

*Clinical paradigms***Anemia of chronic disease: A harmful disorder or an adaptive, beneficial response?**

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**A**nemia of chronic disease is a hypoproliferative anemia that develops in response to systemic illness or inflammation.<sup>1</sup> It was first described in the 1930s and was more fully characterized by Cartwright and Wintrobe in the 1950s.<sup>2</sup> Although the second most prevalent after anemia caused by iron deficiency, it is the commonest among patients with chronic illness.<sup>3</sup> A variety of clinical conditions can lead to anemia of chronic disease, including infection, cancer and autoimmune conditions.

In comprehensive population-based studies, precise estimates of prevalence are difficult to ascertain because many patients with anemia are not investigated sufficiently to establish the cause. Moreover, no consensus research criteria exist for the diagnosis of anemia of chronic disease, and patients may have multifactorial causes for anemia, wherein anemia of chronic disease is only a part.

Anemia of chronic disease varies in severity. Patients typically present with mild (> 100 g/L) or moderate (85–100 g/L) reductions in hemoglobin concentrations. In a minority of patients, severe reductions can occur.

The prevailing opinion is that anemia of chronic disease is an adverse consequence of systemic illness. The general assumption is that anemia is a disorder and that patients would be better off without it. In a review of the topic, Weiss and Goodnough<sup>1</sup> concluded that it is logical to treat anemia of chronic disease, stating that, “[d]espite management guidelines, anemia of chronic disease remains underrecognized and undertreated.” We do not believe there is sufficient evidence to support such a conclusion.

We hypothesize that anemia of chronic disease is a beneficial and adaptive response to an underlying disease state. We will support this hypothesis with 3 arguments:

- The observation that anemia is associated with a poor prognosis in many disorders is not sufficient reason to attribute causation.
- Anemia of chronic disease has the characteristics of an adaptive physiologic response.
- Treatment of mild to moderate anemia of chronic disease appears to increase mortality.

**Why anemia of chronic disease is assumed to be deleterious**

Two principal notions underlie the belief that anemia of chronic disease is deleterious. First, the reduction in red blood

cell mass is presumed to compromise oxygen delivery to tissues and thus obligate the organism to compensate for reduced oxygen-carrying capacity.<sup>1</sup> Second, anemia is associated with a poor prognosis in many clinical disorders.<sup>1</sup> These 2 notions have led to the conclusion that treatment of anemia of chronic disease is beneficial. However, fundamental flaws exist in these arguments.

**Anemia and oxygen delivery**

There is little debate that severe anemia is associated with impaired oxygen delivery. However, in patients with anemia of chronic disease, the anemia is generally mild to moderate. Under normal circumstances, oxygen consumption in the resting human body is approximately 4 times less than oxygen delivery to the tissues.<sup>4</sup> Increased extraction of oxygen from the tissues, combined with a rightward shift in the oxygen–hemoglobin dissociation curve, is sufficient to maintain normal oxygen delivery in the presence of mild to moderate anemia.<sup>5,6</sup>

Experiments designed to quantify the cardiovascular response to anemia have generally done so by the acute induction of severe anemia below 80 g/L.<sup>7–9</sup> Induced acute anemia is associated with a progressive increase in heart rate and cardiac output;<sup>10,11</sup> however, these changes are not found in patients with stable mild or moderate anemia. Studies involving adults with chronic anemia showed no consistent changes in cardiac output until hemoglobin levels fell below 70 g/L or 50% of normal.<sup>12–14</sup> Thus, physiologic compensatory mechanisms in adults with non-acute mild anemia, although incompletely characterized, appear to differ from the changes seen in response to acute severe anemia. One obvious limitation of these studies is that testing was performed on resting participants. In people who are exercising, reductions in hemoglobin levels have been shown to reduce maximal oxygen consumption and endurance performance, but this is of uncertain relevance to chronically ill patients.<sup>15</sup>

**Anemia as a marker of poor prognosis**

Anemia is known to be associated with mortality in many disorders. Meta-analyses of large numbers of studies have established this association in renal failure,<sup>16</sup> congestive heart failure<sup>17</sup> and cancer.<sup>18</sup>

