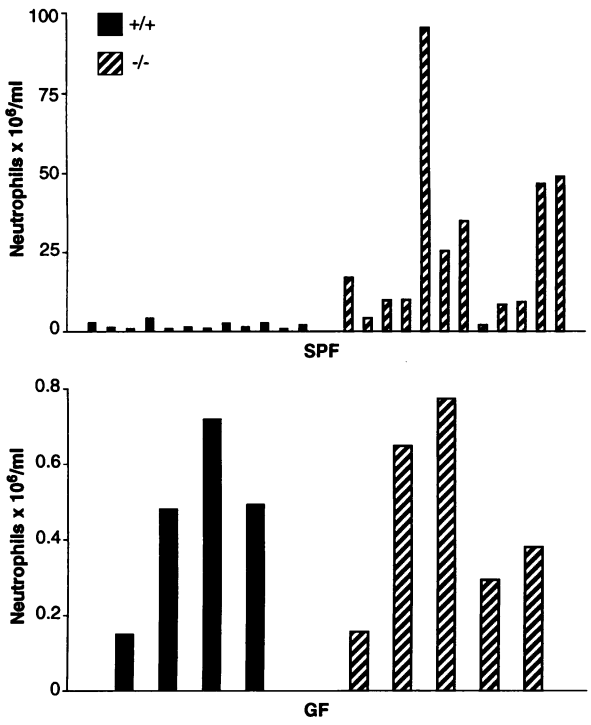

Fig. 1. Peripheral blood neutrophils from IL8Rh(+/+) and (−/−) mice derived under SPF and GF conditions. Blood was collected by retro-orbital venous puncture and was analyzed in a Serono-Baker Diagnostics System 9000 Diff Model Hematology Analyzer. Blood smears were stained with hematoxylin and eosin for differential cell counts performed microscopically. The total number of neutrophils was determined by multiplying the percentage of neutrophils by total white cell counts. Bars represent individual mice.

and periodontal disease are also observed with LAD type II where β_2-integrin expression is normal, but neutrophils have altered L-selectin expression and reduced efficiency to egress into tissues (6). Our experience with LAD cattle suggests that cytokine and chemoattractant production by tissues encountering normal flora or pathogens is not effectively down-regulated, as the eliciting agents are not removed by normal inflammatory processes. Not down-regulating inflammatory cytokine production (for example, granulocyte-macrophage colony-stimulatory factor) in infected tissues could be expected to result in the observed histopathological changes in the host, such as a progressive neutrophilia. In support of this hypothesis, the neutrophilia is much lower in LAD animals raised under germ-free conditions (3) than they are in animals raised conventionally.

The work of Cacalano *et al.* shows that mice lacking the mIL-8Rh, like LAD patients, suffer a marked impairment in neutrophil recruitment, and the hematological and histological changes in these mice are nearly identical to those associated with LAD. Furthermore, some of these mice suffer growth retardation and abnormal dentition (7).

Together, these data suggest that a severe impairment to neutrophil recruitment, whether through absence of adhesion molecules or chemoattractant receptors, reduces host defense to normal bacterial exposure and leads to compensatory changes in the immune system. This conclusion leads to the more significant implication that ligands of the mIL-8Rh must be essential for the surveillance function of neutrophils, at least in mice. Apparently, none of the other neutrophil chemoattractants—for example, leukotriene B4, complement fragments, or bacterial products—enable adequate neutrophil recruitment for normal host defense in the absence of the mIL-8Rh.

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REFERENCES

1. G. Cacalano *et al.*, *Science* **265**, 682 (1994).
2. Y. Ohashi, T. Yambe, S. Tsuchiya, H. Kikuchilt, T. Konno, *Hum. Mutat.* **2**, 458 (1993); J. E. Sligh Jr., M. Y. Hurwitz, C. Zhu, D. C. Anderson, A. L. Beaudet, *J. Biol. Chem.* **267**, 714 (1992); C. Lopez-Rodriquez *et al.*, *Eur. J. Immunol.* **23**, 2792 (1993); D. E. Shuster, M. E. Kehrli Jr., M. R. Ackermann, R. O. Gilbert, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 9225 (1992); U. Giger, L. A. Boxer, P. T. Simpson, B. R. Lucchesi, R. F. Todd III, *Blood* **69**, 1622 (1987); G. Trowald-Wigh, L. Hakansson, A. Johannisson, L. Norrgren, C. Hard af Segerstad, *Vet. Immunol. Immunopathol.* **32**, 261 (1992).
3. M. E. Kehrli *et al.*, in *Structure, Function, and Regulation of Molecules Involved in Leukocyte Adhesion*, P. E. Lipsky, R. Rothlein, T. K. Kishimoto, R. B. Faanes, C. W. Smith, Eds. (Springer-Verlag, New York, 1993), pp. 314–327.
4. R. O. Gilbert *et al.*, *J. Am. Vet. Med. Assoc.* **202**, 445 (1993).
5. H. K. Hawkins, S. L. Heffelfinger, D. C. Anderson, *Pediatr. Pathol.* **12**, 119 (1992); M. E. Kehrli *et al.*, *Am. J. Vet. Res.* **51**, 1826 (1990); W. A. Hagemoser, J. A. Roth, J. Lofstedt, J. A. Fagerland, *J. Am. Vet. Med. Assoc.* **183**, 1093 (1983); H. Nagahata, H. Noda, K. Takahashi, T. Kurosawa, M. Sonoda, *J. Vet. Med. Ser. A* **34**, 445 (1987); K. Takahashi *et al.*, *Jpn. J. Vet. Sci.* **49**, 733 (1987).
6. A. Etzioni *et al.*, *N. Eng. J. Med.* **327**, 1789 (1992).
7. M. Moore, personal communication.

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Response: Shuster *et al.* point out some similarities in the phenotype of leukocyte adhesion deficient (LAD) animals and the IL-8 receptor–deleted mice [IL-8Rh(−/−)] that we have generated. There are some differences in the two animal models. In the LAD animals, adhesion and extravasation are blocked, whereas in the IL-8Rh(−/−) mice, only the chemokine-stimulated migration is affected. The IL-8Rh(−/−) mice do not show the extreme susceptibility to infections that occurs in LAD animals. In both cases, the net result is a dramatic increase in neutrophil production. Thus, one can hypothesize that blocking neutrophil function causes a stimulation of granulopoiesis in an apparent attempt to replenish the "lost neutrophil activity." In the discussion portion of our report, we raised the possibility of compensatory mechanisms being responsible for the elevated neutrophils and plasmacytosis. In order to test directly whether an impaired pathogenic response is involved in the increased neutrophil production, we compared IL-8Rh(−/−) mice bred in our conventional specific pathogen–free (SPF) environment to those rederived in a germ-free (GF) condition. Our initial results indicate that in GF conditions, the blood level neutrophils are not elevated (Fig. 1). This result shows that environmental pathogens are required for the neutrophilia observed in the IL-8Rh(−/−) mice. This may indicate that the inability to properly survey tissues and eliminate external pathogens results in the release of cytokines that, in turn, stimulate neutrophil production.

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