Fundamental Pain Mechanisms in Endometriosis

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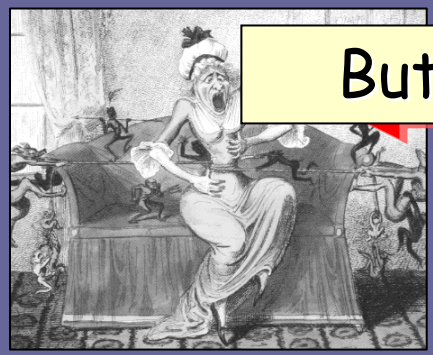
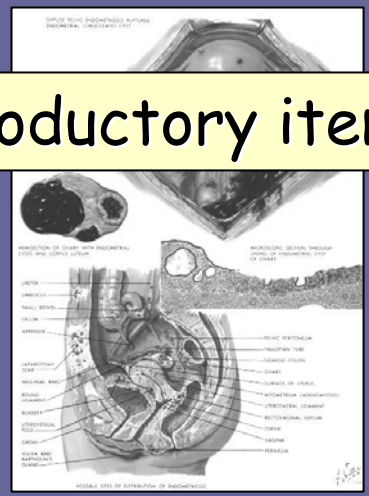
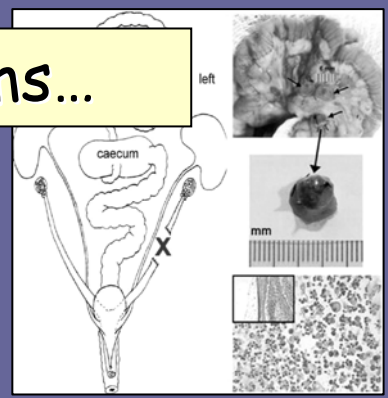


But first, five introductory items…





#1

CURRENT LAB MEMBERS

Front row: Guohua Zhang, MD, PhD; KJB, PhD; Natalia Dmitrieva, PhD; ZackBrown

Back row: Sean Kaplan; Hiroshi Nagabukuro, PhD; Briane Accius; Kristina McGinty; Stacy McAllister; Ken Winnard

Not shown: David Resuehr, PhD; Chris Martin

OTHER BASIC & CLINICAL RESEARCH COLLABORATORS


Maria Adele Giamberardino, MD


Charles Hubscher, PhD


Heather Bradshaw, PhD


Yan Liu, PhD


Andrea Rapkin, MD


Ray Papka, PhD


Ken Mackie, MD

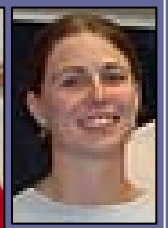

Patrick Wall, MD


Yuko Sato, Ph.D.


Ann Robbins-Sakai, PhD

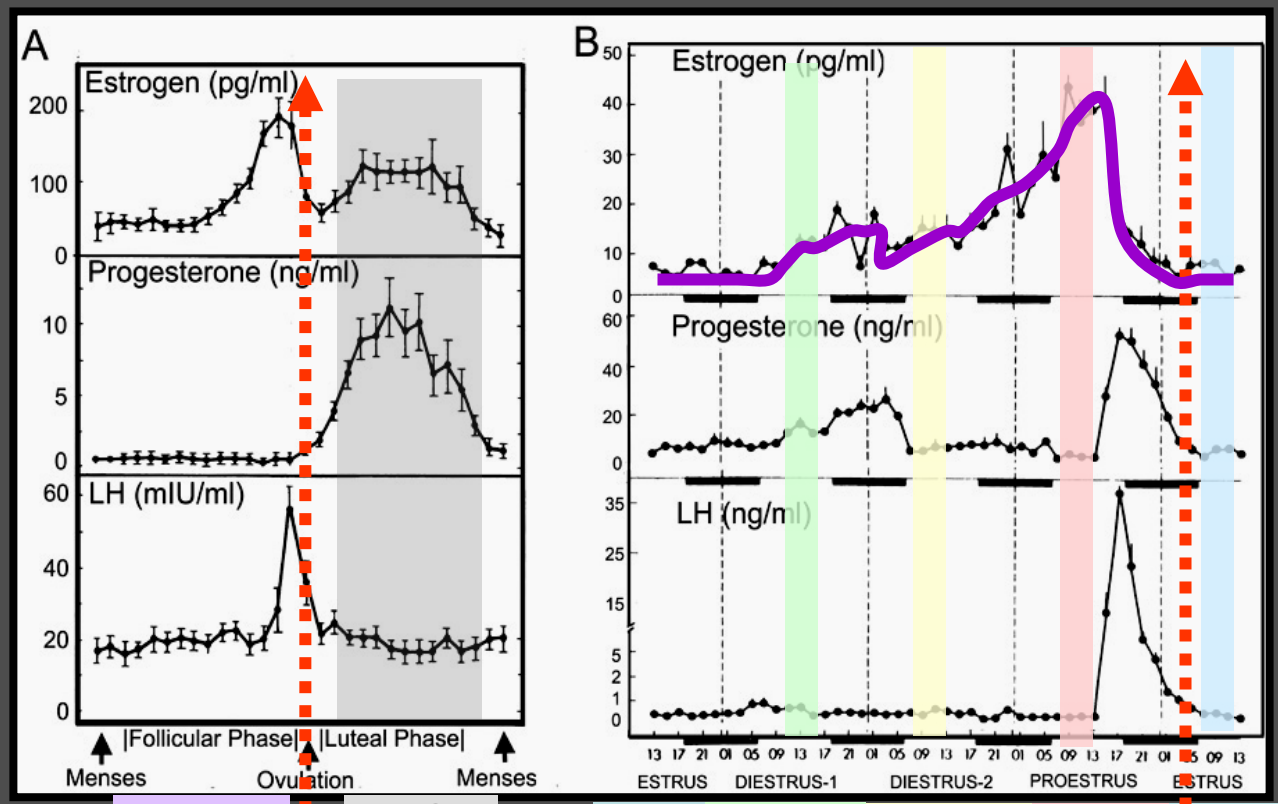

Elizabeth Wood


Trevor Morrison. MD


Angie Cason, PhD

2

THE OVARIAN CYCLE



FOLLI-CULAR

LUTEAL

ovulation

ES-TRUS

DI-ESTRUS

MET-ESTRUS

PROES-TRUS

ES-TRUS

ovulation

NIH Consensus Meeting: The Art and Science of Endometriosis: Standardizing the Measurement of Pain and Diagnostic Criteria (20 Oct 06 New Orleans, LA)