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The observed association of anemia with increased mortality is not evidence of causation and should not be interpreted as such. Instead, both the degree of anemia and the direness of the prognosis likely reflect the severity of the underlying disease.<sup>18</sup> Moreover, few of the studies adjusted for parameters such as cytokine levels or C-reactive protein that would help to distinguish between death from the anemia and death from the underlying inflammatory state. In a single study of heart failure that adjusted for cytokine levels, anemia lost significance as a predictor of death.<sup>19</sup> In another study, anemia also lost prognostic significance after adjustment for clinical variables reflecting disease severity.<sup>20</sup> A systematic review of studies involving patients with lung cancer showed that anemia was not an independent predictor of survival in the majority of studies that adjusted for other clinical factors.<sup>21</sup>

Although many other studies identify anemia as an independent predictor of poor prognosis, interpreting those studies requires careful consideration. Routinely measured clinical variables are unlikely to fully register the severity of underlying inflammatory processes and stress responses,<sup>18</sup> which makes it hard to adjust for these effects completely. Excess deaths among chronically ill patients with anemia are generally not due directly to the anemia or to processes on which the anemia would be expected to have a major impact. Treatment of the anemia would not be expected to improve a patient's overall prognosis if the anemia is simply a marker of a serious, and possibly undiagnosed, underlying condition. Indeed, as discussed later in this article, treatment of anemia has repeatedly been found to worsen rather than improve clinical outcomes.

## Anemia as an adaptive physiologic response

Anemia of chronic disease appears to be a highly coordinated and genetically conserved response to systemic disease and has features of a biologically adaptive response.<sup>22,23</sup> The effectors of this response, such as hepcidin, a major regulator of iron metabolism, are evolutionarily ancient, based on their presence in such distant species as zebra fish.<sup>24</sup>

Several mechanisms independently contribute to anemia of chronic disease (Figure 1). Iron sequestration is the best studied. However, suppression of erythropoietin production, inhibition of erythroid progenitors and decreased red blood cell survival all occur and likely contribute to the active downregulation of hemoglobin concentration. The relative contribution of each of these mechanisms is uncertain. The occurrence of several independent processes, each contributing in concert to the reduction in hemoglobin, further suggests a process of evolutionary adaptation.

The sequestration of iron within macrophages is a hallmark of anemia of chronic disease that could have several beneficial effects. Iron is an essential nutrient required for the growth of many microorganisms. Iron loading promotes infection and facilitates the growth of malignant cells.<sup>25</sup> Plasma itself demonstrates antimicrobial properties that are attenu-

ated by the addition of iron, whereas inhibition of bacterial growth occurs in iron-deficient conditions.<sup>25-27</sup> Hypoferremia is therefore thought to be an innate antimicrobial strategy. This may explain the increased rates of infection seen among patients with  $\beta$ -thalassemia major who have iron overload.<sup>28</sup>

Free iron is toxic and its concentration tightly regulated. In the context of the increased oxidant stress that characterizes inflammation, suppression of the Fenton reaction (production of hydroxyl free radicals catalyzed by ferrous iron) by sequestration of iron may be especially important in attenuating the production of reactive oxygen species.

Anemia of chronic disease could have adaptive benefits beyond iron sequestration. Decreased bone marrow production reduces nutrient utilization in times of stress. Moderate anemia and compensatory expansion of plasma volume reduces blood viscosity, which decreases left ventricular stroke work and may improve microvascular perfusion. Decreased margination of platelets and decreased scavenging of nitric oxide may also reduce thrombosis. Although these hypotheses have not been proven, they also have not been tested. Furthermore, the relative importance of each potential mechanism remains unknown.

## Potential harms of treatment

If anemia of chronic disease is a protective measure, one should expect adverse consequences associated with efforts to override it and increase hemoglobin concentration. This hypothesis is supported by numerous studies that have evaluated red blood cell transfusion or the use of erythropoiesis-stimulating agents. Although the studies we cite in the following sections were not specifically designed to investigate anemia of chronic disease, all involved patient populations in which this condition is highly prevalent.

