Feeling safe is a basic human need. But for much of human existence we have lived in a relatively unsafe world. This has lead to the evolutionary selection of a system primed for threat and thus the threat or stress response is the default response. However, when safety is present a cascade of psychological, emotional, behavioral, and physiological responses are set in motion than turns off the default stress response. The present talk will provide an overview of the default stress response and its implications for health. Importantly, I will highlight the critical role of the perception of safety and propose that it is perceptions of safety, and not perceptions of threat, that drive the system. This is a radical departure from traditional stress models with far ranging theoretical as well as practical consequences.