Anemia. Not just an innocent bystander
Arch Intern Med 2003; 163: 1400-4

In this commentary, the authors review the growing evidence indicating that anemia: (1) occurs commonly, (2) is frequently overlooked and considered merely secondary to other underlying illnesses, and (3) has an independent impact on both length and quality of life (QOL).

Granted that an estimate of the prevalence of anemia in both the general population and ill people is confounded by the lack of a standardised definition of anemia (for the purposes of this review anemia was defined as haemoglobin levels <13 g/dL in men or <12 g/dL in women, as recommended by the WHO), the likelihood of this condition is greater in the elderly.

Data for the prevalence of anemia associated with disease have been studied in more depth in patients with chronic liver disease, rheumatoid arthritis, human immunodeficiency virus infection, cancer and cancer treatment, inflammatory bowel disease, radiation therapy and congestive heart failure (CHF).

Higher mortality rates are almost always observed in anaemic patients with CHF or in patients undergoing maintenance haemodialysis. Prospective randomised trials in patients with CHF demonstrated that anaemia was an independent predictor of subsequent death, showing that for every 1% decrease of haematocrit, the mortality rate increased by 1.6%.

In addition to its impact on mortality, anaemia also significantly influences morbidity: prospective trials in patients with end-stage renal disease have demonstrated a relationship among haematocrit, left ventricular dilatation and left ventricular hypertrophy. An intriguing association has also been observed between anaemia and disease progression among patients undergoing radiotherapy for cancer, particularly in those with cervical carcinoma or with squamous cell carcinoma of the head and neck.

In addition, anemia has been found to be significantly associated with an impaired QOL, which improves after the treatment of anemia.

Whatever the cause of the anaemia (nutritional deficiency, blood loss, haemolysis or chronic disease) once the pathogenesis of the anemia has been ascertained, appropriate therapy can be appropriately utilised in individual patients.

In summary, the time has come to address anemia as a serious public health condition and not just as an "innocent bystander".

WBC reduction of RBC transfusions is associated with a decreased incidence of RBC alloimmunization
Transfusion 2003; 43: 945-52

The aim of this retrospective cohort study was to determine whether leucocyte (WBC) reduction of blood components can decrease the risk of alloimmunisation to red blood cells (RBC). Two cohort of patients were retrospectively studied. In the first, the prevalence of newly detected (RBC) alloimmunisation was determined in patients with acute myeloid leukaemia (AML) receiving non-WBC-reduced or WBC-reduced transfusions in the periods before and after WBC reduction of blood components was introduced: the immunohaematologic follow-ups were frequent and thorough. In the second, the incidence of newly detected RBC alloimmunisation was determined in patients with acute myeloid leukaemia (AML) receiving non-WBC-reduced or WBC-reduced transfusions in the periods before and after WBC reduction of blood components was introduced: the immunohaematologic follow-ups were frequent and thorough. In the second, the incidence of newly detected RBC alloimmunisation in all transfused hospital patients was determined in three annual periods (1987, 1999 and 2001) during which the prevalence of WBC reduction ranged from 0 to 100%.

The alloimmunisation rate in AML patients was 8.2%
in those receiving non-WBC reduced RBC and platelets transfusions (n=195) and 2.8% in those receiving only WBC-reduced components (n=215).

The alloimmunisation incidence rate in all hospitalised patients decreased from 3.47 per 1,000 antibody screens in 1987 (no WBC reduction) to 2.97 per 1,000 in 1999 (40% of transfusions WBC reduced) to 2.38 per 1,000 in 2001 (100% of transfusions WBC-reduced). The decrease in alloimmunisation was observed in both males and females although it was more marked in males.

Although these data cannot rule out that WBC reduction has a role in modulating secondary immune responses, they are more consistent with a reduction in primary immune responses.

These preliminary data suggest that WBC reduction of blood components may lead to reduced allosensitisation to RBC antigens, in accordance with the hypothesis that allogeneic WBC stimulate the type 2 immunological response (Th 2), that is the humoral immune response, particularly involving specific IgG subclasses of antibodies.

These findings require further investigations and confirmation.

