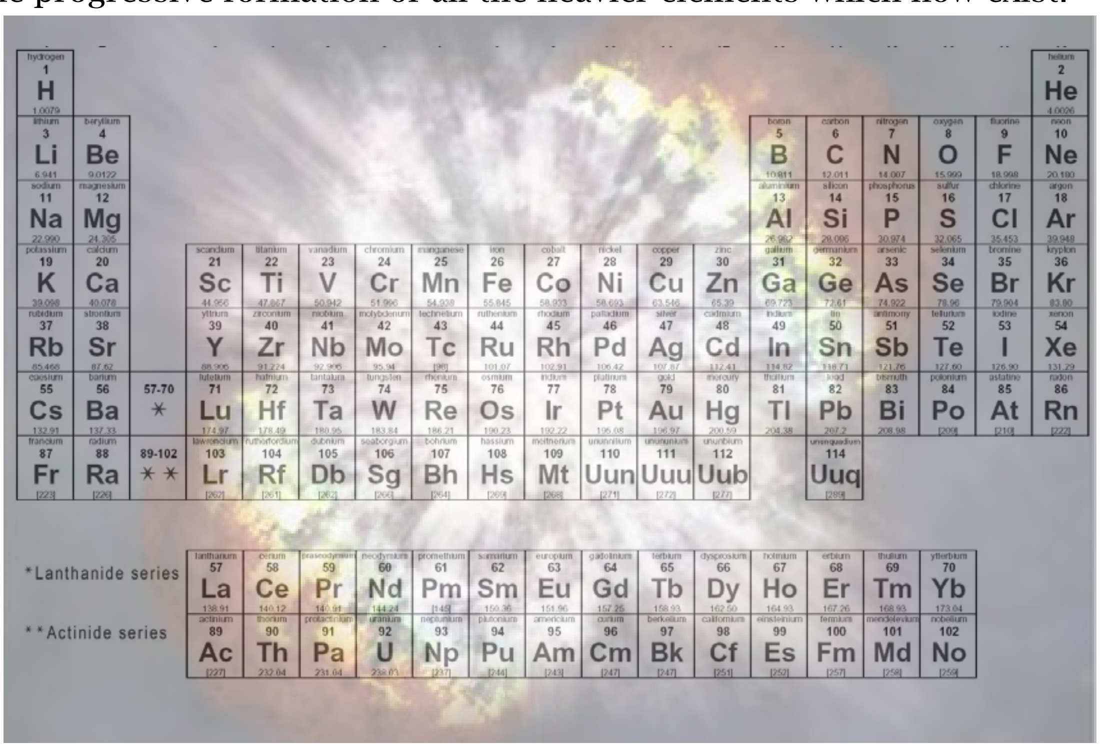
Helium-carbon collisions/fusions produced oxygen. Further fusions created neon, magnesium, and silicon. At this point, though, a crisis began to develop. Although the concentric shells of oxygen, carbon, helium, and hydrogen continued to produce enormous quantities of fusion-derived energy, the accumulating silicon core was approaching a thermodynamic dead end. The temperature of the central silicon core had reached 4 billion degrees as silicon fusion forged a new element, iron, into existence. The nuclear stability of the rapidly forming iron atoms, however, was greater than that of any other, even more massive, as yet unformed elements that might result from further fusion. Therefore, iron in the stellar core could not serve as fuel for exothermic nuclear fusion and provide the immense energy output necessary to heat the core and counterbalance the persistent struggle toward gravitational collapse.



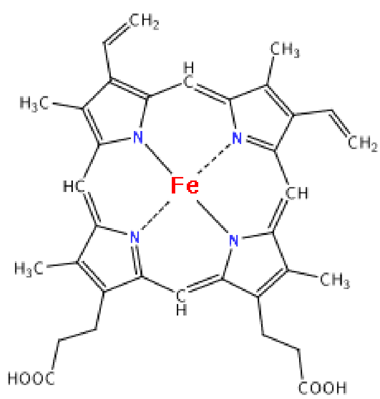




Courtesy NASA/JPL-Caltech

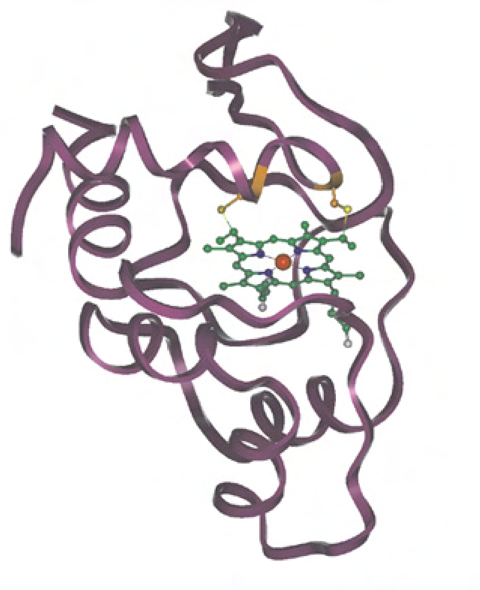
The iron core cooled, compressed, and the temperature increased in response to this compression – indeed this had been the same pattern followed in each of the previous steps in the sequential development of the stellar core. What had occurred before, however, was that the nuclei in the plasma of the core would begin to fuse into larger, more stable nuclei, release energy, and raise the thermostat yet another notch. But iron's high stability sealed its fate. As the core heated, the iron nuclei instead succumbed to high-energy gamma radiation and photodissociated into helium, triggering a catastrophically sudden collapse under the tremendous gravitational pressures of the outer layers. At the incredible densities generated, electrons penetrated protons, forming neutrons and neutrinos. The rebounding shock wave of this collapse accelerated neutrons and neutrinos outward, while the bulk of the core became sealed off forever as a new black hole was formed. The outer layers of the star exploded outward at speeds approaching 0.1 **c**, becoming a supernova. As neutrons riding the shock wave of the core collapse overtook the exploding layers of silicon, oxygen, carbon, and lighter elemental nuclei, collision with these elements resulted in neutron capture and the progressive formation of all the heavier elements which now exist.



