anterior (apical) lobes of the lungs, driven by the forces on the forelegs. These two cylinders work in antiphase to each other, both at the stride frequency. The third cylinder represents the posterior (diaphragmatic) lobes of both lungs, driven by the oscillations of the abdominal viscera at twice the stride frequency. The whole complicated system is driven by the movements of trotting.

This complex pattern of ventilation may be an almost inevitable consequence of the dynamics of trotting. It may, however, bring positive benefits. If all the lobes of the lungs filled and emptied simultaneously in a simple tidal flow, the bronchi would be dead space: Air that was still in a bronchus at the end of inspiration would be breathed out again without entering the alveoli where gas exchange occurs. Asynchronous ventilation of the lobes must make air move between them, flushing out the connecting bronchi. The angles at which the bronchi meet (schematically indicated in the diagram) must tend to promote air movement between lobes. These angles have been thought to be important in ensuring one-way circulation of air through the lungs of birds (*11*).

The most pressing question now seems to be: What are the physiological consequences of these complex patterns of ventilation? The modulation of diaphragm oscillations presumably confers an advantage, for there is nothing inevitable about the contractions of the diaphragm. The asynchronous ventilation of the lobes of the lungs may be unavoidable in a trotting animal, but its consequences should also be explored. We need to know about the flow of air and the fluctuations of oxygen concentration in the major airways, phenomena that will not be easy to investigate.

References

1. D. M. Bramble and D. R. Carrier, *Science* **219**, 251 (1983).
2. D. M. Bramble and F. A. Jenkins Jr., *ibid.* **262**, 235 (1993).
3. I. S. Young, R. D. Warren, J. D. Altringham, *J. Exp. Biol.* **164**, 283 (1992).
4. R. V. Baudinette *et al.*, *ibid.* **129**, 251 (1987).
5. R. I. Griffiths, R. E. Shadwick, P. J. Berger, *Proc. R. Soc. London B* **249**, 199 (1992).
6. R. McN. Alexander, *J. Zool., London* **218**, 69 (1989).
7. I. S. Young *et al.*, *J. Exp. Biol.* **166**, 19 (1992).
8. J. D. Altringham and I. S. Young, *ibid.* **157**, 381 (1991).
9. C. J. Pennycuick, *ibid.* **63**, 775 (1975).
10. R. McN. Alexander, *Elastic Mechanisms in Animal Movement* (Cambridge University Press, Cambridge, 1988).
11. D. O. Kuethe, *J. Exp. Biol.* **136**, 1 (1988).

To Be^{2+} or Not To Be^{2+}: Immunogenetics and Occupational Exposure

Lee S. Newman

The lungs are engaged in a Sisyphean struggle with the environment. With every breath, we inhale unwanted particles and gases, most of which are innocuous but others of which injure the lungs through their effects on the immune system. Scavenger phagocytes in the lungs can engulf the foreign particles and present them as antigens to T lymphocytes, triggering an antigen-specific cellular immune response and lung inflammation. Nowhere is this confrontation between the environment and human immunologic defense as apparent as in occupational situations in which workers are exposed to immunotoxins. Only a subset of these exposed workers develop disease, likely because environmentally induced lung disease results from a complex interaction of the toxin with the genetic constitution of the individual. But proof of this hypothesis has been thwarted by an inability to identify the genetic features that help account for an individual's risk.

