The etiology of pelvic pain in endometriosis is not well understood and new therapeutic approaches, which are desperately needed, would benefit from a better understanding of the underlying mechanisms. Our laboratory has actively pursued the hypothesis that cells of the innate immune system, and their inflammatory products, are key to this clinical puzzle. In this presentation the concept of "neuroangiogenesis" will be introduced, an hypothesis that links the functional innervation and vascularization of endometriosis lesions. Microarray analyses were used to characterize neurotrophins (NTs) in eutopic endometrium of endometriosis cases and matched controls, and immunohistochemistry (IHC) experiments in 8 micron paraffin sections were used to co-localize specific NTs and nerve fibers in situ. As predicted by the severe pain symptoms associated with deep invasive endometriosis, these lesions demonstrated high density nerves decorated with PGP9.5, but were not noted in the striated muscle surrounding the lesions. Brain-derived neurotrophic factor (BDNF) was highly concentrated within glands and stroma of the lesions, in close proximity to small nerves and capillaries. In some cases, BDNF was observed to be localized in the lesion microvasculature itself. Using isolated stromal cells derived from subjects with endometriosis, we observed that estradiol and IL-1beta stimulate BDNF expression in vitro. The findings support the theory that endocrine and paracrine factors, which predominate in the setting of endometriosis, can promote pain via inflammatory signal transduction pathways. Funded by the NIH, Eunice Kennedy Shriver NICHD U01 HD66439.