



**FIGURE 87e-3** **A.** Theoretical human disease network illustrating the relationships among genetic and environmental determinants of the pathophenotypes. Key: D, secondary disease genome or proteome; E, environmental determinants; G, primary disease genome or proteome; I, intermediate phenotype; PS, pathophysiologic states leading to P, pathophenotype. **B.** Example of this theoretical construct applied to sickle cell disease. Key: Red, primary molecular abnormality; gray, disease-modifying genes; yellow, intermediate phenotypes; green, environmental determinants; blue, pathophenotypes. (Reproduced with permission from J Loscalzo et al: *Molec Syst Biol* 3:124, 2007.)