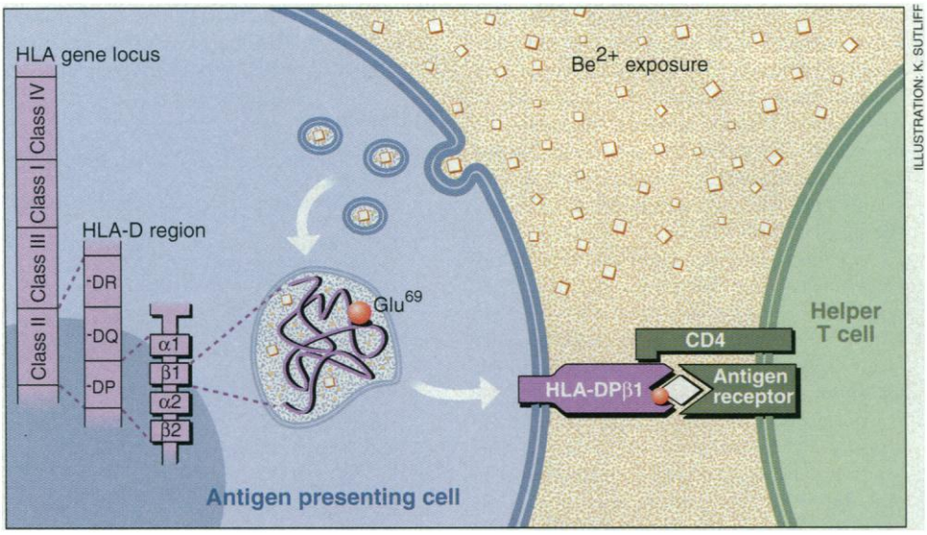
In this issue of *Science* (p. 242), Richeldi and co-workers break the stalemate by describing a genetic marker in workers who have an immunologic lung disease resulting from inhalation of the metal beryllium (*1*). They observed that 32 of 33 occupationally exposed workers with chronic beryllium disease (CBD) exhibit the amino acid glutamate in a potentially critical location (position 69) in a cell-surface glycoprotein that participates in antigen recognition. Of those beryllium-exposed workers who did not have CBD, only 30% have glutamate in this position. The authors present convincing evidence that this small difference in the genetic sequence in the major histocompatibility complex (MHC) allele HLA-DPβ1 identifies humans who, if exposed to beryllium, are at increased risk of developing CBD.

CBD is a 20th-century, man-made disorder that continues to occur in diverse industries—high-technology ceramics, electronics, dental alloy preparation, nuclear weapons, metal extraction, and aerospace (*2*). Exposed individuals become sensitized to beryllium and accumulate pathologic clusters of immune cells called granulomas around beryllium particles in the walls of alveoli (*3*). Blood lymphocytes from individuals sensitive to beryllium proliferate in vitro when cultured in the presence of beryllium salts. This reaction is the basis of the beryllium lymphocyte proliferation test (BeLT) that is now used to make a specific diagnosis of CBD (*4*) and for detecting early CBD in industrial screening programs (*5*).

What does the association of CBD with the MHC allele HLA-DPβ1-Glu^{69} tell us about the mechanism of the disease? We now know that if a person is exposed to beryllium, he or she has an increased risk of developing CBD, but we do not yet know how this occurs. Thus far the HLA-DPβ1-Glu^{69} marker is only guilty by association. But its location in a key region of an immunologically essential locus suggests that it may directly contribute to the unusually strong immunological response of these individuals to beryllium.

As shown in the figure, the human MHC locus (HLA), includes a class II D region that is subdivided into multiple subregions, at least three of which participate in the presentation of antigens to T lymphocytes—HLA-DR, -DQ, and -DP. Each D subregion contains genes encoding the α and β chains of heterodimeric, cell-surface glycoproteins that present antigens to CD4+ (helper) T lymphocytes. These HLA class II molecules are highly polymorphic so that they can embrace a wide variety of antigens in their antigen binding groove and present them to diverse T lymphocyte antigen receptors, triggering antigen recognition (*6*, *7*). Amino acids located at key positions along the α-helical portions of these HLA heterodimers dictate which peptide antigens can bind. Even single amino acid substitutions in these regions may alter the shape of the HLA-peptide binding pocket sufficiently to change its specificity. In patients with CBD, Richeldi and co-workers found a glutamate (instead of a positively charged lysine) at position 69, likely one of the hypervariable sites of the HLA-DP allele (*7*). This glutamate could allow the presentation of beryllium, likely bound to an intracellular peptide, and the generation of an antigenic response. Perhaps the other common allele—containing the lysine—cannot accommodate this hypothetical complex. Thus, the HLA-DPβ1-Glu^{69} molecule may not only be a genetic marker for CBD, but may par-

The author is in the Occupational and Environmental Medicine Division and Pulmonary Division, National Jewish Center for Immunology and Respiratory Medicine and in the Departments of Medicine and Preventive Medicine–Biometrics, University of Colorado School of Medicine, 1400 Jackson Street, Denver, CO 80206.