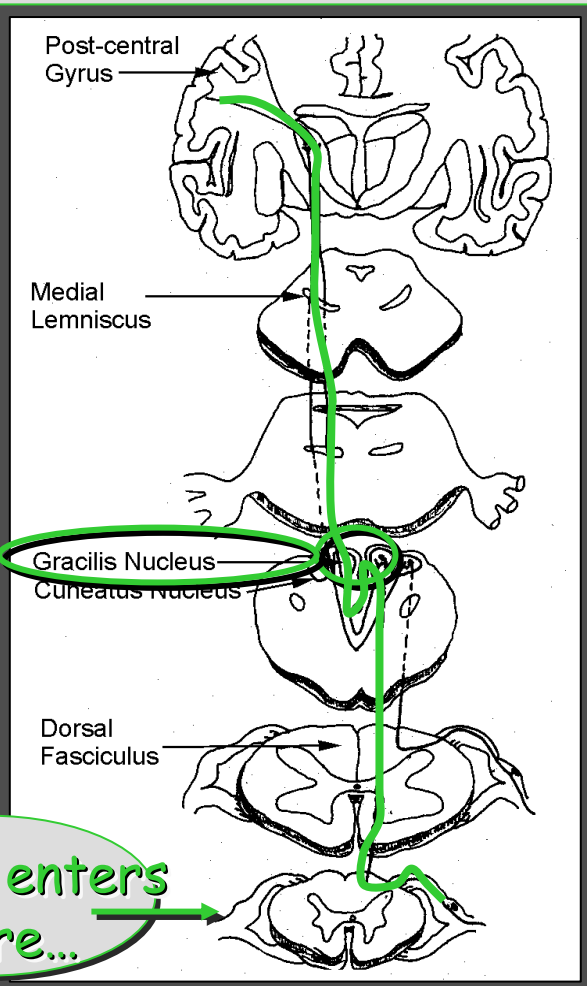
#3, #4, and #5

THREE QUESTIONS

3

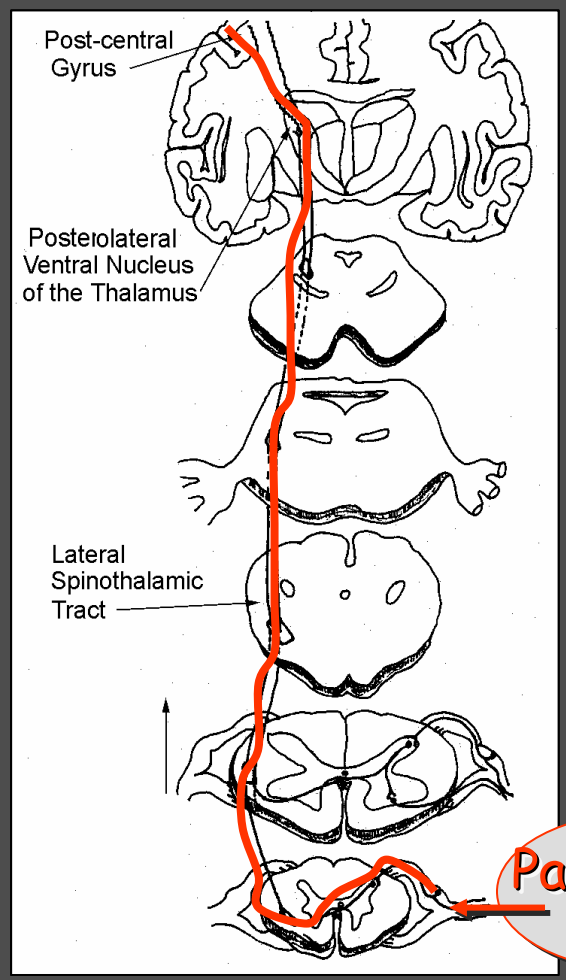
MECHANISMS OF TOUCH & PAIN (traditional view)

TOUCH PATHWAY



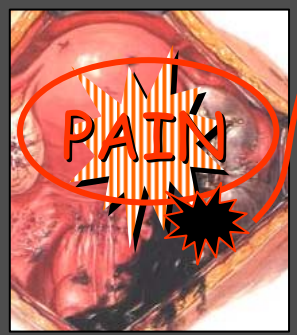
Touch enters here...

PAIN PATHWAY



Pain enters here...

3 MODERN TRADITIONAL VIEW



Gray's Anatomy

Does this 400 year-old view make sense?

"Pain Matrix"

Fig. 6.2 Schematic representation of ascending pathways, subcortical structures and cerebral cortical structures involved in processing pain. ACC, anterior cingulate cortex; Amyg, amygdala; BG, basal ganglia; HT, hypothalamus; M1, primary motor cortex; PAG, periaqueductal grey; PB, parabrachial nucleus of the dorsolateral pons; PCC, posterior cingulate cortex; PF, prefrontal cortex; PPC, posterior parietal complex; SI and SII, first and second somatosensory cortical areas; SMA, supplementary motor area. (Adapted from Price 2000.)

From: Bushnell MC and Apkarian AV. Representation of pain in the brain. In: Wall & Melzack's Textbook of Pain, McMahon S, Koltzenberg M (eds), 5th ed., 2006.

Hsieh, Belfrage, Stone-Elander, Hansson & Ingvar. Pain 63:1995:225-326.

4 A growing and hopeful list of pain treatments

DRUGS		SOMATIC		SITUATIONAL	
Primary analgesics	**Adjuvants**	**Simple**	**Invasive**	**Clinician**	**Interactive**
NSAIDS	antihistamines	heat/cold	surgery	education	hypnosis
acetaminophen	laxatives	exercise	radiation Rx	attitude	biofeedback
opioids	neuroleptics	massage	dorsal col. stim.	clinic arrangemt	support groups
Other analgesics	phenothiazines	vibration	nerve blocks	**Self**	advocacy groups
β adrenerg.antag.	**Routes/Timing**	relaxation	neurectomy	education	networking
antidepressants	i.v., i.m., i.p.	**Minimally invas.**	local gang. blks	meditation,	self-help groups
anticonvulsants antiarrhythmics	buccal, sublingual	Physical therapy	sympathectomy	art, poetry	**Structured settings**
Ca++ chan. block.	intranasal, oral	traction	rhizotomy	music, theatre	group therapy
cannabinoids?	vaginal, rectal	manipulation	DREZ lesions	virtual reality	family counseling
corticosteroids	topical	ultrasound	punctate myel.	sports, humor	job counseling
Cox 2 inhibitors	transdermal	TENS	commis. myel.	diet, gardening	cog / behav. Rx
$GABA_B$ antag	epidural	acupuncture	cordotomy	aroma therapy	psychotherapy
hormonal Rx	intrathecal	local anes.	brain stim.	religion	multidisipl. clinic
serotonin antag..	slow release		brain lesions	pets	hospice

Why then are so many women with endometriosis still in pain?

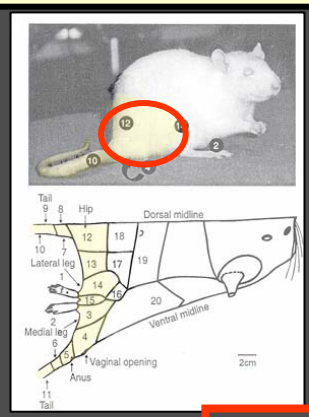
Is there a better way to use this table?

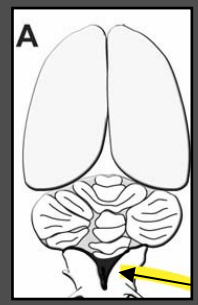
Could a different conceptualization of pain mechanisms help?

Could basic science help?

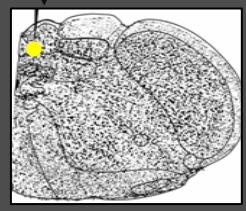
…for example…

#5a This neuron in the GRACILE NUCLEUS responds to stimulation of skin, bladder, cervix, uterus, colon and vagina in a complex way (i.e., with combination of inhibition and excitation).



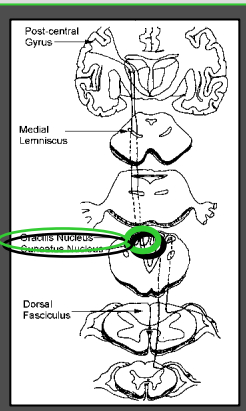


Gracile n.

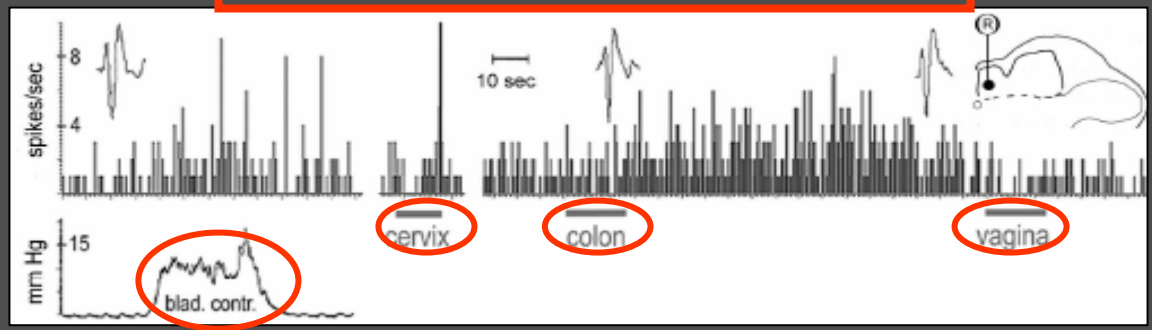


skin: +
bladder: +
cervix: -/+
uterus: ∅
colon: + [delay]
vagina: -

TOUCH PATHWAY



RESPONSES OF ONE NEURON



- Berkley KJ, Hubscher CH. Nature Med 1995;1:766-73.
- Bradshaw HB & Berkley KJ J Neurosci 2000;20:7722-7.
- Peng W, Dmitrieva N, Berkley KJ. 2002

