The spleen: another mystery about its function

Andrej A. Romanovsky and Scott R. Petersen
Trauma Research, St. Joseph's Hospital and Medical Center, Phoenix, Arizona 85013

CONTINUING THE RECENT SERIES of articles on the pathogenesis of lipopolysaccharide (LPS)-induced fever (8, 9, 11–16, 21, 25, 26), a study by Feleder et al. (7) in this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* reports a novel finding: an exaggeration of the febrile response to LPS in guinea pigs after splenectomy. The authors attribute this exaggeration to the observed increase in LPS uptake by Kupffer cells. They conjecture that the spleen naturally limits the fever response by inhibiting the avidity of Kupffer cells to LPS. The results of this elegant study are both clinically important and highly unexpected.

The clinical importance of these results stems from two facts. First, the spleen often must be removed surgically in several forms of hypersplenism and in abdominal trauma (4). Second, it has long been recognized that splenectomy increases the incidence of infection with the pneumococcus, other encapsulated bacteria, and organisms that are usually not pathogenic in humans (20). Infection after splenectomy often results in fulminant sepsis; the increased sensitivity to infection lasts for many years (4). Consequently, the prophylaxis (vaccination) and early recognition of infection are of great importance. Even a low-grade fever in an asplenic patient is an indication to search aggressively for infection, start antibacterial therapy, or both. Clinicians need to know whether and how the febrile response is modified by removal of the spleen. This is the question asked by Feleder et al. (7).

The answer their study provided does not agree readily with the existing literature. In addition to participating in specific immunity via the production of antibodies, the spleen is involved in nonspecific host-defense responses (reviewed in Refs. 4, 7). Due to its high content of phagocytes (~15% of the body's population of "fixed" tissue macrophages) and direct connection to the bloodstream, the spleen has a role in the clearance of circulating microorganisms, particles, and some large molecules, such as LPS. Splenic macrophages take up ~3% of an intravenous dose of LPS (5). In endotoxemia, they become activated and produce inflammatory cytokines and lipid mediators (18, 24); some of these macrophages migrate to the liver, where they become Kupffer cells (see Ref. 18). The number of Kupffer cells in the liver changes little after splenectomy, with the exception of the acute (1–2 day) postoperative period, when it increases as a result of the

intra-abdominal intervention (3). However, the LPS-induced increase in the number of Kupffer cells, which normally occurs due to the migration of splenic macrophages, is strongly inhibited by splenectomy (3). Likewise, splenectomy inhibits the responsiveness of Kupffer cells (3) and other macrophages (4) to inflammatory stimuli. Clearance of LPS is either unchanged (1) or slightly decelerated (19) after this surgery. Accordingly, most responses to LPS (from production of pyrogenic cytokines and other inflammatory mediators to hemoconcentration and hypotension) are either unchanged or inhibited after splenectomy (2, 18, 19). The responses that are either unaffected or inhibited by splenectomy include the development of LPS tolerance (1, 10). Even the lethal activity of LPS is either unchanged (6) or decreased (1) by this surgery.

Hence, the literature data suggest that febrile responsiveness to LPS is likely to be unchanged or decreased, but not exaggerated, after splenectomy. This suggestion has been confirmed. In two experiments involving 82 rabbits, Greisman et al. (10) found that splenectomy does not affect the febrile response to systemic LPS. The same article reports the results of three patients who had undergone posttraumatic splenectomy 7–11 years earlier. No changes in their fever response to systemic LPS were found compared with six volunteers with intact spleens. In this context, the finding of Feleder et al. (7) of increased febrile responsiveness after splenectomy in guinea pigs is surprising.

In support of their finding, the authors cite clinical observations of frequent fevers in asplenic patients. Although such fevers are well recognized and agree with our own clinical practice, they can be explained by a variety of factors. For example, the association of splenectomy with a suppressed immune defense against infection (4) increases the frequency of infectious complications and, consequently, of infection-associated fevers. In the early postoperative period, an ischemic lesion to the pancreas can cause fevers (22). Although we have not seen signs of such a lesion in our patients, others consider it a common complication of splenectomy (22). The most frequent indication for the removal of spleen is lymphoproliferative conditions such as Hodgkin's disease. Patients with these conditions develop fevers regardless of whether they have undergone a splenectomy (17). Last but not least, an attenuated development of pyrogenic tolerance (10) can also account for increased febrile responsiveness, because a nontolerant host responds to the same pyrogenic stimulus with a higher fever. This latter mechanism might have contributed to the results of some, but not all, experiments conducted by Feleder et al. (7),

who administered LPS to guinea pigs twice, 7 and 30 days after surgery.

Although the exaggeration of LPS fever in guinea pigs after splenectomy contradicts the earlier work by Greisman et al. (10) and is supported by little existing literature, the contradiction may reflect some of the multiple differences in the structure and function of the spleen across species (4). The unexpected finding of Feleder et al. (7), even if it applies only to some species, represents a discovery of a novel function of the spleen: inhibition of the febrile response. The history of medicine reflects many contradictory ideas and even completely opposite views on the role of this mysterious organ. For centuries, ancient humoralists viewed the spleen as the organ of laughter, whereas Paracelsus (1493–1541) argued that the spleen is concerned not with laughter, but with weeping (see Ref. 23). Such contradictions stimulate new studies and, hence, help our knowledge progress.

