

proportion of drugs including anesthetics still have no infant labeling. Sufficient research to demonstrate efficacy or safety has simply not been done. Almost 200 yr after Dr. Buchan made his observations, infants are still relatively disadvantaged.

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# The Aged Erythrocyte: Key Player in Cancer Progression, but Also in Infectious and Respiratory Complications of Blood Transfusion?

*To the Editor:*—We read with interest the study of Atzil *et al.*<sup>1</sup> on the deleterious effect of storage of erythrocytes on cancer progression in two tumor rat models. Using different transfusion products, the impact of erythrocytes, leukocytes, and leukocyte-derived soluble factors on host ability to clear circulating cancer cells and host survival rates was assessed. Blood transfusion was found to be an independent risk factor for cancer progression. Surprisingly, aged erythrocytes (9 days and older), rather than leukocytes or soluble factors, mediated the effects. The authors hypothesized that aged erythrocytes may preoccupy host-innate immune effector cells, leaving tumor cells unattended.

Besides cancer progression, other adverse effects of blood transfusion may also be influenced by storage time of erythrocytes. Transfusion of nonleucoreduced aged erythrocytes was found to be associated with an increase in postoperative infectious complications.<sup>2,3</sup> To date, the mechanism of this phenomenon is not clear. A role for leukocytes and/or soluble factors in the stored blood products has been suggested. The results of the present study may suggest another mechanism of blood transfusion-related infections. It could be hypothesized that patients transfused with aged erythrocytes may develop a disturbed host immune defense, either *via* suppression of the interaction of host immune cells with bacteria, or *via* suppression of cytokine secretion, which may result in a vulnerability to develop pneumonia or other infections. If erythrocytes indeed play a role, this may explain why studies comparing leucoreduced with nonleucoreduced red blood cell transfusions showed no effect on the incidence of infectious complications.<sup>4</sup>

Besides infectious complications, transfusion of outdated erythrocytes is associated with the onset of acute lung injury,<sup>2,5</sup> which may be mediated by biologically active lipids and/or cytokines that accumulate during storage of blood products.<sup>6,7</sup> In our laboratory, we performed preliminary experiments with transfusion of healthy rats with stored erythrocytes from the same animal species. Stored erythrocytes resulted in respiratory symptoms and worsening of the condition of the

animals, suggestive of acute lung injury. Did the authors of the article under discussion notice any respiratory failure in the animals transfused with stored erythrocytes, as compared with controls transfused with fresh erythrocytes or saline, before the inoculation of the cancer cells?

In conclusion, the authors have pointed to aged erythrocytes as mediators of cancer progression, raising questions about potential other effects of storage of erythrocytes on host immune response. We would like to call for further experimental and clinical studies assessing the role of aged erythrocytes in transfusion-related infectious complications and on transfusion-related acute lung injury.

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# Patient Blood Management and Transfusion

*To the Editor:*—We have read with great interest both the editorial by Spahn *et al.*<sup>1</sup> and the article by Atzil *et al.*<sup>2</sup> in the December issue of *ANESTHESIOLOGY*. We fully agree with the argumentation, but we want to go further into this debate.

The above letter was sent to the authors of the referenced article by Atzil *et al.* The authors did not feel that a response was required.—James C. Eisenach, M.D., Editor-in-Chief.

The very well designed animal study of Atzil *et al.*<sup>2</sup> is very interesting, expressing the independent role of blood transfusion in cancer progression and, more precisely, the role of aged erythrocytes more than leukocytes. The editorial of Spahn *et al.*<sup>1</sup> related to this article summarizes brilliantly the numerous disadvantages of homologous blood transfusion.

Red blood cell transfusion is a frequently performed activity in routine anesthetic practice. There are great differences between Euro-