### Critical care

Among critically ill patients, 2 observational studies showed red blood cell transfusion to be an independent predictor of death.<sup>29,30</sup> More substantial evidence is provided by a prospective, randomized controlled trial that reported increased mortality among patients randomly assigned to receive a liberal transfusion strategy (transfusion if hemoglobin levels fell below 100 g/L) compared with those assigned to receive a conservative transfusion strategy (transfusion if hemoglobin levels fell below 70 g/L).<sup>31</sup> Mortality was significantly increased among less critically ill patients (16.1% in liberal-strategy group v. 8.7% in conservative-strategy group); the number needed to harm was 13. Critically ill patients have many reasons for anemia, but because systemic inflammation typically underlies critical illness, almost all can be expected to have some degree of anemia of chronic disease.

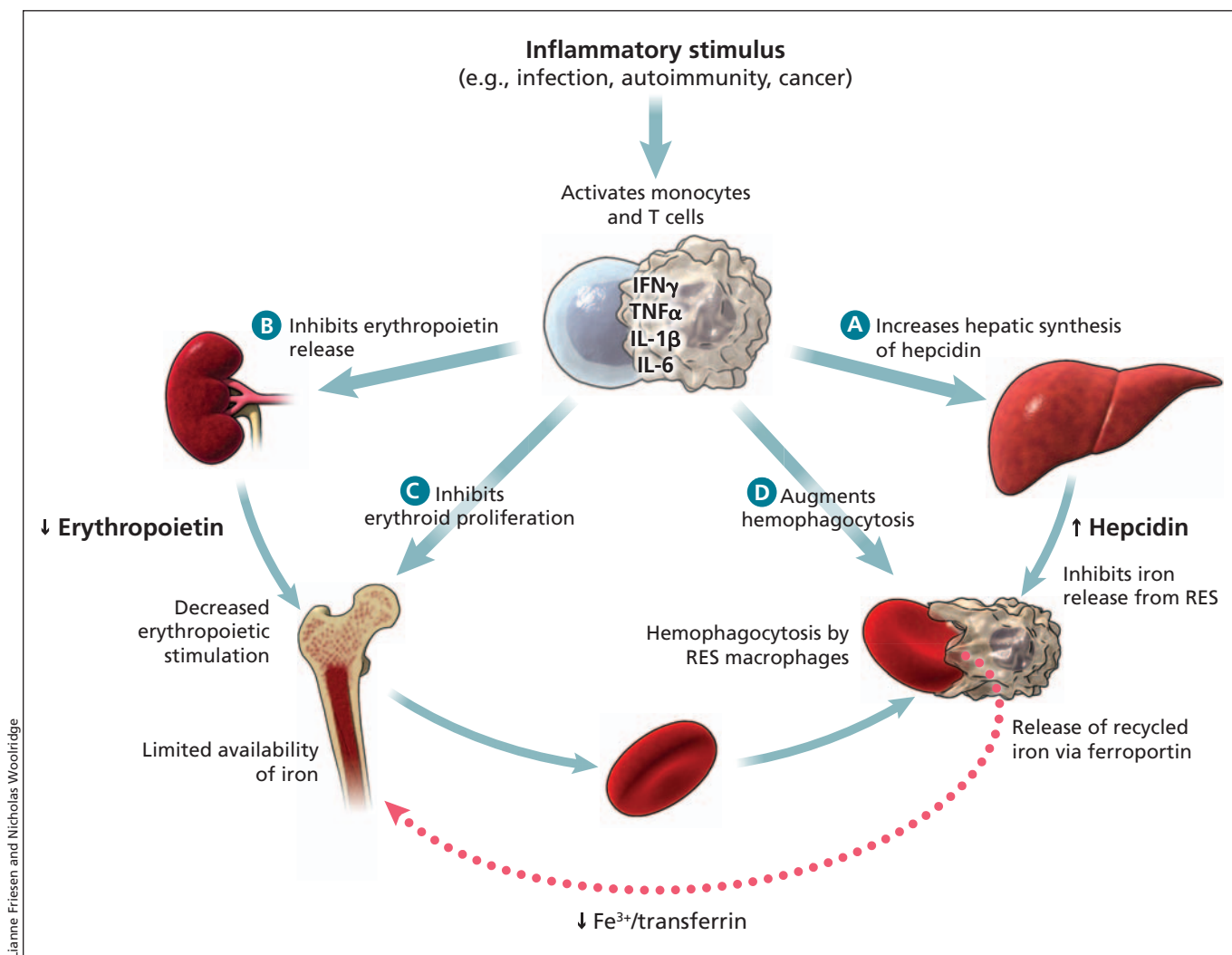
Transfusion in patients with anemia was also associated with increased mortality in 3 observational studies involving patients admitted with acute coronary syndrome and myocardial infarction.<sup>32-34</sup> Among patients who received red blood cell transfusion, the predicted probability of death was higher among those with a pretransfusion hematocrit above 0.25–0.30 than among those with a lower hematocrit. In other