Warkentin TE, Roberts RS, Hirsh J et al.
An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients
Arch Intern Med 2003; 163: 2518-24

According to the standard definition, the diagnosis of immune heparin-induced thrombocytopenia (HIT) is usually based on a fall in platelet count below 150x10⁹/ L. This definition may be inappropriate for postoperative patients, who often develop a postoperative thrombocytosis.

The aim of this study was to determine an improved definition of thrombocytopenia indicating HIT in postoperative orthopaedic patients who receive unfractionated or low-molecular-weight heparin following elective hip arthroplasty.

The sensitivity and specificity of various definitions of thrombocytopenia as indicating the appearance of HIT were evaluated in 362 patients with HIT antibodies detected by laboratory tests (both the platelet ¹⁴C-serotonin release assay and an enzyme immunoassay to confirm that antiplatelet factor4/heparin IgG antibodies were present in the samples positive in the platelet serotonin release assay).

The improved definition of HIT resulted to be a 50% or greater platelet count fall from the postoperative peak (up to postoperative day 14). This definition had greater sensitivity (50% vs 25%) than the standard definition for identifying HIT IgG and a similarly high specificity (99.1% vs 99.4%).

Patients identified using the improved definition had a higher frequency of thrombosis than did patients without HIT. Moreover the improved definition highlighted an even greater absolute difference in the frequency of HIT between recipients of unfractionated and low-molecular-weight heparin than did the standard definition.

In conclusion, a 50% or greater fall in the platelet count from the postoperative peak is a sensitive definition indicating possible HIT that is associated with an increased risk of thrombosis.

Wucherpfennig KW
Mechanisms for the induction of autoimmunity by infectious agents
J Clin Invest 2001; 108: 1097-104

Experimental models of autoimmunity have shown that autoimmune diseases can be transferred by activated, but not resting, autoreactive T cells indicating that activation of T cells is required for the development of autoimmune diseases. Infectious agents have long been considered as possible culprits in the activation of autoreactive T cells.

This review examines the mechanisms by which an infection can lead to an autoimmune process in experimental animal models and discusses their relevance to human disease.

The mechanisms based on microbial products (peptides or superantigens) are: (i) activation of autoreactive T cells by peptides from microbial proteins that have sufficient structural similarity to self-peptides (the so called molecular mimicry), and (ii) activation of large numbers of autoreactive T cells that express particular Vß gene segments with formation of a subpopulation of these activated cells specific for a self-antigen.

In contrast, there are three different mechanisms of autoimmunity with a common basis of an inflammatory setting: (i) enhanced presentation of autoantigens by antigen-presenting cells (APC) recruited to an inflammatory site, followed by priming of autoreactive lymphocytes, (ii) expansion of previously activated T cells at an inflammatory site (bystander activation), and (iii) viral infection of lymphocytes (such as infection of B cells by hepatitis C virus) resulting in enhanced antibody production. In chronic autoimmune diseases associated with an inflammatory process the activation and expansion of T cells can produce additional autoantibody specificities (epitope spreading).
The human autoimmune diseases associated with defined infectious agents include the following:

**Post-infectious syndromes**
1. Guillan-Barré syndrome, with peripheral nerve as the target organ and *Campylobacter jejuni*, Epstein-Barr virus, and Cytomegalovirus as the pathogens.
2. Rheumatic fever, with heart muscle and valves, kidney and CNS as the major target organs, and group A streptococci as the pathogens.

**Acute and chronic inflammatory diseases**
1. Lyme fever with the large joints as the target organ and *Borrelia burgdorferi* as the pathogen.
2. Reactive arthritis with the axial skeleton as the target and *Yersinia*, *Shigella*, *Salmonella* and *Chlamydia trachomatis* as the pathogens.

**Immune-complex mediated disease**
Mixed cryoglobulinaemia, with blood vessels, kidney, lung as the target organs and HCV as the pathogen.

An association has been found between the majority of autoimmune disease and alleles of the MHC genes. The strongest association is between acute and chronic inflammatory disease and MHC class II molecules, presenting peptides to CD4+ cells, whereas ankylosing spondylitis and reactive arthritis are strikingly associated with the MHC class I molecule HLA-B27.

