

# V I S I O N

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## Vulvar Vestibulitis as a Neuro-inflammatory Condition: a proposed model and potential treatment options

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**Editorial Comment:** Dr. Foster's research and conclusion are so exciting, we wanted to print it in its entirety. This is the second installment of this article. Part 1 can be seen on our web site at [www.pevpain.org](http://www.pevpain.org). Please see resource section.

### Part 2

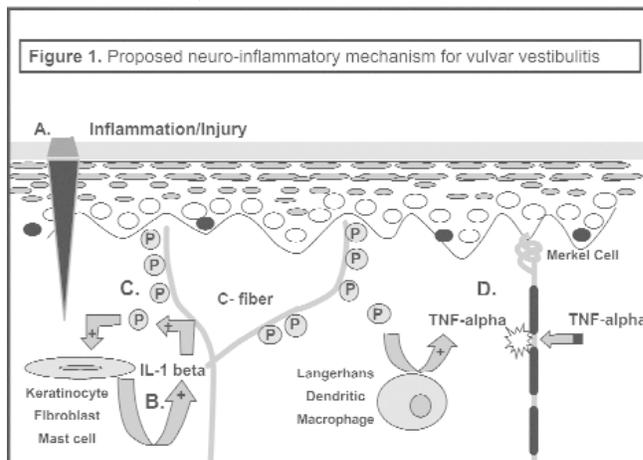
#### Genetics of vulvar vestibulitis syndrome

Genes coding for IL-1 $\alpha$ , IL-1 $\beta$ , and IL-1 Receptor Antagonist (IL-1 RA) are located in close proximity to each other on chromosome 2q13-21. The IL-1 RA gene is polymorphic in humans.<sup>16</sup> Acting as a dummy ligand to the IL-1 receptor, the IL-1 RA gene product competitively blocks receptor activation by IL-1 $\beta$ . The presence of allele 2 of the IL-1 RA gene (IL-1RA\*2) has been associated with a number of disorders including periodontitis, Grave's disease, multiple sclerosis, Sjogren's syndrome, and ulcerative colitis.<sup>17,18</sup> Paradoxically, the IL-1RA\*2 polymorphism is associated with increased production of IL-1 $\beta$ .<sup>19</sup> In VVS cases, 53% were homozygous for IL-1RA\*2 compared to 8.5% of a sample of asymptomatic women.<sup>20</sup> If one compares the percent IL-1RA\*2 homozygosity found in conditions mentioned above, VVS carries the highest proportion of cases. This unique genotype may help to explain the elevated regional IL-1  $\beta$  concentration found in VVS but the relationship between IL-1RA\*2 and increased pro-inflammatory cytokines in VVS remains to be confirmed.

#### Model of Neuro-inflammation for VVS

Based upon the brief overview above, a model of peripheral neuro-inflammation can be suggested for VVS and illustrated in Figure 1. VVS may originate from (A.) a myriad of inflammatory insults on the female genital tract. In the susceptible individual (possibly genetically predisposed), a highly localized region of the lower genital tract develops a syndrome of chronic burning pain, hyperalgesia, and allodynia. Pro-inflammatory cytokines (B.) such as IL-1 $\beta$  and TNF- $\alpha$ , accumulate above normal levels in the hymeneal carunculae or vulva in proximity to Hart's line. Elevated levels of pro-inflammatory cytokines (C.) interact with neurokinines, such as substance P (SP) stimulating release from peripheral

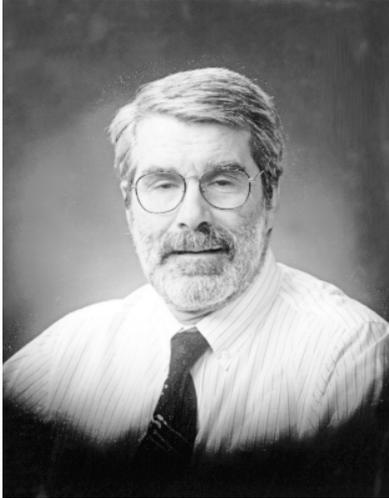
nerve, erythema, edema, and pain. A significant part of the chronic pain state may result from the action of cytokines on peripheral nerve (D) as well as the development of "central sensitization", described below.



#### Another dimension to chronic pain: "central sensitization"

Animal models demonstrate that persistent nociceptive activity enhances responsiveness at the level of the dorsal horn, which is known as "central sensitization". Dorsal horn mediators of "central sensitization" include N-methyl-D-aspartate (NMDA) receptors, c-fos, nitric oxide synthetase (NOS), glutamate, dynorphin, and protein kinase C (PKC).<sup>21</sup> Two phenomena of "central sensitization" include an increased sensitivity of mechanoreceptors to painful stimuli (increased mechanical hyperalgesia), and a widened cutaneous area with lowered threshold for heat, touch, or cold stimuli known as receptive field expansion.<sup>22-28</sup> Although the development of mechanical hyperalgesia is not completely understood, the phenomenon of central sensitization may result from prolonged and intensified nociceptive C-fiber

## The President's Perspective



John C. Slocumb, M.D., FACOG • President

While the IPPS has actively recruited members from specialties that focus on pelvic symptoms and has presented conferences in association with national meetings of those specialties, I would like to address a concern that is illustrated in a recent article published in *The American Journal of Obstetrics and Gynecology*, September 2001, Volume 185, page 545. In this paper by B. Harlow, L. Wise and E. Stewart from Harvard Medical School a random survey of 303 women between the ages of 20 to 59 years concerning their chronic vulvar burning and itching, and the presence of sharp, knife-like pain or contact pain was obtained. They reported that 16.7% of women under the age of 30 had sharp contact pain, less so in older age groups, that 40% of those with symptoms did not seek medical care and of those that did, 40% remain undiagnosed. 30% sought care from three or more doctors. Many women either suffer in silence or where they seek care are misdiagnosed or are offered ineffective treatment.