By this process, the interstellar medium became enriched in the full spectrum of elements, with the abundance of iron settling at a relatively high 0.1%. Within a molecular cloud in a spiral arm of the (as yet unnamed) Milky Way galaxy, gravitational collapse pulled matter into a rotating accretion disk, in the center of which enough mass concentrated at sufficient density to trigger nuclear fusion: our Sun began to shine. Further out, planetesimals and then planets formed and grew by accumulation of the material orbiting this new star. As hydrogen and helium blew away in the solar wind, the relative abundance of heavier elements increased on the terrestrial inner planets. On Earth, iron became the most abundant element (35%), with oxygen (30%), silicon (15%), and magnesium (10%) close behind. Most of the iron became concentrated in the planet's core, but the crust still contained 6% iron by mass.




heme

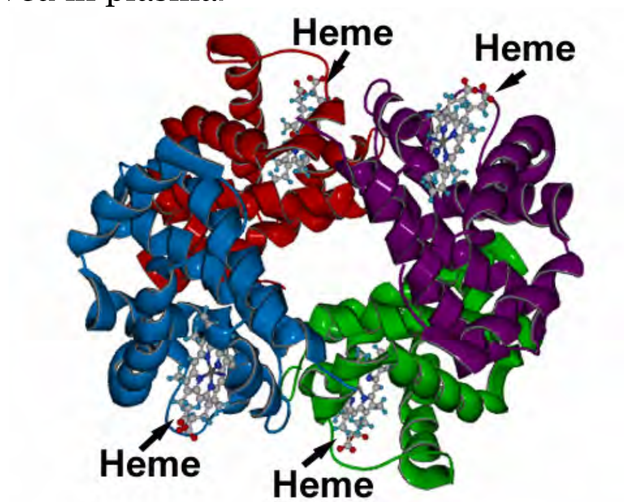


cytochrome

As early life forms developed on Earth, iron was called into play as the central cog of the porphyrin ring structures that formed the heme groups of cytochromes, which are the critical functional elements of the electron transport chain. The ability of iron to gain an electron and be reduced ($Fe^{+++} \rightarrow Fe^{++}$) and subsequently lose an electron and be oxidized ($Fe^{++} \rightarrow Fe^{+++}$) allowed the electron flow that powered the thermodynamic engines of anaerobic respiration and photophosphorylation (photosynthesis) and then, once an oxygen-rich atmosphere had developed, of oxidative phosphorylation. Of note, the huge planetary content of available iron became a reservoir that trapped by reactive oxidation (rust) the molecular oxygen produced for eons by cyanobacterial photosynthesis. Only after 3 billion years of incessant photosynthetic splitting of water and release of $O_2$, did equilibrium conditions develop and significant amounts of $O_2$ begin to accumulate in the atmosphere. Subsequent formation of ozone ($O_3$) in the stratosphere provided shielding from ultraviolet radiation and allowed survival of life on land.

Later on, proper handling and delivery of molecular oxygen became increasingly important to the multicellular creatures that demanded an aerobic metabolic state; the iron-containing heme group moiety again appeared in a central role. Hemoglobin functioned to reversibly bind oxygen in gills or lungs and release it for the actively metabolizing cells of the peripheral tissues.

In humans, each erythrocyte contains about 280 million molecules of hemoglobin, which is a tetrameric protein. Molecular oxygen associates reversibly with iron contained in heme moieties, which reside in hydrophobic pockets in each of the four globin polypeptide chains. Hemoglobin partially transfers an iron atom electron from ferrous ($Fe^{++}$) heme to $O_2$ during this interaction. Of note, 97% of the $O_2$ carrying capacity of blood is attributable to hemoglobin association; only 3% of the $O_2$ is dissolved in plasma.




Low concentrations of circulating hemoglobin (as in the blood-loss anemia present in our patient) can result in insufficient $O_2$ delivery in metabolically active tissue (such as myocardium). Under the subsequent anaerobic conditions, cellular metabolism proceeds by fermentation of glucose and production / accumulation of lactate, which causes lowering of tissue pH. This causes ischemic changes on the electrocardiogram, and symptoms of angina, just as experienced when $O_2$ delivery is limited by coronary arterial stenosis or occlusion.

In our patient, limiting activity (and thus metabolic demand) minimized symptoms. GI consultation was requested; subsequent evaluation included upper endoscopy, which demonstrated two areas of duodenal ulceration. Treatment of the duodenal ulcers eliminated the gastrointestinal source of blood loss. Recheck hematocrit was 25%. After some discussion with the patient, decision was made not to administer blood transfusions. Provision of iron (in the form of oral $FeSO_4$) allowed hemoglobin synthesis and erythropoeisis to restore a normal hematocrit value. Within two weeks, our patient had returned to full activity without symptoms.