**Andreone P, Gramenzi A, Lorenzini S, et al.**
*Post-transplantation lymphoproliferative disorders* 

Post-transplantation lymphoproliferative disorders (PTLD) are lymphoid proliferations or lymphomas that develop in a recipient of a solid organ or bone marrow allograft. More than 90% of these disorders are Epstein-Barr virus (EBV)-associated lesions of B-cell origin and seem to represent B-cell or, rarely, T-cell proliferations, that occur in a setting of decreased T-cell immune surveillance due to immunosuppressive drugs used to prevent graft rejection.

PTLD occur in 1% to 20% of transplant recipients, but in the case of bone marrow transplants the incidence is as high as 24% among patients who receive T-cell-depleted allogeneic transplants.

The pathogenesis of PTLD is complex and, probably, multifactorial. Drug-induced immunodeficiency and chronic antigenic stimulation exerted by the graft play important roles. Other risk factors include the type of transplanted organ, the type of the disease leading to transplantation and, finally, the type, duration and intensity of immunosuppressive drug treatments.

Although the disease is extremely variable, an infectious mononucleosis-like presentation is common in PTLD occurring less than about a year after transplantation (early PTLD), whereas PTLD that manifest later than about a year after transplantation (late PTLD) are likely to be more anatomically circumscribed, produce fewer systemic symptoms and follow a more gradual clinical course.

In the absence of effective therapy for PTLD, the best strategy for their management is currently focused on prevention, remembering the importance of primary EBV infection as a significant risk factor for these disorders (EBV serostatus should be determined in all potential transplant recipients).

Although no controlled clinical trials with therapeutic interventions have yet been performed, the most important initial strategy in the management of this disease is to reduce and, if possible, discontinue the immunosuppressive drug therapy.

**Anderson K**
*Broadening the spectrum of patient groups at risk for transfusion-associated GvHD: implications for universal irradiation of cellular blood components [editorial]* 
Transfusion 2003; 43: 1652-4

Transfusion-associated graft-versus-host disease (TA-GvHD) is a rare, but almost uniformly fatal, complication of cellular blood component transfusions and is the result of engraftment of immunocompetent viable donor lymphocytes into the recipient, who is usually profoundly immunodepressed.

In this editorial, the author presents two important articles on the subject, published in the same issue of the journal. In the first paper, Leitman et al. (see later) report a case of fatal TA-GvHD in a patient with systemic lupus erythematosus who received fludarabine therapy. Previous reports of transfusional GvHD exclusively regarded patients receiving fludarabine for haematological malignancies. The second accompanying article describes ten cases of TA-GvHD, also fatal, in a retrospective review of transfusions performed over a 10-year period at *The American University of Beirut-Medical Center*. All ten cases involved immunocompetent hosts, who received fresh non-leucoreduced and non-irradiated blood components (Aoun et al., Transfusion 2003; 43: 1672-6).

This editorial had two distinct purposes: to draw the attention of specialists in Transfusion Medicine to the fact that not only immunodepressed recipients but also other categories of patients are at risk of TA-GvHD, and to suggest a wider use of irradiated cellular blood components.
Gamma irradiation is not particularly expensive, is readily achievable and free of side effects and the editorialist underlines the need to consider universal irradiation of cellular blood components in the future practice of Transfusion Medicine.

Leitman SF, Tisdale JF, Bolan CD, et al.

Transfusion-associated GvHD after fludarabine therapy in a patient with systemic lupus erythematosus

Transfusion 2003; 43: 1667-71

The authors describe a case of fatal transfusion-associated graft-versus-host disease (TA-GvHD) in a 42-year old female with refractory lupus nephritis, who received three monthly cycles of fludarabine (30 mg/m²/day, days 1 to 3) and cyclophosphamide (500 mg/m² on day 1). Three months after the last dose of fludarabine, the patient received non-irradiated cellular blood components (2 packed red blood cell concentrates, 2 single donor and 6 random donor platelet concentrates) from unrelated volunteers. Two weeks later, she developed a classical picture of TA-GvHD (fever, rash, raised levels of aminotransferase, hyperbilirubinaemia and pancytopenia). Skin biopsy confirmed the diagnosis of GvHD. In spite of prompt and suitable treatment (granulocyte colony-stimulating factor, antithymocyte globulin and cyclosporine) the patient died of disseminated Candida albicans infection.

HLA typing of the patient's circulating lymphocytes, performed during the course of the GvHD reaction, revealed additional alleles: these alleles were identical to those of an unrelated donor whose non-leucoreduced, single platelet concentrate had been transfused 90 days after the last dose of fludarabine and 10 days before the onset of the GvHD symptoms.

