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Iron and Nitric Oxide in Anemia of Chronic Disease (ACD)

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1. Introduction

Anemia of chronic disease (ACD) may also be referred to as anemia of inflammation and this develops in subjects with diseases involving acute or chronic immune activation. Anemia, which could be described as an immunopathological feature in most established infection, may also be a consequence of host response to invading pathogens. Infections with pathogens normally activate macrophages triggering a strong cytokine production among which are tumor necrosis factor (TNF), γ-interferon (IFN-γ) and nitric oxide (NO). The immune response mounted against such infections is required for parasite clearance but its persistence can cause collateral damage to the host with occurrence of anemia as the major pathology. Inflammation results as a part of this natural immune response. The inflammation triggers the release of chemicals that signal the iron regulation mechanism to adopt a defense mode. Thus this type of anemia is usually characterised by an imbalance between erythrophagocytosis and erythropoiesis, which is linked to, perturbed iron (Fe) homeostasis including altered Fe sequestration and recycling by macrophages and/or sustained and overproduction of NO. The exact mechanism of ACD is not fully understood although studies suggest that the syndrome may partly be due to the influence of hepcidin production on iron metabolism. Moreover complex relationships between Fe and NO has been demonstrated and may be linked to iron deficient anemia during infection.

Both iron and nitric oxide play important roles in the progression and outcome of ACD essentially through the promotion of free radical generation and/or altered homeostasis. Increased iron status may promote free hydroxyl radical generation in cellular systems and thus potentiate cellular damage. Subsequently continuous and sustained production of nitric oxide resulting from persistent infection could contribute to oxidative damage via the formation of peroxynitrite, a very reactive free radical, which may promote lipid peroxidation of key biomolecules and membranes. It should also be noted that production of nitric oxide during infection episodes affects iron metabolism and vice versa. This suggest that a delicate homeostatic balance exist between iron and nitric oxide in living cells such that a disruption or perturbation of this strictly regulated balance would physiologically affect the cellular system. The fact that strong link that has been demonstrated between iron and nitric oxide indicates that the duo play crucial physiological roles in cellular processes.

2. Iron metabolism

Iron metabolism may be referred to as the set of biochemical reactions maintaining the homeostasis of iron. Iron is an essential but potentially harmful nutrient. The control of this necessary but potentially toxic substance is an important part of many aspects of human health and disease. Iron contributes to many important physiologic functions in the body essentially because of its unusual flexibility to serve as both an electron donor and acceptor. Iron being critical to a number of synthetic and enzymatic processes by play unique roles in electron transfer and oxygen utilization as heme and non-heme bound proteins. Although most of the body iron is part of hemoglobin molecule where iron serves a key role in oxygen transport, it is also required for proper maintenance of immune functions affecting leukocytes, endothelial cells and cytokine production. Iron also have capacity to promote free radical generation through the Fenton and/or Haber-Weiss reactions, thereby triggering secondary chain reactions in the oxidative modification of lipids, proteins and DNA within cellular systems. Unless appropriately chelated or removed, iron, due to its catalytic action in one-electron redox reactions, plays a key role in the formation of harmful oxygen radicals that may ultimately cause oxidative damage to vital cell structures. To ensure iron availability and to eliminate the toxicity of free iron in addition to its accessibility for invading pathogens, mammals have evolved a strictly regulated system for iron homeostasis. Metabolism of iron is highly regulated within narrow limits. Iron can be recycled and thus conserved by the body. Cellular systems are equipped with exclusive mechanisms that maintain adequate amounts of iron for synthesis of physiologically functional iron-containing molecules and yet keep "free iron" at its lowest possible concentration. Many proteins, hormones and iron itself have been demonstrated to affect iron metabolism by various mechanisms at different regulatory levels. Physiologically, the cellular system acquires iron from plasma glycoprotein, transferrin (Tf). In most cases body iron is sequestered and recycled by the reticuloendothelial system, which breaks down senescent red blood cells (RBCs). Iron metabolism in mammals is a highly regulated phenomenon. This process, which ensures iron availability to meet cellular demand, is necessary in order to eliminate toxicity and free accessibility for invading pathogens.

Iron demands are met obviously through two main sources; acquisition from diet, iron is an absolute requirement for most forms of life, including humans, most microorganisms, plants and animals; therefore it is found in a wide variety of food sources. And also from destruction of heme and non-heme proteins which in most cases are being recycled for reutilization.