Charles Hubscher

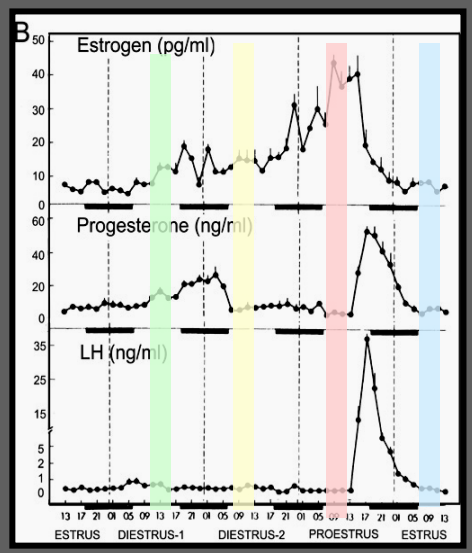
Weimin Peng
Natalia Dmitrieva

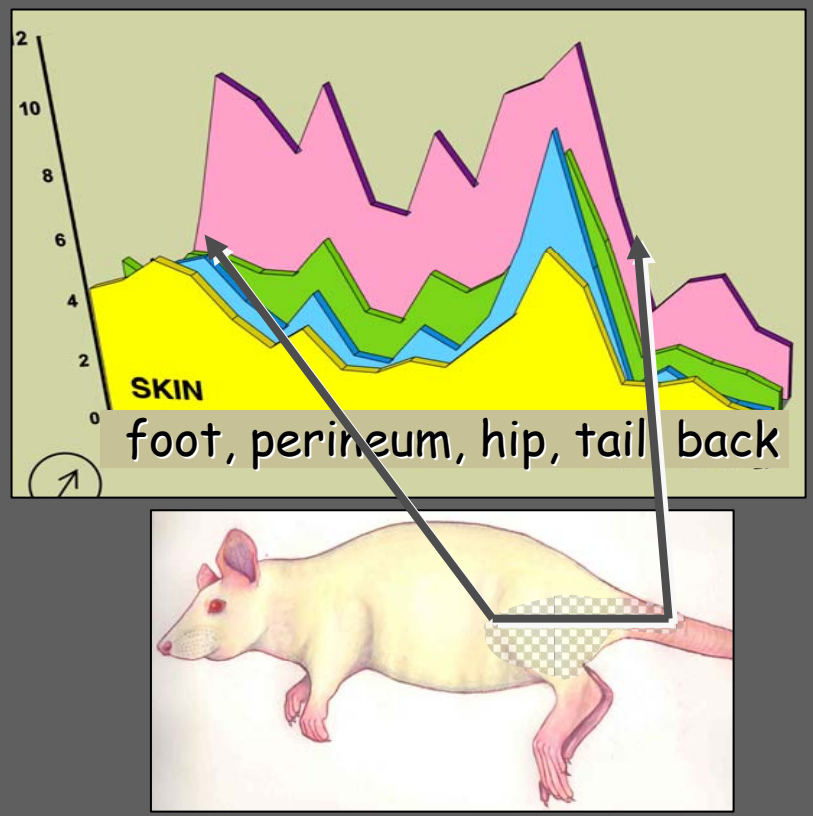
Heather Bradshaw

#5a PLASTICITY… Furthermore the responses can change dramatically during the ovarian cycle (a natural, non-pathophysiological process).

Response magnitudes to gentle brushing of the skin of perineum, hip, and tail, but not foot and back were greater in proestrus (■) than other stages.

Heather Bradshaw, PhD





Bradshaw HB, Berkley KJ. J Neurosci 2000;20:7722-7727.

Are such convergent response properties and dynamic characteristics really surprising?

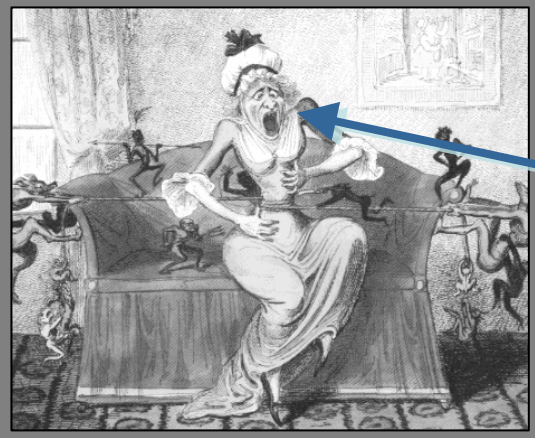
Does the answer suggest other ways of conceptualizing pain mechanisms?

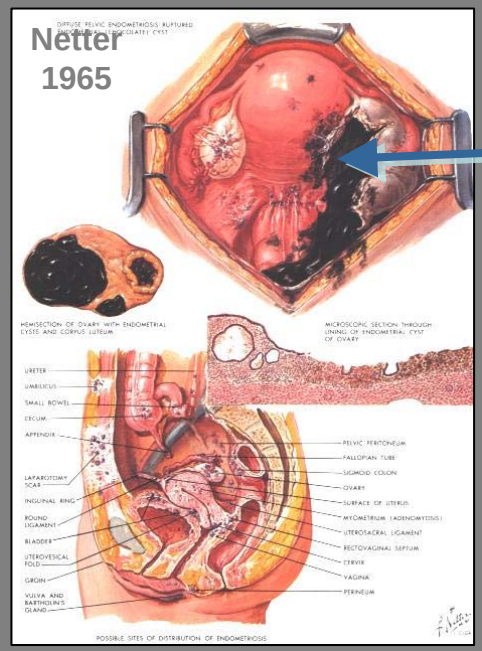
..and therefore modifying diagnostic strategies?

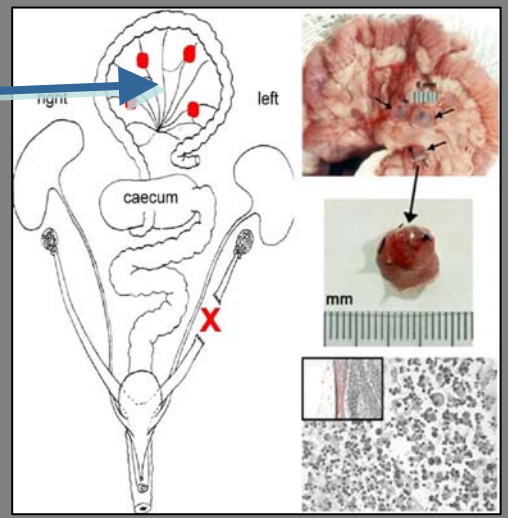
…and, therefore, how to use the table of pain therapies more effectively?

A TRANSLATIONAL ADVENTURE*

ENDOMETRIOSIS



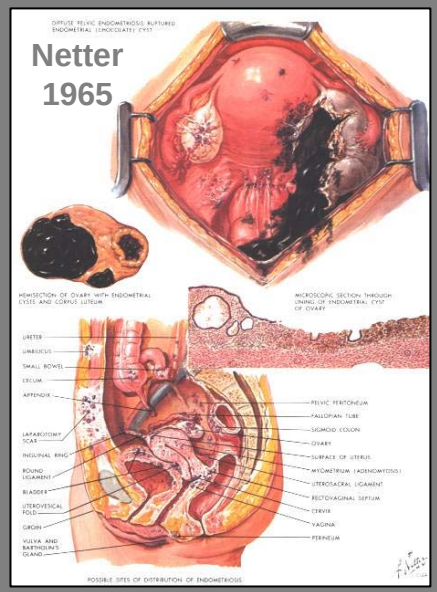




*ongoing…

NIH Consensus Meeting: The Art and Science of Endometriosis: Standardizing the Measurement of Pain and Diagnostic Criteria (20 Oct 06 New