As fludarabine and other purine analogues are increasingly being used in the treatment of disorders other than haematological malignancies, it is important to include patients so treated in the groups at risk of TA-GvHD.

Bowman J

Thirty-five years of Rh prophylaxis

Transfusion 2003; 43: 1661-6

John Bowman, a paediatrician at the University of Manitoba (Canada) and well-known expert in Rh haemolytic disease of the newborn, uses this commentary to celebrate the 35th anniversary of the licensing of the first Rh immunoglobulin (RhoGam Ortho) in the United States. He reports the glorious history of the prevention of Rh immunisation, also providing some information relevant to the matter but unknown to most specialists: for example, already in the same year (1900) that Landsteiner described the ABO blood group system, von Dungern injected ox RBC into rabbits to demonstrate, first, the axiom that active immunisation to an antigen is prevented by the presence of passive antibodies (in this case, rabbit antibodies to ox RBC).

The article reviews all aspects of Rh prophylaxis: standard prevention procedures, causes of its failure after delivery, immunisation during pregnancy, the grandmother theory and also some remaining problems.

These last problems include women with very weak anti-D antibodies.

Despite the fact that women with a Rh antibody demonstrable only by an automated method (Autoanalyzer) habitually show no progression of their Rh immunisation after the delivery of a D-positive infant, the author's advice is to give prophylaxis every time they give birth to a D-positive child. In constrast, in cases in which the antibody is demonstrable by an enzyme technique but not by an indirect antiglobulin test, administration of RhIg has been unsuccessful: 21 of 36 women with such antibodies developed full-blown Rh immunisation, despite the administration of anti-D immunoglobulins at 6-week intervals during the pregnancy. Therefore, Rh prophylaxis is not recommended in these women.

Finally, the author faces the ever-growing difficulty of provision of anti-D immunoglobulins. In the past, RhIg was produced by fractionation of high titre anti-D plasma obtained from Rh negative women immunised by a D+ pregnancy.

With the success of Rh prophylaxis, such women are disappearing and anti-Rh plasma is now, for the most part, obtained from deliberately immunised male Rh negative volunteers, exposed to D+ RBC.

The ethical question of exposing healthy people to human RBC has been raised. So, the supply of high titre anti-D plasma is an emerging problem.

Several experiments with anti-monoclonal antibodies (MoAb) have been carried out. Anti-D MoAb must be of human origin, because the mouse does not recognise human D as antigenic.

Efforts to produce such anti-D MoAbs have been continuing for more than 10 years, but, as yet, with only partial success.
Tolerance of granulocyte donors towards granulocyte colony-stimulating factor stimulation and of patients towards granulocyte transfusions: results of a multicentre study
Vox Sang 2003; 85: 322-5

This paper reports the experience of 13 Transfusion Services (12 in Germany and 1 in Austria) on granulocyte transfusions in order to: (i) record adverse effects in donors of granulocyte colony-stimulating factor (G-CSF) stimulation and granulocyte aphaeresis; (ii) follow-up stimulated donors, as suggested by ethical considerations, and; (iii) document the side-effects of G-CSF-mobilised granulocytes in recipients. The final aim of the study was to develop a common preparation protocol. The data collected regarded 507 granulocyte donations from 183 donors. G-CSF was administered at a dose of 5 µg/kg body weight, subcutaneously, 8-16 h before aphaeresis and no additional steroids were used. Hydroxymethyl starch (HES), of both low and high molecular weight (mw), was used as the sedimentation agent. The mean granulocyte yield was 4.3x10^10; high mw HES resulted in a significantly greater yield than did low mw HES. The more frequent side-effects of G-CSF use in donors were: bone pain, headache, fatigue, myalgia, dizziness, itching, arrhythmia, chills and skin rashes. The reactions were usually mild and severe reactions were rare. No fatal reactions were observed in donors. Mild, but not severe, adverse transfusion reactions were recorded in 16% of the recipients, but 24% of the patients developed leucocyte alloimmunisation. Eighty-five percent of volunteers stated that they would donate granulocytes again by aphaeresis. In conclusion, G-CSF stimulation and transfusion of G-CSF-mobilised granulocytes were well tolerated by donors and recipients, respectively.