2.1 Iron acquisition from diet

Dietary iron represents a viable source for acquisition of iron to meet the body demands. The absorption of dietary iron is a variable and dynamic process that ensures the amount of iron absorbed compared to the amount ingested is typically low. The efficiency of iron absorption from diet depends largely on the source and demand for iron. Heme iron (obtainable from animal and plant foods) is best absorbed compared to non-heme iron (iron salts). Dietary iron is absorbed in the duodenum by enterocytes of the mucosal cells. The dietary iron must be part of a protein or be in its ferrous (Fe^{2+}) state in order to be absorbed. An enzyme, ferric reductase located on the enterocytes' brush border, Dcytb, reduces ferric Fe^{3+} to Fe^{2+} by lowering the pH. A transport protein called divalent metal transporter-1 (DMT-1 also called Nramp-2) then transport the iron across the enterocyte's cell membrane

and into the cell cytosol. The mucosal cells can either store the iron as ferritin which is accomplished by oxidizing Fe^{2+} to Fe^{3+} and subsequent binding to apoferritin to form ferritin (FHC) or translocate the iron through ferroportin-1 (FPN-1) to the portal circulation, which is finally delivered to tissues and the erythroid bone marrow. Hephaestin, a ferroxidase found in the mucosal cells and capable of oxidizing Fe^{2+} to Fe^{3+} may assist ferroportin-1 in transfer of iron. Each of the steps involved in dietary iron acquisition is strictly regulated in response to body need for iron. For instance, cells in response to iron deficiency anemia produce more Dcytb, DMT-1 and ferroportin-1 thus implicating genetic involvement. Several factors including total iron stores, the extent to which bone marrow is producing new red blood cells, the concentration of hemoglobin in the blood, and the oxygen content of the blood all contribute to the rate of iron absorption through the mucosal cells. Infection or inflammation may also affect the rate of iron absorption from diet. Lesser iron is usually absorbed during inflammation and/or infection episodes leading to ACD precipitation. Dcytb is confined to iron transport across the duodenum, while ferroportin-1 is distributed throughout the body on all iron storing cells suggesting that ferroportin-1 is central to cellular iron availability. And indeed, recent discoveries have indicated inflammation leading to hepcidin-induced restriction on iron release from enterocytes via the regulation of ferroportin-1 as responsible for ACD.

2.2 Iron bound proteins

Iron is usually bound to hemoglobin, myoglobin, cytochromes, transferrin, lactoferrin and/or ferritin to restrict pathogen access to iron, although most microorganisms or pathogens have developed sophisticated iron-acquiring system that are able to compete successfully with iron-binding proteins of the host. In mammals hemoglobin of red blood cells contain more than 60% of body iron. Much of the remaining is in storage form in ferritin. In physiological conditions, tissue macrophages, in particular liver-associated Kupffer cells recover Fe^{2+} via engulfment of senescent red blood cells (RBCs) from circulation. In addition, these cells internalize the iron-containing hemoglobin; degrade it extracting Fe^{2+} through the action of heme-oxygenase-1 (HO-1) resulting in the release of ferrous iron (Fe^{2+}), carbon (II) oxide and bilverdin. Iron is then transported from the phagosome into the cytosol via the DMT-1, the main Fe^{2+} transporter, from where it can be either stored intracellularly via ferritin (FHC) or exported extracellularly via ferroportin-1(FPN-1) depending on the demand for iron. The extracellular Fe^{2+} after conversion to ferric iron (Fe^{3+}) through ceruloplasmin (CP), will bind to transferrin (Tf) and transported mainly to the bone marrow to fuel erythropoiesis. Consequently, limitations in iron (Fe^{3+}) availability may exert a strong negative impact on erythropoiesis and contribute to ACD. Hence maintaining physiological levels of RBCs relies on a subtle balance between RBC uptake and RBC generation as well as iron homeostasis.