Hypothetical interaction of Be^{2+} with an antigen presenting cell containing HLA-DPβ1-Glu^{69}.

ticipate in the pathological response to beryllium in these individuals.

It is appealing to speculate that HLA-DPβ1-Glu^{69} plays a direct role in triggering antigenic recognition of beryllium, as proposed in the figure, but this may be too simplistic. Development of CBD could also depend upon other genes working in concert with this marker. But HLA-DP alleles are not often linked to other D region sequences and HLA-DR and -DQ are the HLA class II molecules more conventionally associated with antigen presentation and more commonly associated with risk of inflammatory diseases (8). In addition, Richeldi and colleagues probed for but found no linkage between the HLA-DPβ1-Glu^{69} marker and the gene for the proinflammatory cytokine tumor necrosis factor (*1*, 9), which is encoded telomeric to the HLA-D loci on chromosome 6.

What is the relation between HLA-DPβ1-Glu^{69} and beryllium exposure? All of the CBD patients and beryllium workers in Richeldi's study were exposed to beryllium, yet one had disease but no genetic marker and many others inherited the marker but had no disease. These findings suggest that Glu^{69} only tells part of the story. Our best chance to fill in the blanks will come by not only looking for other associated genes, but by studying exposure as something more than a dichotomous variable. Does the chemical structure of the beryllium moiety itself dictate immunogenicity, as some suggest (*10*), or is the exposure risk related to particle size, frequency of exposure, and magnitude of the dose? And in particular, what is it about this lightweight metal (atomic weight, 9.01) that makes it an antigenic heavyweight? It seems unlikely that beryllium itself is the antigen. We assume that beryllium binds to exogenous or endogenous peptides that are viewed by the T lymphocyte as the foreign antigen. But we do not know what the beryllium antigen looks like, how it may be processed by the antigen presenting cell, or how it may appear to the T lymphocyte antigen receptor. With the discovery of HLA-DPβ1-Glu^{69} as a marker for CBD, there are now at least two risk factors for CBD—exposure to the metal and inheritance of the genetic marker—but we have a lot to learn about their interaction.

Now that we have a genetic marker for CBD, will it help us prevent disease? Although CBD prevalence among all beryllium-exposed workers has remained at 2 to 5%, in the ceramics and nuclear weapons industries, certain jobs and work tasks are associated with disease rates as high as 15.8% (5). So by further improving industrial hygiene and reducing exposure, many cases of CBD can be avoided. In addition to primary prevention, secondary prevention can be accomplished by screening large numbers of former and current beryllium workers with the blood BeLT, successfully identifying individuals who are at early stages of CBD often years before symptoms develop. By adding a genetic marker to workplace screening, employers could potentially reduce beryllium exposures for the high-risk workers and more effectively target them for intensified medical monitoring and early disease detection. Employers could also plan to deny or discourage employment of workers with genetic risk of CBD. But it is premature to advocate such an approach to prevention. Almost all people with CBD have a genetic marker, but most of the people with the marker do not have the disease. Only a population-based study can answer the questions that are necessary for the design of a genetic screening test: What proportion of employees with the marker develop the disease (positive predictive value) and what proportion of workers without the marker do not have the disease (negative predictive value)? The disease ankylosing spondylitis offers a relevant analogy: Although nearly 90% of people with that disorder are positive for the genetic marker HLA-B27, only 2% of the HLA-B27–positive individuals in the general population develop the disease (*11*). Even if most CBD patients are HLA-DPβ1-Glu^{69}–positive, it may not be helpful to identify up to 30% of the potential workforce as at risk if the prevalence of CBD among exposed workers is only 5%. Rather, we must study the immunogenetic mechanisms and nature of the antigen and merge genetic and epidemiologic data from large workforces. Continued efforts must be made to reduce workplace exposure for all workers and improve CBD detection, at the same time as we consider the ethical and societal issues raised by genetic screening in the workplace (*12*).