ENDOMETRIOSIS IN WOMEN



...an 'estrogen-dependent' condition,

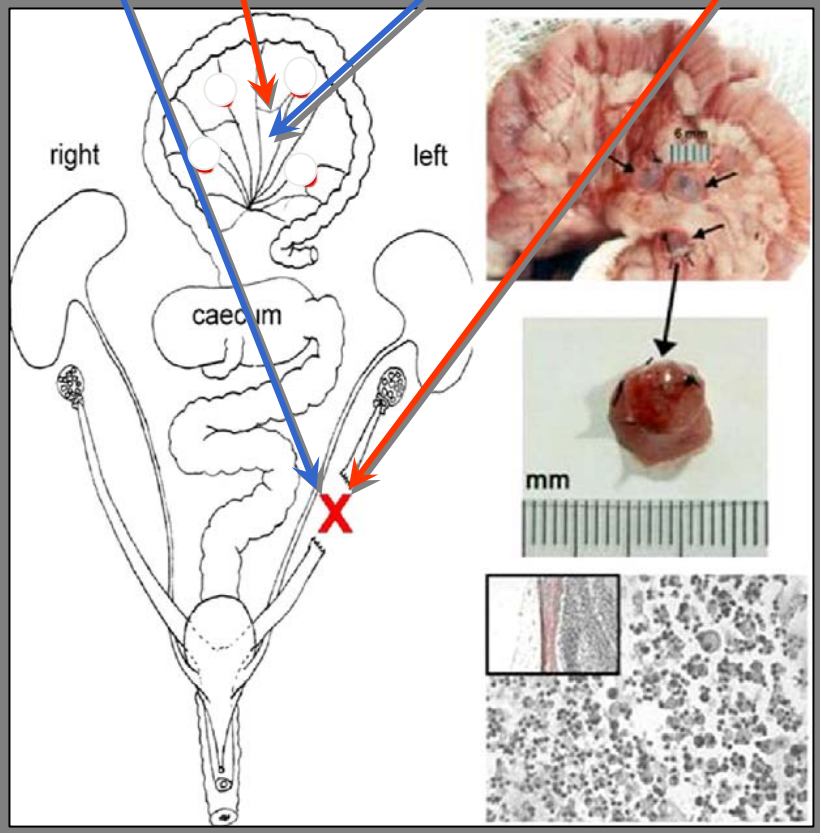
SIGNS: growths of endometrial tissue in abnormal locations

SYMPTOMS: NONE (!), subfertility, severe dysmenorrhea, dyspareunia (vaginal hyperalgesia), dyschezia, chronic pelvic pain

CO-OCCURRENCE with: interstitial cystitis, irritable bowel syndrome, ureteral and kidney stones, temporomandibular disorder, migraine, fibromyalgia, vulvodynia.

ENDOMETRIOSIS IN RATS

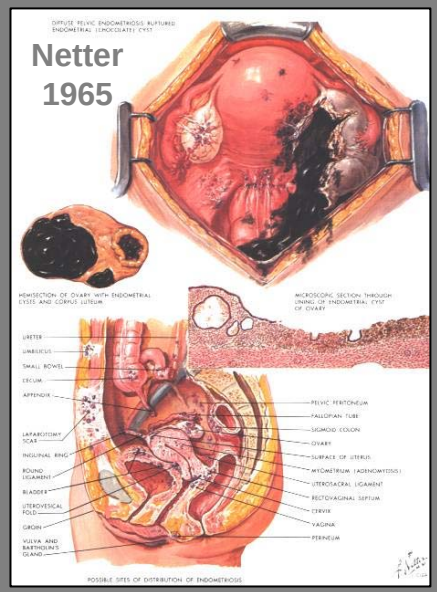
ENDO: autotransplant pieces of uterus on arteries in abdomen.
ShamENDO: remove small part of uterus; autotransplant fat



Vernon MW, Wilson EA. *Fertil Steril* **44**;1985:684-694.

- The autotransplants become vascularized and develop into fluid-filled cysts that contain inflammatory cells.
- The cysts grow rapidly over a 1-mon period, stabilize by 2 mon.
- Cysts disappear after OVX & reappear after E2 replacement.
- Rats are subfertile.
- ShamENDO: no cysts, fertile

ENDOMETRIOSIS IN WOMEN



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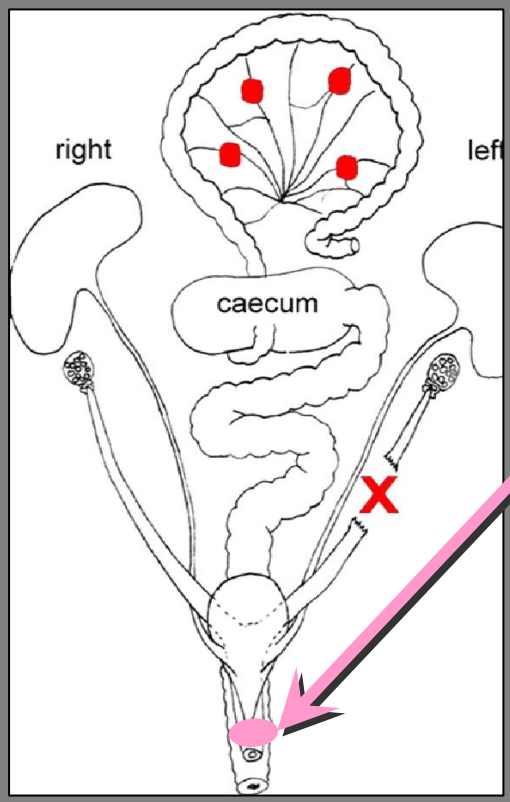
How does ENDO in rats affect vaginal nociception?



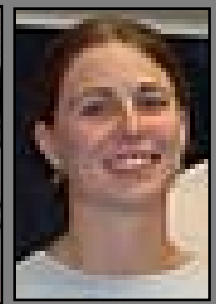
Berkley KJ, Wood E, Scofield SL, Little M. Behavioral responses to uterine or vaginal distension in the rat. Pain 1995;61:121-131.

Bradshaw HB, Temple JL, Wood E, Berkley KJ. Estrous variations in behavioral responses to vaginal and uterine distention in the rat. Pain 1999;82:187-197.

Cason A., Samuelsen C, Berkley KJ. Estrous changes in vaginal nociception in a rat model of endometriosis. Horm Behav 2003;44:123-131.

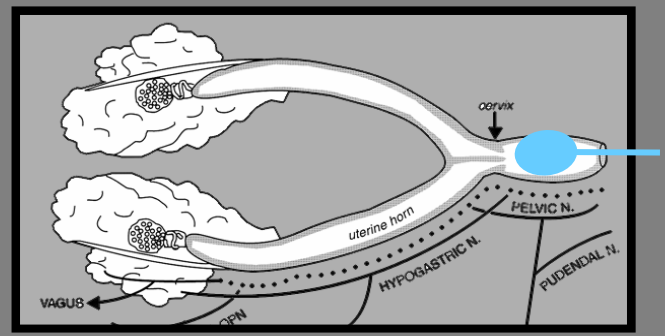

Elizabeth Wood


Heather Bradshaw, PhD


Angie Cason, PhD


Chad Samuelsen

Assessment of vaginal nociception in the rat: probability of escape response to 8 distention volumes.