Unique to iron homeostasis are cytosolic iron regulatory proteins (IRP1 and IRP2). These proteins, which are responsive to circulating iron levels, affect iron metabolism by binding to specific nucleotide sequences, termed iron-responsive elements (IREs). Iron-responsive elements (IREs) are usually present in mRNAs for numerous proteins involved in iron metabolism. The binding of IRP1 and IRP2 to IREs affect proteins involved in iron uptake (transferrin receptor-1; TfR1 and DMT-1), utilization (erythroid d-aminolevulinic acid synthase), storage (ferritin) and export (ferroportin-1). IRP1 is a 98-kDa bifunctional protein with mutually exclusive functions of RNA binding and aconitase activity and shares a 30%

identity with mitochondrial aconitase an enzyme of the Krebs cycle. IRP2, a second IRE-binding protein, was initially identified in rat hepatocytes, and had been cloned from a variety of mammalian tissues and cells subsequently. Recent discoveries have shown that IRP2 shares 62% amino acid sequence identity with IRP1 but differs in a unique way by possessing a 73-amino acid insertion in its N-terminal region as well as lacking the [Fe-S] cluster. IRP2 does not have aconitase activity, probably due to the absence of the [Fe-S] cluster. The Fe-S cluster in IRP1 may serve to sense iron level signals. Observations from the several investigations implicated cellular iron as an important factor in the interactions of IRPs with IREs with a consequence affecting the regulation of iron metabolism. When cellular iron becomes depleted, IRP1 and 2 acquire high affinity binding state. The binding of IRPs to the IRE in the 5`- untranslated region (UTR) of ferritin mRNA blocks the translation of ferritin, whereas the association of IRPs with IREs in the 3`- UTR of TfR mRNA stabilizes this transcript. On the other hand, when intracellular iron is abundant, IRP1 acquires aconitase activity and loses IRE binding activity, while IRP2 is degraded, resulting in efficient translation of ferritin mRNA and rapid degradation of TfR mRNA. Also contributing to the regulation of systemic iron homeostasis is the circulating peptide hormone, hepcidin. Hepcidin is usually increased during inflammatory conditions. This ensures cellular iron effluxes are limited by (i) binding to ferroportin-1 and (ii) inducing its internalization.

3. Influence of iron and nitric oxide interaction on anemia

RBCs circulate throughout the body engaged in gaseous exchange, oxygen transport, and carbon (iv) oxide removal. Erythropoiesis (Epo) must maintain steady state levels of circulating RBCs and respond to acute challenges. The bone marrow is a highly dynamic organ that produces two to three million red cells every second. These red cells are filled with haemoglobin and are replaced after 75–150 days. This process is controlled by the hypoxia sensing mechanism of the kidney, which responds by modulating the output of Epo, which in turn determines the level of erythropoietic activity. When red cell production fails to match red cell destruction, the result is anaemia.

Iron deficiency anaemia is one of the most common disorders in the world. It however remains an under managed feature of many gastroenterological conditions. About one third of inflammatory bowel disease (IBD) patients suffer from recurrent anaemia. Anaemia has significant impact on the quality of life of affected patients. Chronic fatigue, a frequent IBD symptom itself, is commonly caused by anaemia and may debilitate patients as much as abdominal pain or diarrhoea. Both iron deficiency and anaemia of chronic disease (ACD) contribute mostly to the development of anaemia in IBD. Cobalamin or folate deficiency and various other causes of anaemia such as haemolysis occur infrequently. IBD associated anaemia has been successfully controlled with a combination of iron sucrose and erythropoietin, which then positively affect the misled immune response in IBD.

NO is known to increase the affinity of the intracellular iron-regulatory protein for iron-responsive elements in transferrin receptor and ferritin mRNAs, and a recent study has indicated that NO may affect iron metabolism through disruption of the iron-sulfur complex of iron-regulatory protein 1.

The effects of NO on the regulation of cellular iron metabolism and on the erythropoiesis in anemia of chronic disease has been described extensively; however, there are few studies on

the NO production during the various stages of iron deficiency anemia and during iron supplementation. Moreover, data for correlation coefficients between NO production and erythropoiesis in iron deficiency anemia are limited.

3.1 Infection influences iron homeostasis leading to anemia

Infections or inflammation conditions in most cases are characterized by anemia (ACD) with profound changes in iron homeostasis usually mediated by cytokines. Following n exposure to a wave of pathogen particles, the host immune system becomes activated leading to the production of cytokines initially by the T-helper cells type-1 (Th-1) and subsequently by T-helper cells type-2 (Th-2). The initial activation of macrophages promotes largely the production of pro-inflammatory cytokines. These cytokines including mainly tumor necrosis factor (TNF), γ-interferon (IFN-γ) and nitric oxide (NO) are key to host defence against the invading pathogens but on the other hand are crucial to promoting inflammatory condition. Inflammation, being a major pathogenic feature during chronic infection may ensue secondary to release of these pro-inflammatory signals by activated macrophages. Also noteworthy is the fact that though the released cytokines are meant to provide an environment necessary for parasite clearance but may also have some physiological effects which include the alteration of iron and subsequently nitric oxide homeostasis with far reaching consequence to the initiation and progression of ACD.