I would like to challenge all of our members who are experienced with vulvar vestibulitis syndrome to contact local primary care organizations in order to inform them of advances in understanding and treatment of this very common and debilitating malady. Every year I have presented at our state family practice meeting and am astounded by how few people have heard of VVS. We should start with family medicine and internal medicine residencies as new graduates can influence their partners in practice. Programs for nurse practitioners and physical therapy also will affect early contact with patients seeking care.

Lastly, women need validation that they have a recognized medical condition such that articles in lay women's magazines, handouts at health and wellness conferences, and health care organizations such as Planned Parenthood and family health clinics would be of value.

A handwritten signature in blue ink that reads "John C. Slocumb, M.D.".

John C. Slocumb, M.D.

President, IPPS

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activity, which sensitizes wide dynamic range (WDR) neurons to low threshold A- $\beta$  fiber mechanical activity. Receptive field expansion may result from "crosstalk" of interneurons, which spreads neural activity to adjacent spinal segments serving a widened cutaneous receptive field. Many purported mediators of "central sensitization", such as the NMDA receptor antagonists, have become therapeutic targets in pain research, as discussed below. The phenomenon of central sensitization likely occurs in vulvar vestibulitis and may explain concurrent conditions such as urethral instability but research on VVS and "central sensitization" is limited.<sup>29</sup>

### **Future directions for therapy: Local cytokine antagonism**

Bearing in mind a potential role for pro-inflammatory cytokines in the development of VVS, therapeutic antagonism of IL-1 $\beta$  and TNF- $\alpha$  may prove useful. Systemic administration of the anti-inflammatory cytokine, interleukin 10 (IL-10), has been found to be well tolerated in humans, to suppress pro-inflammatory cytokines, IL-1 $\beta$  and TNF- $\alpha$ , and after intralesional injection, provide prolonged symptomatic improvement of psoriasis. Huhn et al<sup>30</sup> studied healthy volunteers undergoing a single intravenous bolus and found that IL-1  $\beta$  production was markedly suppressed (17 to 49%) at 2 hours and suppression extended to 48 hours at higher

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doses (25 to 100 mg/kg). Inhibition of TNF- $\alpha$  was also observed following IL-10 administration for 12 hours or greater and TNF- $\alpha$  synthesis was suppressed at the highest-dose (100 mg/kg) for greater than 24 hours. In a second study, Huhn et al.<sup>31</sup> found pronounced suppression of lipopolysaccharide-induced TNF- $\alpha$  for greater than 12 hours and IL-1  $\beta$  for greater than 24 hours. Asadullah et al.<sup>32</sup> found significantly lower levels of IL-10 mRNA in psoriatic skin in contrast to atopic dermatitis and mycosis fungoides. Treatment of psoriatic patients with IL-10 produced no adverse effects and all patients reported loss of skin itching. Loss of itching and a significant reduction in TNF- $\alpha$  extended beyond 4 days after cessation of IL-10 therapy. Another option for pro-inflammatory cytokine antagonism involves anti-TNF- $\alpha$  therapy. The injection of neutralizing antibodies to TNF- $\alpha$  (specifically to TNF receptor-1) produces a reduction of mechanical hyperalgesia after chronic constriction nerve injury in animal studies.<sup>8</sup> Several anti-TNF- $\alpha$  products are available for treatment of chronic inflammatory conditions such as rheumatoid arthritis and Crohn's disease and TNF $\alpha$  antagonism be useful for VVS.

### Future directions for therapy: Modulation of central sensitization

With respect to the varied mediators of "central sensitization" mentioned above, the NMDA receptor holds a pivotal role in chronic pain development and NMDA receptor antagonism has been a focus of drug development. The best-known NMDA receptor antagonist in clinical use is ketamine, a "dissociative" anesthetic/analgesic. Ketamine has been used clinically for neuro-inflammation in the treatment of post-herpetic and post-traumatic neuralgia.<sup>33-35</sup> Ketamine, along with the shorter-acting NMDA receptor antagonist, phencyclidine ("angel dust"), are known for hallucinatory side effects and abuse potential. Selective NMDA NR2B antagonists, such as ifenprodil have been developed to exploit the benefits of anti-nociception combined with a reduced side-effect profile. Earlier clinical reports focused on the utility of ifenprodil on elderly individuals with arterial occlusive disease and demonstrated enhanced walking distance and improved quality of life.<sup>36,37</sup> In the rat model ifenprodil induces effective anti-nociception without disruption of motor behavior suggesting better specificity of chronic pain relief may be possible though this or related agents.<sup>38</sup> Effective use of drugs that modulate central sensitization in VVS remains to be explored.

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