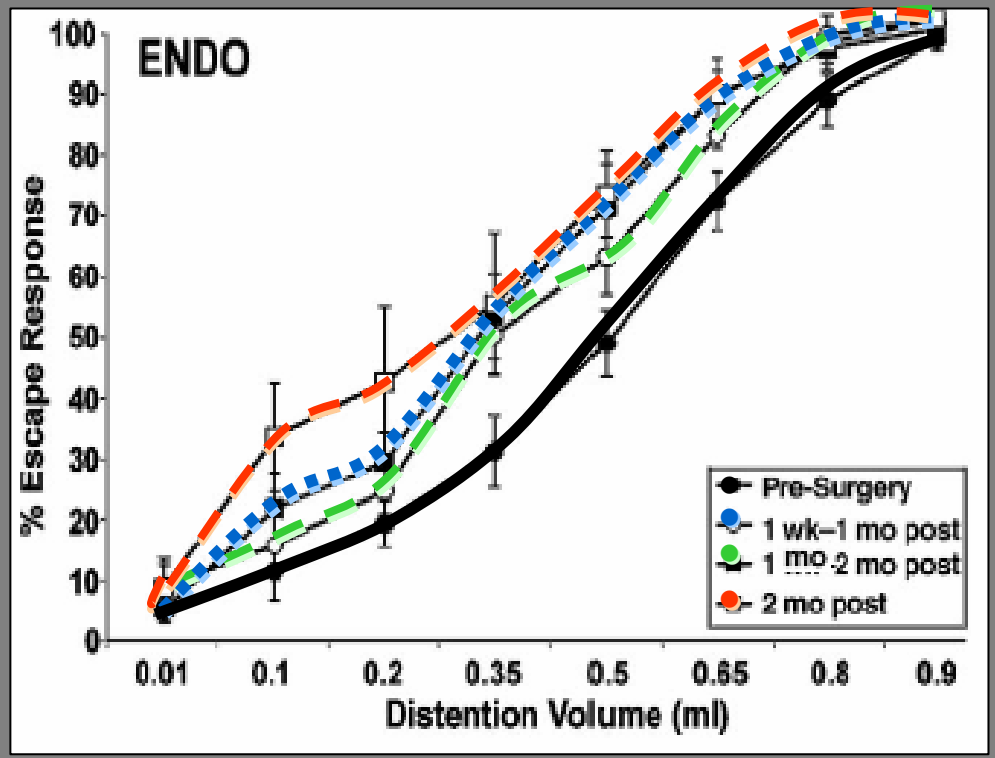


Don Donaldson

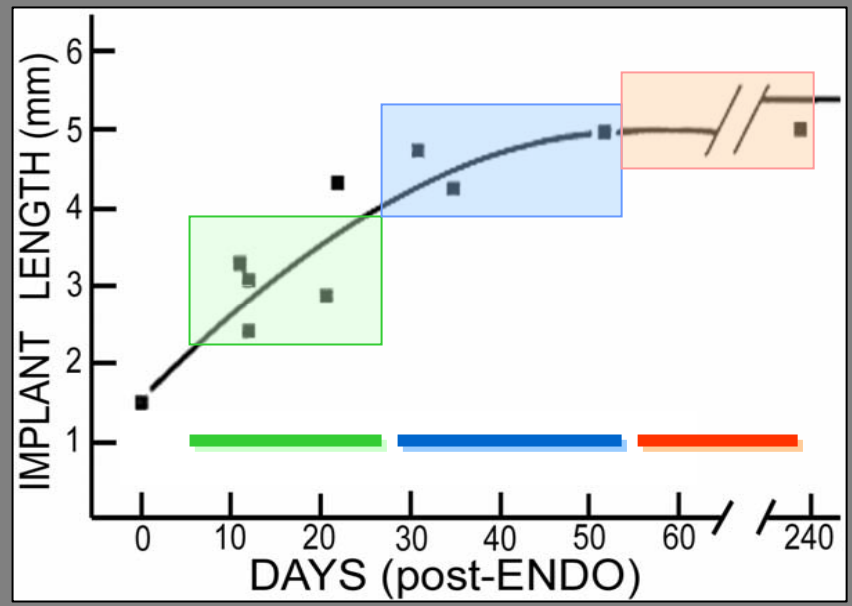
Paul Hendrick

Ross Henderson

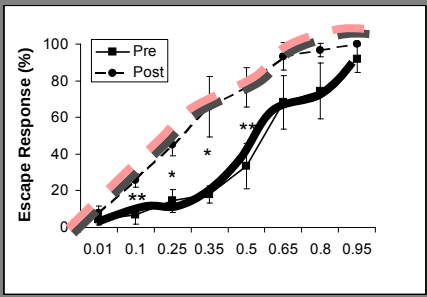
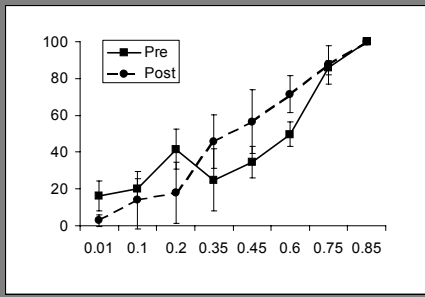
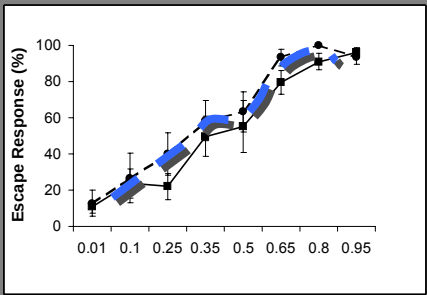
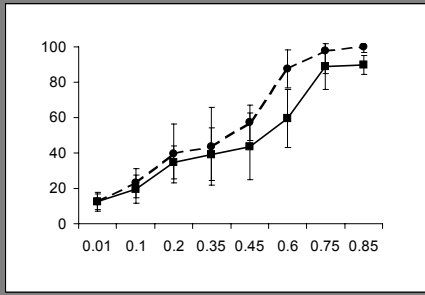
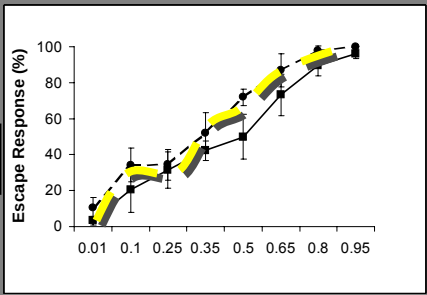
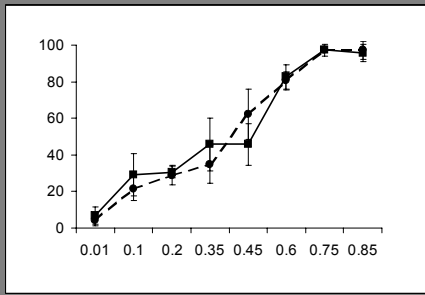
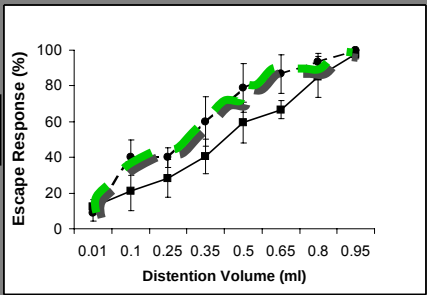
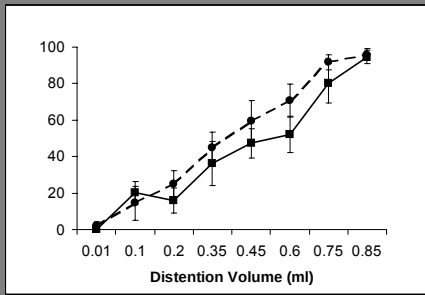
ENDO induces vaginal hyperalgesia. The hyperalgesia develops in parallel with the cysts.



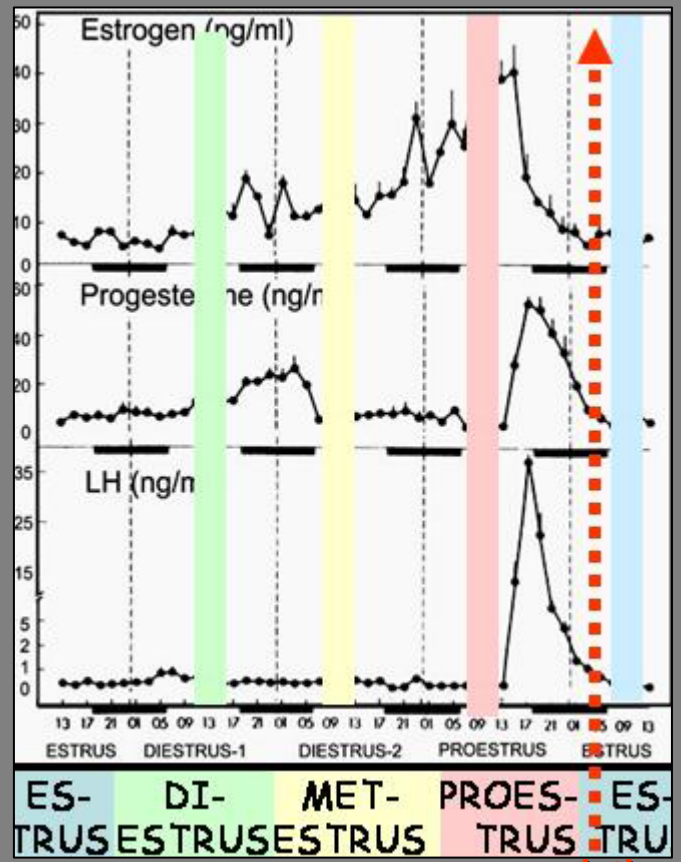
FROM: Cason A, Samuelson C, Berkley KJ. *Horm Behav* 2003;44:123-131



FROM: Vernon MW, Wilson EA. Studies on the surgical induction of endometriosis in the rat. *Fertil Steril* 1985; 53:921-925.

	ENDOMETRIOSIS	shamENDOMETRIOSIS
PROESTRUS		
ESTRUS		
METESTRUS		
DIESTRUS		

ENDO → vaginal hyperalgesia, whose severity correlates with estradiol levels.