Central to iron homeostasis is the activation of macrophages essentially following exposure to infection. Macrophages are normally responsible for the processing of hemoglobin iron from senescent red blood cells (RBCs) and subsequent supply to the bone marrow for erythropoiesis. As explained earlier, the intracellular iron homeostasis is under the control of cytoplasmic iron regulatory proteins (IRP1 and IRP2), which regulate the expression of several proteins by binding to iron-responsive elements (IREs) on the respective mRNA. Furthermore in addition to its activity being regulated by cellular iron, cytokines also modulate the binding activity of IRP. Cytokines are produced by activated macrophages following contact with infectious agent. The immune cells so activated release cytokines among which is the nitric oxide (NO), tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) amongst others. The T-helper cells type-1 (Th-1)-derived cytokines have been demonstrated to also affect iron homeostasis by different mechanisms. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are able to induce hypoferramia by modulating iron metabolism. Pro-inflammatory and anti-inflammatory cytokines produced by T-helper cells type-1 and 2 respectively are major contributors to development of ACD by influencing iron homeostasis. Cytokines do not only affect iron metabolism, but also have inhibitory effects on erythropoiesis by blocking proliferation and differentiation of erythroid progenitor cells limiting their ability to respond to erythropoietin as well as causing deficiency in the production of erythropoietin.

The mononuclear phagocytes acquire iron as a result of erythrophagocytosis during the normal process of removal of senescent blood red cells (RBCs). However the mechanisms involved in the liberation of iron by these cells in order for it to be returned to the circulation is yet to be understood clearly. It is assumed that during inflammatory disease or infection, there is tendency for macrophages to retain more iron in order to restrict pathogen access and this can eventually lead to anemia (ACD).

However, the ability of macrophage-produced nitric oxide (NO) in aiding the release of iron taken up by macrophages through phagocytosis and thereby contributing greatly to the

maintenance of iron homeostasis have been demonstrated by several investigators. The role of NO in such scenario involving the reduction of ferritin synthesis and mobilization for intracellular iron seem to oppose the effect of other cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) which promote iron retention through increased ferritin synthesis. NO production by macrophages is inducible upon introduction of foreign or infectious agent. The implication is that, when an active infection leading to activated macrophages stimulate the production of cytokines in order to get rid of the infectious agent and/or infection, NO acts in opposition to the other cytokines with a resultant effect of maintaining iron homeostasis. Whereas the other cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) act in a concerted manner to ensure iron sequestration and retention by macrophages so as to minimise the iron level available to invading parasites and by so doing disrupt iron homeostasis, the NO counterbalances these effects by ensuring that iron deficit is minimal essentially through increasing the expression of transferrin receptor (TfR), reduction of ferritin synthesis and activation of IRP1.

4. Iron sequestration during infection

Regulating iron balance is necessary especially during infection. Invading pathogens require iron for replication and establishment of infection. Thus it is essential to regulate iron balance such that there is sufficient iron to meet body demands without making too much available to the invading parasites. Although divergent views and conflicting data exist as to the relationship between iron deficiency and infection, recent discoveries have demonstrated that iron depletion protects against and could control infection as well as minimise inflammatory related conditions. Beyond this, the interaction between host and infectious agent is an exciting and complex phenomenon. Yet no theory or experimental model has fully explained it. Several lines of evidence existing illustrate the unique role that iron plays in modulating the battle for survival between mammalian host and the invading pathogens with each organism displaying a unique and competitive mechanism for iron acquisition and maintenance. These mechanisms, which involve enormous genetic investments, are iron responsive and thus able to adapt to the different phases of infection with a variety of tactics on both sides. For instance, in response to poor iron availability in host, pathogens produce siderophores to take the element from host proteins. In response, the mammalian protein lipocalin-2 binds to several kinds of siderophores preventing the pathogen from accessing siderophores-bound iron. However, to evade this strategy, some pathogens produce a glycosylated form of the siderophores preventing its sequestration by lipocalin-2.