REFERENCES

1. **Agarwal MK, Parant M, and Parant F.** Role of spleen in endotoxin poisoning and reticuloendothelial function. *Br J Exp Pathol* 53: 485–491, 1972.
2. **Andrew P, Deng Y, and Kaufman S.** Fluid extravasation from spleen reduces blood volume in endotoxemia. *Am J Physiol Regul Integr Comp Physiol* 278: R60–R65, 2000.
3. **Billiar TR, West MA, Hyland BJ, and Simmons RL.** Splenectomy alters Kupffer cell response to endotoxin. *Arch Surg* 123: 327–332, 1988.
4. **Bowdler AJ** (editor). *The Complete Spleen: Structure, Function, and Clinical Disorders* (2nd ed.) Totowa, NJ: Humana, 2002.
5. **Carey FJ, Braude AI, and Zalesky M.** Studies with radioactive endotoxin. III. The effect of tolerance on the distribution of radioactivity after intravenous injection of *Escherichia coli* endotoxin labeled with Cr^{51}. *J Clin Invest* 37: 441–457, 1958.
6. **Farrar WE Jr.** Endotoxin detoxification by guinea pig tissue homogenates and possible significance of this reaction in vivo. *Proc Soc Exp Biol Med* 118: 218–221, 1965.
7. **Feleder C, Li Z, Perlik V, Evans A, and Blatteis CM.** The spleen modulates the febrile response of guinea pigs to LPS. *Am J Physiol Regul Integr Comp Physiol* 284: R1466–R1476, 2003.
8. **Gatti S, Beck J, Fantuzzi G, Bartfai T, and Dinarello CA.** Effect of interleukin-18 on mouse core body temperature. *Am J Physiol Regul Integr Comp Physiol* 282: R702–R709, 2002.
9. **Gourine AV, Gourine VN, Tesfaigzi Y, Caluwaerts N, Van Leuven F, and Kluger MJ.** Role of α_2-macroglobulin in fever and cytokine responses induced by lipopolysaccharide in mice. *Am J Physiol Regul Integr Comp Physiol* 283: R218–R226, 2002.
10. **Greisman SE, Young EJ, Workman JB, Ollodart RM, and Hornick RB.** Mechanisms of endotoxin tolerance: the role of the spleen. *J Clin Invest* 56: 1597–1607, 1975.
11. **Imai-Matsumura K, Matsumura K, Terao A, and Watanabe Y.** Attenuated fever in pregnant rats is associated with blunted syntheses of brain cyclooxygenase-2 and PGE_2. *Am J Physiol Regul Integr Comp Physiol* 283: R1346–R1353, 2002.
12. **Ivanov AI, Pero RS, Scheck AC, and Romanovsky AA.** Prostaglandin E_2-synthesizing enzymes in fever: differential transcriptional regulation. *Am J Physiol Regul Integr Comp Physiol* 283: R1104–R1117, 2002.
13. **Ivanov AI and Romanovsky AA.** Fever responses of Zucker rats with and without *fatty* mutation of the leptin receptor. *Am J Physiol Regul Integr Comp Physiol* 282: R311–R316, 2002.
14. **Ivanov AI, Scheck AC, and Romanovsky AA.** Expression of genes controlling transport and catabolism of prostaglandin E_2 in lipopolysaccharide fever. *Am J Physiol Regul Integr Comp Physiol* 284: R698–R706, 2003.
15. **Johnson JD, O'Connor KA, Hansen MK, Watkins LR, and Maier SF.** Effects of prior stress on LPS-induced cytokine and sickness responses. *Am J Physiol Regul Integr Comp Physiol* 284: R422–R432, 2003.
16. **Ledeboer A, Binnekade R, Breve JJ, Bol JG, Tilders FJ, and Van Dam AM.** Site-specific modulation of LPS-induced fever and interleukin-1β expression in rats by interleukin-10. *Am J Physiol Regul Integr Comp Physiol* 282: R1762–R1772, 2002.
17. **Meekes I, van der Staak F, and van Oostrom C.** Results of splenectomy performed on a group of 91 children. *Eur J Pediatr Surg* 5: 19–22, 1995.
18. **Mizukami T, Yokoyama H, Okamura Y, Ohgo H, Fukuda M, Kamegaya Y, Kato S, and Ishii H.** Splenectomy attenuates superoxide anion release into the hepatic sinusoids after lipopolysaccharide challenge. *J Hepatol* 31: 235–241, 1999.
19. **Moeniralam HS, Bemelman WA, Endert E, Koopmans R, Sauerwein HP, and Romijn JA.** The decrease in nonsplenic interleukin-6 (IL-6) production after splenectomy indicates the existence of a positive feedback loop of IL-6 production during endotoxemia in dogs. *Infect Immun* 65: 2299–2305, 1997.
20. **Morris DH and Bullock FD.** The importance of the spleen in resistance to infection. *Ann Surg* 70: 513–521, 1919.
21. **Mouihate A, Clerget-Froidevaux MS, Nakamura K, Negishi M, Wallace JL, and Pittman QJ.** Suppression of fever at near term is associated with reduced COX-2 protein expression in rat hypothalamus. *Am J Physiol Regul Integr Comp Physiol* 283: R800–R805, 2002.
22. **Ottolenghi A, Chiamenti C, and Bettili G.** Complications of splenectomy: fever "without cause." *Chir Patol Sper* 19: 443–449, 1971.
23. **Pagel W.** *The Smiling Spleen.* Basel: Karger, 1984.
24. **Qu XW, Rozenfeld RA, Huang W, Crawford SE, Gonzalez-Crussi F, and Hsueh W.** Interaction of platelet-activating factor, spleen and atrial natriuretic peptide in plasma volume regulation during endotoxaemia in rats. *J Physiol* 512: 227–234, 1998.
25. **Scholz H.** Fever. *Am J Physiol Regul Integr Comp Physiol* 284: R913–R915, 2003.
26. **Steiner AA, Antunes-Rodrigues J, McCann SM, and Branco LG.** Antipyretic role of the NO-cGMP pathway in the anteroventral preoptic region of the rat brain. *Am J Physiol Regul Integr Comp Physiol* 282: R584–R593, 2002.