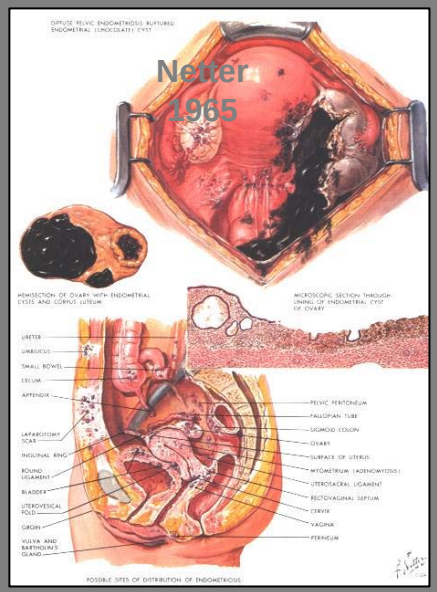


Cason A, Samuelson C, Berkley KJ. Horm Behav 2003;44:123-131

SUMMARY

- Rats with ENDO, but not rats with shamENDO, develop vaginal hyperalgesia in parallel with growth of the cysts.
- The severity of the hyperalgesia correlates with circulating estradiol levels.
- In rats with ENDO, but not in rats with shamENDO, distention of the vaginal canal induces reflexes in abdominal external oblique muscles. (~MUSCLE HYPERALGESIA)
- In rats with ENDO, but not in rats with shamENDO, distention of the vaginal canal increases blood pressure. (BP↑)

ENDOMETRIOSIS IN WOMEN



…an 'estrogen-dependent' condition,

SIGNS: growths of endometrial tissue in abnormal locations

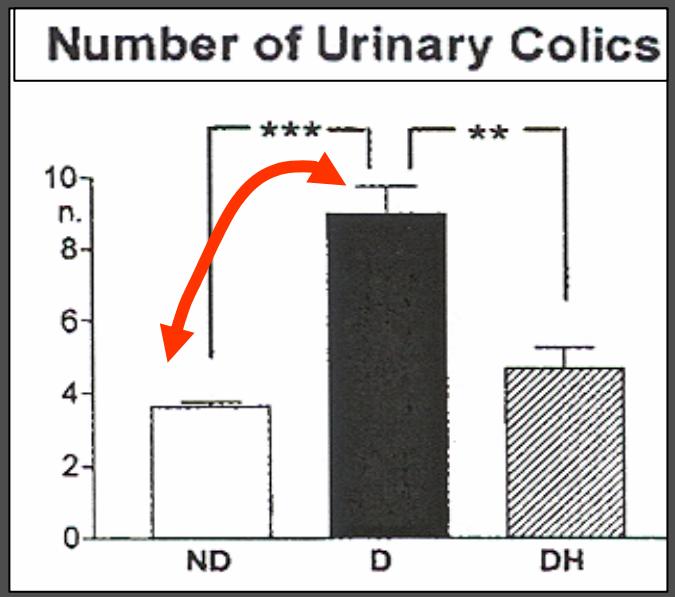
SYMPTOMS: NONE (!), subfertility, severe dysmenorrhea, dyspareunia (vaginal hyperalgesia), dyschezia, chronic pelvic pain

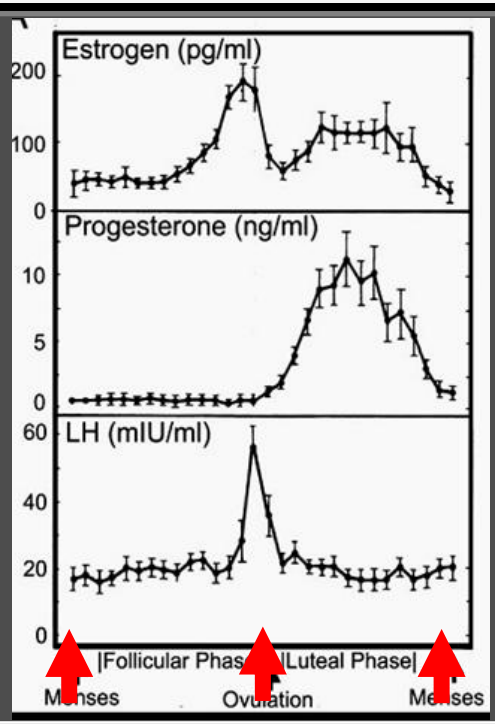
CO-OCCURRENCE: interstitial cystitis, irritable bowel syndrome, kidney and ureteral stones, temporomandibular disorder, migraine, fibromyalgia, vulvodynia.

In women, how does ENDOMETRIOSIS affect pain associated with KIDNEY STONES?

Giamberardino MA, De Laurentis S, Affaitati G, Lerza R, Lapenna D, Vecchiet L. Modulation of pain and hyperalgesia from the urinary tract by algogenic conditions of the reproductive organs in women. *Neurosci Lett*. 2001;304:61-4.

SEVERE DYSMENORRHEA (potential endometriosis) AND PAIN WITH URETERAL STONES





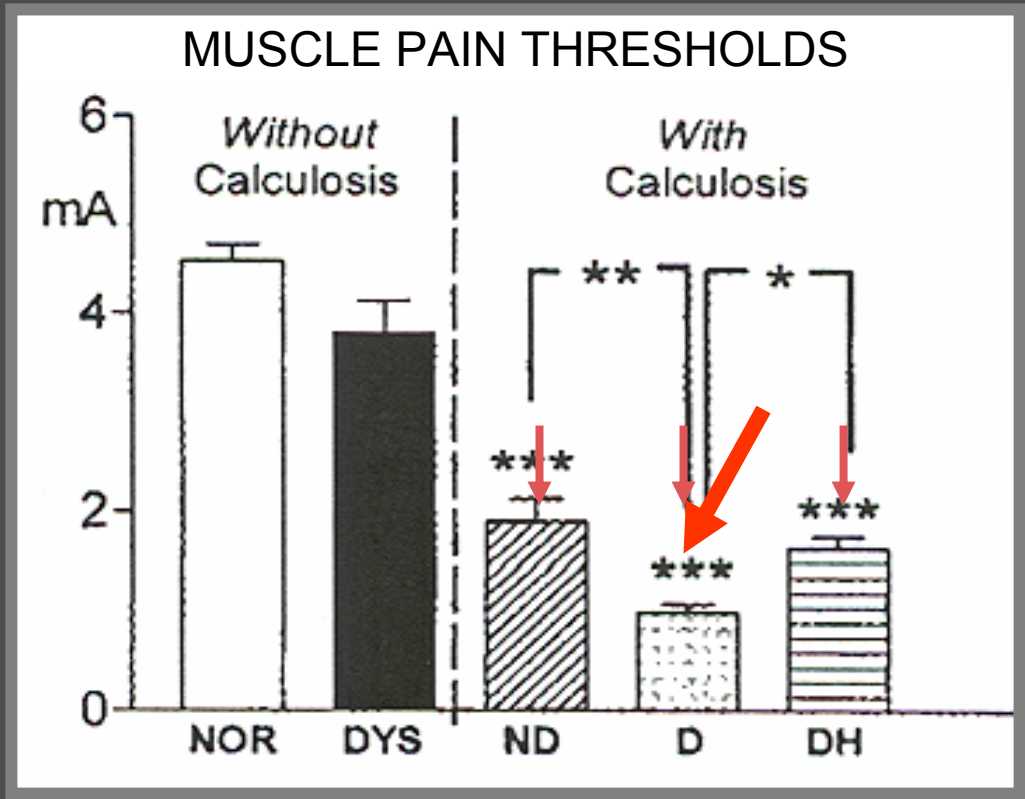
Women with dysmenorrhea (D) have more colic episodes than non-dysmen. (ND) women or D women Rx hormones (DH).

Whereas colics occur throughout menstrual cycle in ND women, they occur only at ovulation or menses in D women.

Giamberardino et al. Neurosci Lett 2001;304:61-4.