words, transfusion appeared to be harmful in patients with mild to moderate anemia but seemed to be beneficial to patients with more severe anemia.

One possible inference from these studies would be that red blood cell transfusion is harmful. Although there are a number of well-established risks associated with red blood cell transfusion, none is estimated to occur with a frequency that could explain more than a small fraction of the mortality risk described above. Other hypotheses (e.g., immunosuppressive and rheologic effects) are plausible but not well established. It is impossible to ascertain the extent to which anemia of chronic disease contributed to the anemia in the patients studied. Other causes of anemia would have also existed. Although any conclusion about anemia of chronic disease

drawn from these studies is necessarily tentative, treatment of anemia by transfusion seems not to be beneficial, even in critically ill patients, who are least able to tolerate anemia and presumed to benefit most from its correction.

If transfusion in itself is harmful, then the use of erythropoiesis-stimulating agents could be expected to circumvent the increased risks associated with transfusion. In a large randomized controlled trial involving critically ill patients that attempted to address this question, administration of erythropoietin increased hemoglobin levels but did not reduce the frequency of transfusion or overall mortality.<sup>35</sup> A meta-analysis of erythropoietin use in critical care was similarly unable to detect a mortality benefit despite erythropoietin's ability to reduce the frequency of transfusion in the overall study population.<sup>36</sup>



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**Figure 1:** In inflammatory diseases, cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in hemoglobin levels: (A) Induction of hepcidin synthesis in the liver (especially by interleukin-6 [IL-6], along with endotoxin). Hepcidin in turn binds to ferroportin, the pore that allows egress of iron from reticuloendothelial macrophages and from intestinal epithelial cells. Binding of hepcidin leads to internalization and degradation of ferroportin; the corresponding sequestration of iron within the macrophages limits iron availability to erythroid precursors. (B) Inhibition of erythropoietin release from the kidney (especially by interleukin-1 $\beta$  [IL-1 $\beta$ ] and tumour necrosis factor  $\alpha$  [TNF $\alpha$ ]). Erythropoietin-stimulated hematopoietic proliferation is in turn reduced. (C) Direct inhibition of the proliferation of erythroid progenitors (especially by TNF $\alpha$ , interferon- $\gamma$  [IFN $\gamma$ ] and IL-1 $\beta$ ). (D) Augmentation of erythrophagocytosis by reticuloendothelial macrophages (by TNF $\alpha$ ). RES = reticuloendothelial system.

Thus, it may not be the red blood cells transfused but, rather, the achieved hemoglobin level that confers risk in critically ill patients with anemia of chronic disease. One further possibility exists: that anemia of chronic disease is harmful but that available interventions that increase hemoglobin levels confer even greater harm.