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pean countries: The number of blood products given to patients in 1,000 inhabitants is 40 in France, 89 in Denmark, and 73 in Germany.<sup>3,4</sup> Nevertheless, we should like to pinpoint the findings of the study by Lienhart *et al.* published in this same journal.<sup>5</sup> This survey used the French death certificates national database to assess mortality related to anesthesia in France in 1999. The major finding of this survey was the reduction by a magnitude of 10 of the anesthesia-related mortality rate in France, as compared with a previous survey 20 yr ago. The analysis of the causes leading to the perioperative deaths was very enlightening. It was estimated from this survey that nearly 100 deaths occur perioperatively in France each year as a result of inadequate blood management. Surprisingly, more deaths partially related to delayed or absent blood transfusion were observed, and only a small proportion of complications occurred after an episode of transfusion. In many cases point-of-care monitoring of hemoglobin was not used to estimate blood loss, although it is likely that these inexpensive devices were already available in most hospitals at that time. Blood loss associated with delayed or absent blood transfusion caused not only intraoperative hypotension and hypovolemic shock, but also postoperative myocardial ischemia and infarction in patients with preexisting coronary artery disease. It seems impossible to know if the use of restrictive threshold for blood transfusion is responsible for this situation. After this nationwide study, the French Society of Anesthesia sent to its members key messages focusing on blood transfusion during the perioperative period: Quick diagnosis, threshold respect, and guideline implementation.<sup>6,7</sup>

On one hand, a body of evidence is growing on short-term and long-term complications of homologous transfusion, but on the other hand, facts suggest that patients may die of mistreated perioperative anemia.

We wanted to emphasize this point after reading these articles, but of course "our own blood is still the best thing to have in our veins."<sup>8</sup>

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**In Reply:**—We thank Dr. de Saint Maurice *et al.* for their comments regarding our editorial view<sup>1</sup> and share their concerns over perioperative deaths as a result of inadequate blood management. We could not agree more with their view that not measuring the hemoglobin concentration consecutively during major hemorrhage is substandard care, as is not treating severe hypovolemia or hypotension in such situations.

This is what patient blood management is all about; patient blood management is not "just say no to blood transfusions." Patient blood management is based on three pillars: Detecting and treating preoperative anemia, reducing the loss of red blood cells perioperatively, and optimizing the treatment of anemia. Red blood cell transfusions may be administered if all other options have been used and the patient starts showing signs of inadequate oxygenation. Of course, the quick cor-

rection of hypovolemia, hypotension, tachycardia, and arrhythmia is an integral part of patient blood management.

It is of utmost importance not to confound the momentary helpful effect of red blood cell transfusion on hypotension and hypovolemia with an outcome benefit. Red blood cell transfusions are indisputably associated with an increase in mortality,<sup>2,3</sup> major adverse cardiac and noncardiac outcome,<sup>4</sup> acute lung injury,<sup>5</sup> nosocomial infection,<sup>5</sup> tumor growth,<sup>6</sup> duration of hospitalization, and cost.<sup>7</sup>

Therefore, there is an urgent need for change, and the Governments of Western Australia and the Canton of Zurich, Switzerland, are to be congratulated again for taking the lead in sustainably implementing patient blood management and thereby improving patient outcome.

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Dr. Spahn has received honoraria for consulting or lecturing from the following companies: Abbott AG, Baar, Switzerland; Alliance Pharmaceutical Corporation, San Diego, California; Astra-Zeneca AG, Zug, Switzerland; Bayer (Schweiz) AG, Zürich, Switzerland; B. Braun Melsungen AG, Melsungen, Germany; CSL Behring GmbH, Hattersheim am Main, Germany; Fresenius SE, Bad Homburg, v.d.H., Germany; Galencia AG, Bern, Switzerland (including Vifor SA, Villars-sur-Glâne, Switzerland); GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany; Janssen-Cilag AG, Baar, Switzerland; Novo Nordisk A/S, Bagsværd, Denmark; Octapharma AG, Lachen, Switzerland; Organon AG, Pfäffikon/SZ, Switzerland; and Roche Pharma (Schweiz) AG, Reinach, Switzerland. Dr. Hofmann has received honoraria for consulting or lecturing from Amgen, Zug, Switzerland; Australian Red Cross Blood Service, Brisbane, Australia; CSL Behring, Marburg, Germany; Haemonetics, Boston, Massachusetts; Janssen-Cilag, Vienna, Austria; Novo Nordisk A/S, Bagsværd, Denmark; and Western Australian Department of Health, Perth, Australia. Dr. Isbister has done advisory consultancies for Novo Nordisk Pharmaceuticals Pty. Ltd., Baulkham Hills, New South Wales, Australia; CSL Limited, Victoria, Australia; Amgen Australia Pty. Ltd., Sydney, New South Wales, Australia; and Australian Red Cross Blood Service, Melbourne, Victoria, Australia.