References and Notes

1. L. Richeldi, R. Sorrention, C. Saltini, *Science* **262**, 242 (1993).
2. L. S. Newman, in *Hazardous Materials Toxicology*, J. B. Sullivan Jr. and G. R. Krieger, Eds. (Williams & Wilkins, Baltimore, 1992), pp. 882–890; C. S. Rose and L. S. Newman, in *Interstitial Lung Disease*, M. I. Schwarz and T. E. King Jr., Eds. (Mosby–Year Book, St. Louis, ed. 2, 1993), pp. 321–253.
3. D. G. Frieman and H. L. Hardy, *Hum. Pathol.* **1**, 25 (1970); W. Jones Williams and D. Kelland, *J. Clin. Pathol.* **39**, 900 (1986).
4. P. E. Epstein, J. H. Dauber, M. D. Rossman, R. P. Daniele, *Ann. Intern. Med.* **97**, 213 (1982); M. D. Rossman *et al.*, *ibid.* **108**, 687 (1988); L. S. Newman, K. Kreiss, T. E. King Jr., S. Seay, P. A. Campbell, *Am. Rev. Respir. Dis.* **139**, 1479 (1989).
5. K. Kreiss, L. S. Newman, M. M. Mroz, P. A. Campbell, *J. Occup. Med.* **31**, 603 (1989); M. M. Mroz, K. Kreiss, D. C. Lezotte, P. A. Campbell, L. S. Newman, *J. Allergy Clin. Immunol.* **88**, 54 (1991); K. Kreiss, S. Wasserman, M. M. Mroz, L. S. Newman, *J. Occup. Med.* **35**, 267 (1993); K. Kreiss, M. M. Mroz, B. Zhen, J. Martyny, L. S. Newman, *Am. Rev. Respir. Dis.*, in press.
6. R. D. Campbell and J. Trowsdale, *Immunol. Today* **14**, 349 (1993); J. G. Bodmer *et al.*, *Immunogenetics* **36**, 135 (1992); D. Kappes and J. L. A. Strominger, *Rev. Biochem.* **57**, 991 (1988).
7. J. H. Brown, *Nature* **364**, 33 (1993); P. J. Bjorkman, *ibid.* **329**, 512 (1987).
8. J. L. Strominger, *J. Clin. Invest.* **77**, 1411 (1986); T. H. M. Ottenhoff, B. G. Elferink, J. Hermans, R. R. DeVries, *Hum. Immunol.* **13**, 1015 (1985); J. A. Todd, *et al.*, *Science* **240**, 1003 (1988).
9. T. Bost, L. Newman, D. Riches, *Chest (Suppl.)* **103**, 138S (1993).
10. A. L. Reeves, in *Immunotoxicology*, G. G. Gibson, R. Hubbard, D. V. Parke, Eds. (Academic Press, London, 1983), pp. 261–282; M. Hoover, Ed., *Overview and Publications of the Inhalation Toxicology Research Institute Beryllium Research Program* (Inhalation Toxicology Research Institute, Albuquerque, NM, 1990).
11. R. Benjamin and P. Parham, *Immunol. Today* **11**, 137 (1990).
12. U.S. Congress, Office of Technology Assessment, *Genetic Monitoring and Screening in the Workplace* (Publication OTA-BA-455, Government Printing Office, Washington, DC, 1990); Council on Ethical and Judicial Affairs, *J. Am. Med. Assoc.* **266**, 1827 (1991).

13. I thank S. Tinkle, T. Potter, B. Kotzin and M. Mroz for helpful discussions. Supported by the National Institutes of Health (HL273353, ES06538, ES00173).