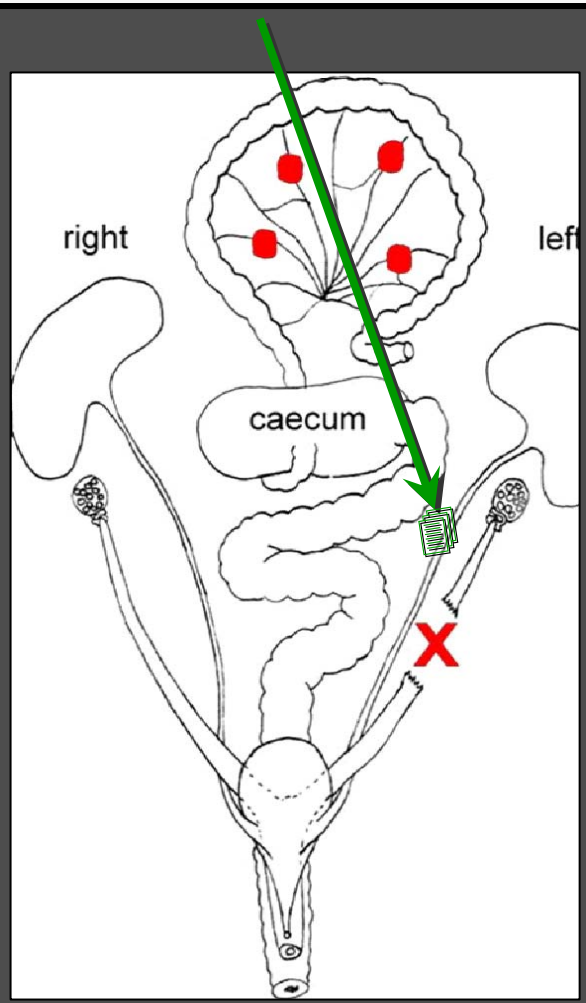
REFERRED PAIN

- Muscle pain thresholds in the referral region of the ureter are lower in women with stones than in women without them.
- This referred hyperalgesia is worse in D women than in ND women (or women who have been treated for D)

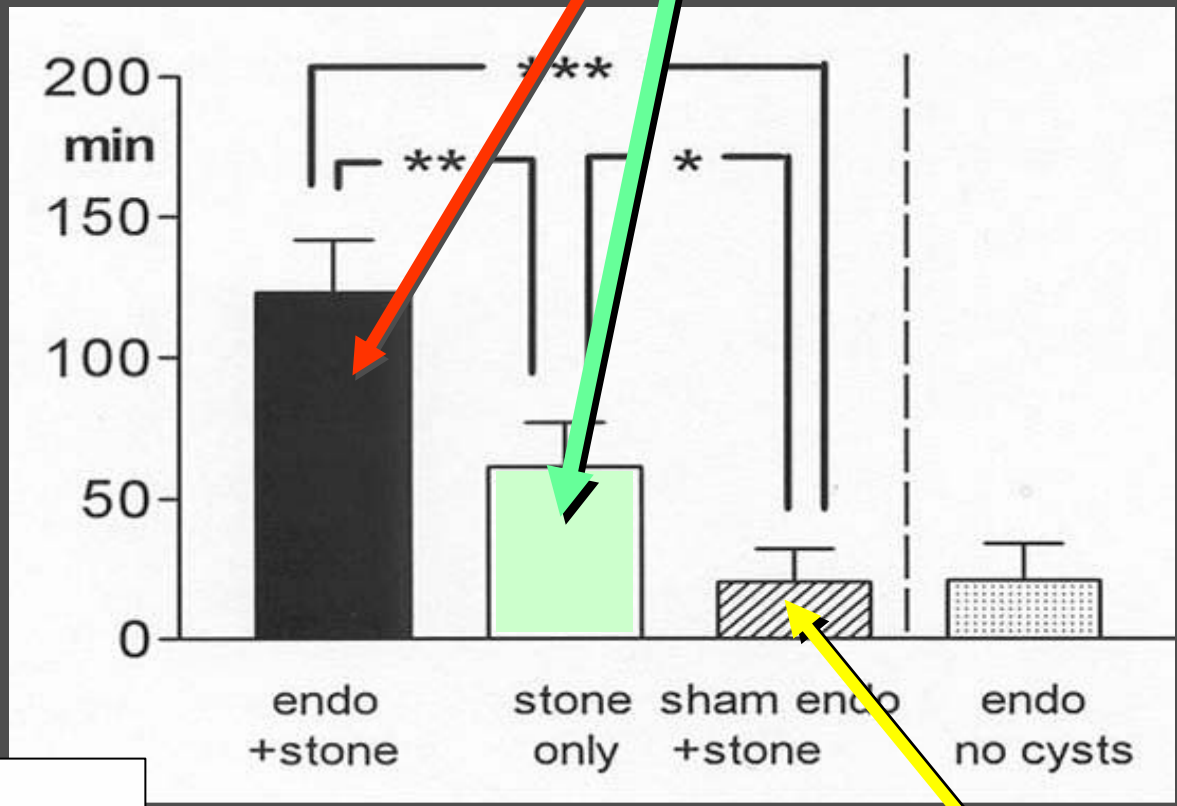


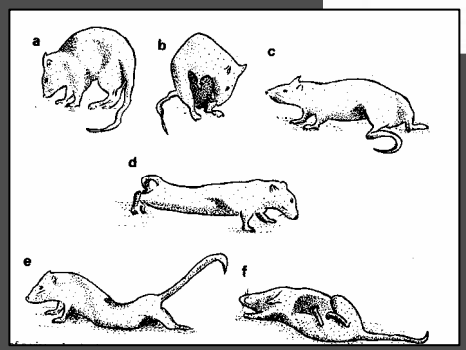
In rats, how does ENDOMETRIOSIS affect pain behaviors induced by a URETERAL STONE?

Giamberardino MA, Berkley KJ, Affaitati G, Lerza R, Centurione L, Lapenna D, Vecchiet L. *Pain*. 2002;95:247.



ENDO surgery increases pain behaviors associated with a ureteral stone….

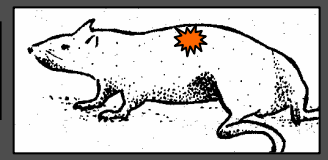




..but sham ENDO surgery decreases them!!
"SILENT STONES"

Giamberardino MA, Berkley KJ, Affaitati G, et al. *Pain*. 2002;95:247-57.

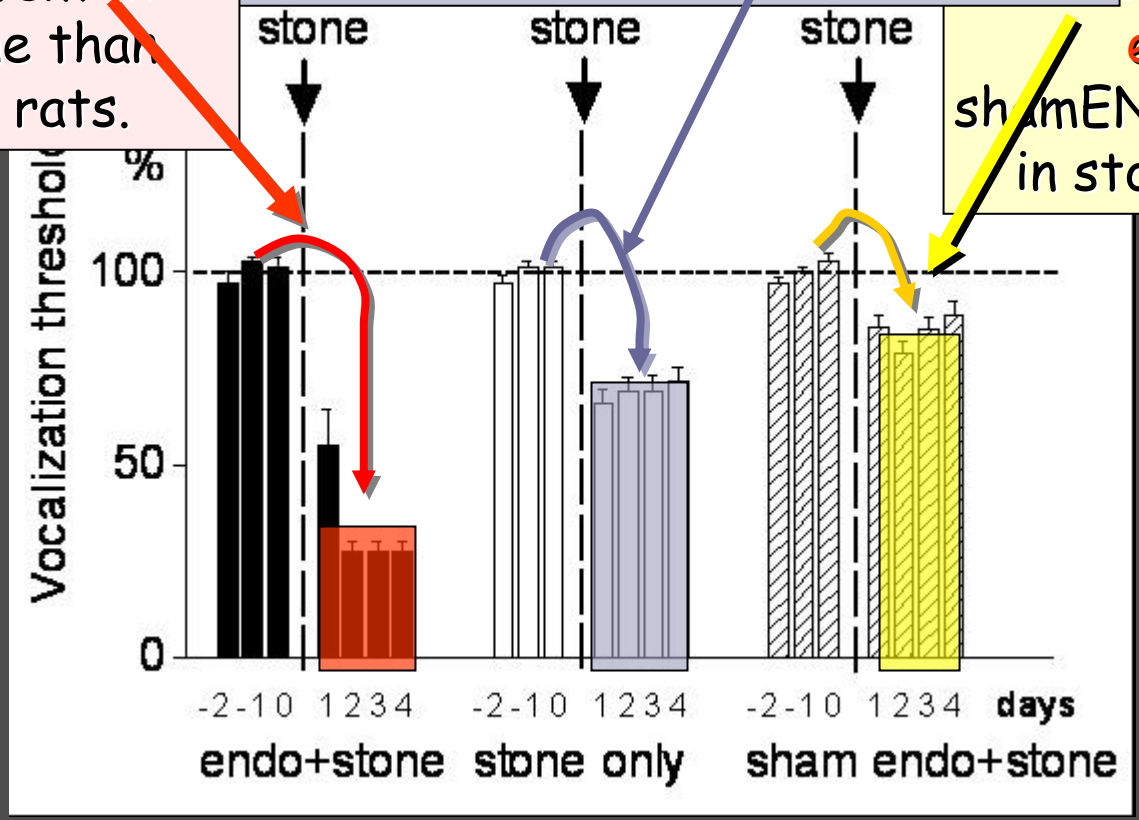
The same effect occurs for referred muscle nociception.