5. Role of nitric oxide in modulating iron regulatory proteins

In Biological systems, Nitric Oxide (NO), a small free-radical molecule, has been implicated in a vast array of cellular activities, which ranges from acting as a cytotoxic host defence molecule to being an intercellular signal. Two major routes of NO delivery to cells and tissues have being identified; this could be via Nitric oxide donors as: S-nitroso-N-acetyl Penicillamine (SNAP) and sodium nitroprusside (SNP) or via L-arginine in a reaction catalyzed by nitric oxide synthase.

The activity of iron regulatory protein (IRP), is modulated by both NO donors, SNAP and SNP. This may consequently affect iron uptake through transferrin receptor expression. IRP-

1 and IRP-2 are used by cells, to adjust intracellular iron concentration to levels that are adequate for their metabolic needs, but below the toxicity threshold. The proteins therefore, not only sense the status of cytoplasmic iron but also controls Ferritin and transferrin receptor.

The element regulated by the two IRPs, Fe, is essential for all fundamental and vital activities in the cells, so much so that, its deprivation threatens cell survival. While low iron body stores results in iron deficiency, a number of disease states have been pathogenically linked to excess body iron stores. These include acquired or genetic iron overload as well as delocalization of intracellular iron as seen in inflammation and atherosclerosis.

The Two-sided element can be of an advantage or disadvantage to the cell, depending on whether it serves as a micronutrient (advantage) or as a catalyst of free radical reactions (disadvantage). Oxygen radical generation is not the only type of cellular free radical known; the production of nitrogen radicals has also being established. The capacity of readily exchanging electrons makes iron not only essential for fundamental cell functions, but also a potential catalyst for chemical reactions involving free-radical formation and subsequent oxidative stress and cell damage. Cellular iron levels are therefore carefully regulated not only to maintain the body's required concentrations but also to minimize the pool of potentially toxic 'free iron'.

Iron and nitric oxide are intimately associated in various biological processes. Nitric oxide is one of the major pathophysiological stimuli that modulate the activity of IRP-1, a key effector molecule involved in the regulation of intracellular iron metabolism. IRP-1 is a cytoplasmic aconitase (converting citrate into isocitrate) when it contains a [4Fe-4S] cluster, and an RNA-binding protein after complete removal of the metal center. By binding to specific mRNA sequences, the iron responsive elements (IREs), IRP-1 modulates ferritin mRNA translation and transferrin receptor stability.

Contrarily, IRP-2 does not assemble a cluster nor possess aconitase activity, despite structural and functional similarities to IRP-1, it however possess a distinct pattern of tissue expression and is modulated via proteasome-mediated degradation. NO preferentially targets [Fe-S] clusters and the inhibition of aconitase is involved in the cytotoxic effect of NO. Its involvement in a variety of physiological and pathological processes necessitates establishing the role it plays in the IRP-mediated regulation of iron metabolism. The loss of IRP-2 is highly expressed in macrophages even when IRP-1 is activated, this may not be unconnected with the fact that, the improved ferritin synthesis and a decreased transferrin receptor mRNA is accompanied by cytokine-mediated activation of macrophages. While down-regulation of IRP-1 protein levels by NO may have a role to play, IRP-2 has a greater affinity for target IREs.

NO has a number of effects on the key regulators of cellular iron homoeostasis, IRP-1 and IRP-2 in response to fluctuations in the level of the 'labile iron pool', as a result various agents and conditions may affect IRP activity, thereby modulating iron and oxygen radical levels in different patho-biological states. The number of mRNAs regulated through IRE-IRP interactions is on the increase, thereby expanding the role of IRPs from just being iron-regulatory proteins to other roles in essential metabolic pathways.

For instance, the concentration of NO is regulated in the respiratory chain (RC) by a balance between its production and its utilization. This in turn regulates mitochondrial oxygen uptake and energy supply. Cell damage resulting from high concentrations of NO involves

inhibition of a number of cellular processes, such as DNA synthesis and mitochondrial respiration.