### Renal failure

The treatment of severe anemia with erythropoietin has been found to improve well-being and decrease the frequency of transfusion in patients with renal failure. However, a recent meta-analysis of randomized controlled trials found that erythropoietin at a dose designed to achieve normal hemoglobin concentrations was associated with significantly higher mortality and increased thrombosis compared with regimens designed to achieve lower target hemoglobin levels.<sup>37</sup> One of the trials involved 1233 patients with cardiovascular disease and end-stage renal failure; the number needed to harm (death or myocardial infarction) was 18.<sup>38</sup> Another trial included in the meta-analysis involved 1432 patients with non-dialysis-dependent chronic kidney disease; the number needed to harm was 26.<sup>39</sup>

When interpreting these studies, one needs to consider the high prevalence of other illnesses and inflammatory conditions. Anemia in many of these patients will be due to at least 2 components: erythropoietin deficiency and anemia of chronic disease. It is plausible that physiologic correction of the erythropoietin deficiency may be beneficial; however, pharmacologic override of anemia of chronic disease may confer harm. This conceptual model could explain the paradox between observational studies of erythropoietin treatment that have shown improved outcomes associated with increased hemoglobin levels among patients with renal failure<sup>40,41</sup> and randomized trials that illustrated harm associated with higher hemoglobin levels.<sup>38,39,42</sup> The patients in the observational studies who had higher hemoglobin levels may have had less systemic illness and therefore less severe and less prevalent anemia of chronic disease.

### Cancer

Anemia is pervasive among patients with cancer, with multiple contributing mechanisms in different patients. Most intervention studies have evaluated the use of erythropoiesis-stimulating agents to support hemoglobin levels during chemotherapy or radiation therapy, but goals of treatment have varied.

In a meta-analysis of 51 randomized trials investigating the use of erythropoiesis-stimulating agents among 13 611 cancer patients, mortality was increased in the intervention arms (hazard ratio 1.10, 95% confidence interval 1.01–1.20).<sup>43</sup> Those trials in which the intervention was designed to achieve a normal hemoglobin level were more likely to demonstrate harm than the trials that had a lower target hemoglobin level. Among patients with head and neck cancer who received radiotherapy, those given erythropoietin to maintain a normal hematocrit had a higher mortality than those in the control group.<sup>44</sup> A randomized controlled trial of erythropoietin given to patients with breast cancer was

stopped early because of excess mortality in the erythropoietin-treated group.<sup>45</sup>

Erythropoiesis-stimulating agents have also been used to ameliorate symptoms of anemia in cancer patients not receiving chemotherapy or radiation therapy. Although anemia in such patients is likely to be multifactorial, in the absence of myelosuppressive treatment, the anemia seen is more likely secondary to anemia of chronic disease. In randomized controlled trials involving patients with head and neck cancer<sup>46</sup> or non-small-cell lung cancer,<sup>47</sup> darbepoetin therapy was found to increase mortality. The US Food and Drug Administration has subsequently issued a warning against the use of erythropoiesis-stimulating agents in cancer patients not receiving chemotherapy or radiation therapy.<sup>48</sup>

In addition to critical care, renal failure and cancer, erythropoiesis-stimulating agents have been used to treat anemia of chronic disease in patients with rheumatoid arthritis<sup>49</sup> and inflammatory bowel disease.<sup>50,51</sup> These patient populations may be more informative to our hypothesis, since the anemia in such patients may be more consistently attributed to anemia of chronic disease. However, no trials involving these patient populations have reported mortality as a prespecified outcome.

## Conclusions

We argue that anemia of chronic disease is an adaptive response and could be beneficial to patients with inflammatory disease. Multiple lines of evidence support this hypothesis. However, mechanisms of benefit need to be clarified, and clinical trials that specifically address this hypothesis are required. Even if anemia of chronic disease is a beneficial adaptive response, it must be recognized that any adaptive response may at times be excessive or insufficient, and thus maladaptive. Nevertheless, we believe there is sufficient evidence to advocate restraint regarding the treatment of mild to moderate anemia of chronic disease. Given the documented adverse effects in multiple patient populations, the possible risks of treatment, including death, should be weighed carefully against the potential benefits of less fatigue and other improvements in quality of life before therapy to override the anemia of chronic disease is considered. Future therapeutic trials of anemia should attempt to characterize the cause of the patients' anemia. In patient populations where anemia of chronic disease is identified as a major component, trials should be adequately powered to detect differences in mortality between treatment groups.

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