While some of these effects may be direct, others arise from the reaction of NO with O_2 to form peroxynitrite ($ONOO^-$). NO and $ONOO^-$ can cause damage thereby disrupting cellular functions. To differentiate the sites at which both interact with the respiratory chain from the mechanism of inhibition, NO binds to cytochrome c oxidase, the terminal member of the mitochondrial respiratory chain, and NO, as recently reported, may act as an inhibitor of this enzyme at physiological concentrations in a reversible and competitive reaction with oxygen.

$ONOO^-$ however has little or no effect on cytochrome C oxidase, but inhibits respiratory complexes I–III in an apparently reversible manner. Reaction of NO with molecular oxygen results in oxidation products that can react with low molecular weight and protein-associated thiols, such as cysteine, glutathione, and albumin, to form S-nitrosothiols. It is now established that NO shows antioxidant properties, contrary to the deleterious effects of the reactive nitrogen oxide species formed from NO and oxygen.

Since NO biochemistry is dominated by free-radical reactions, its interaction with other free-radical species could lead to either inhibition or potentiation of oxidative damage effect. Iron–sulfur clusters have long been recognized as molecular targets of NO.

Several reports have shown that NO does increase IRP-1 activity and two possible mechanism or hypothesis of such activation have been suggested for the NO effect: The first is the induction of cytoplasmic aconitase's disassembly and switching to IRP-1 when NO bind to its Fe–S cluster, while the second is NO induction of cellular iron release and reduction of the labile iron pool, effects that would be compensated by spontaneous disassembly of the aconitase cluster or by the synthesis of cluster-free IRP-1. A decrease in aconitase activity may not always be accompanied by a consistent increase in IRP-1 activity, as this is dependent on the iron status of the cell. Iron depleted cells, for instance, may respond to nitrogen reactive species by increasing their IRP-1 activity, a process reflecting disassembly of the aconitase cluster by NO or $ONOO^-$.

IRP-2 is invariably inactivated by NO or $ONOO^-$ or in macrophages committed to the formation of reactive nitrogen species after stimulation with cytokines. This effect is attributed to redox modifications of –SH residues exposed by the cluster-free IRP-2, and to redox modifications followed by proteasome-mediated protein degradation. Thus, IRP-2 degradation may account for the enhanced ferritin synthesis and reduced TfR mRNA content observed in cytokine-stimulated macrophages producing NO and $ONOO^-$. The effect of nitrogen reactive species on IRP may therefore explain the iron sequestration pattern that characterizes macrophages under inflammatory conditions. Current on-going patho-physiological studies across the globe will in the nearest future reveal how to use this mechanism to minimize formation and release of free radicals in diseased tissues.

6. Concluding remark

The pathophysiology of ACD may largely be attributed to iron homeostasis, which is affected by several factors. The foregoing discussion has clearly depicted the faces of underlying and intriguing factors that work independently or interdependently to contribute to the initiation and progression of ACD. These factors among which are cytokines produced mainly by activated macrophages in response to prevailing cellular condition at a particular time, more often are responsible for ACD development and also

may predict its outcome. In normal physiological state, abundance of iron limits its acquisition from diet and promotes ferritin synthesis while nitric oxide working in concert with iron proteins increases mobilization for intracellular iron. However, all of these processes become perturbed secondary to introduction of other factors. For instance, in the presence of an infection, production of pro-inflammatory cytokines will promotes ACD while an early skewing toward producing anti-inflammatory signals may reverse the situation. In this regard, iron sequestration and retention by macrophages play key role in ACD. In such cases there is abundance of iron stored away in ferritin and not accessible by erythroid cells hence increased erythrophagocytosis without a commensurate erythropoiesis may precipitate anemia. Of crucial importance are the roles played by intracellular iron levels and nitric oxide in affecting iron homeostasis and eventually ACD. In the absence of an infection however, anemia may develop following inadequate iron supply to meet cellular demands.

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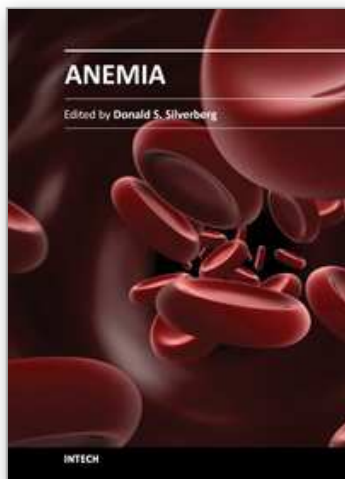
Anemia

Edited by Dr. Donald Silverberg

This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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