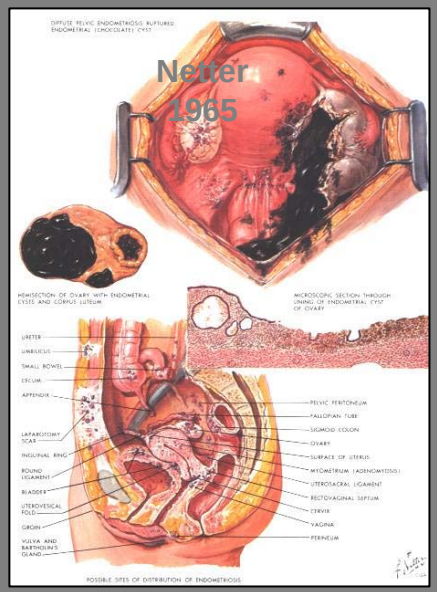
Vocalization thresholds to muscle stimulation to are decreased to a **greater extent** in ENDO+stone than stone-only rats.

..but **vocalization thresholds** to muscle stimulation are reased to a **lesser extent** in shamENDO+stone than in stone-only rats.

uscle pain thresholds are reduced in rats with a ureteral stone.



ENDOMETRIOSIS IN WOMEN



…an 'estrogen-dependent' condition,

SIGNS: growths of endometrial tissue in abnormal locations

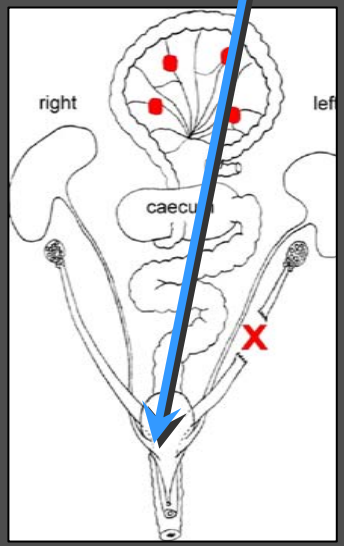
SYMPTOMS: NONE (!), subfertility, severe dysmenorrhea, dyspareunia (vaginal hyperalgesia), dyschezia, chronic pelvic pain

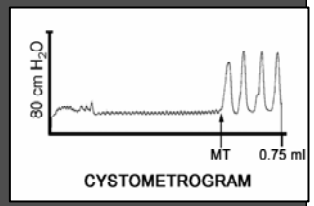
CO-OCCURRENCE: interstitial cystitis, irritable bowel syndrome, kidney and ureteral stones, temporomandibular disorder, migraine, fibromyalgia, vulvodynia.

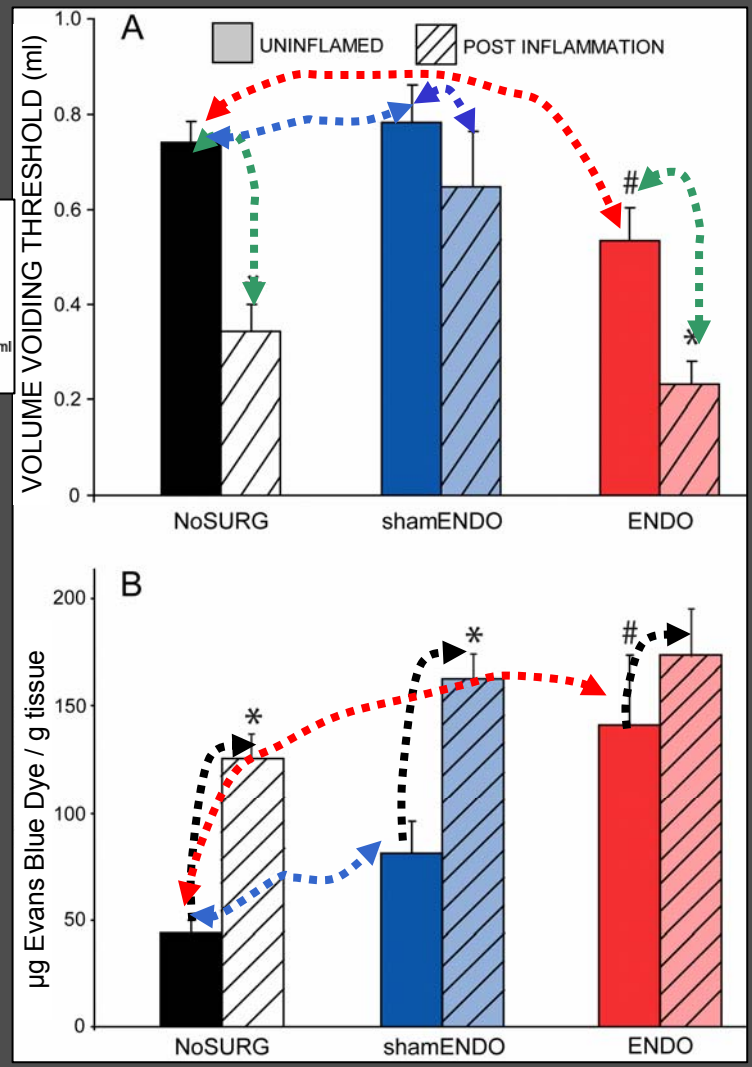
ANESTHETIZED RATS

- ENDO induces bladder inflammation & reduces capacity of healthy bladder.
- ShamENDO does little to the healthy bladder, but, surprisingly, it *prevents* bladder inflammation from reducing bladder capacity: "SILENT BLADDER INFLAMMATION?"

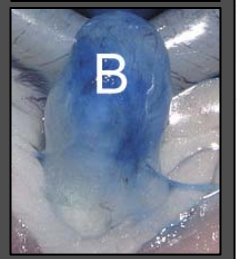
How do ENDO & shamENDO influence the bladder?







Evans blue dye extravasation (a measure of inflammation)




Trevor Morrison MD


Ken Winnard


Natalia Dmitrieva, PhD

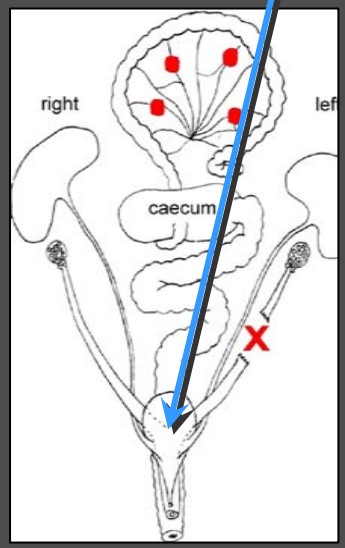
Morrison T, Winnard K, Dmitrieva N, Berkley KJ. Fertil Steril, 2006.

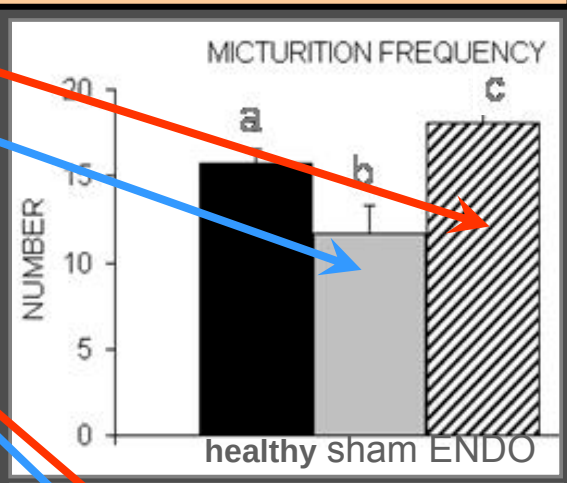
surement of Pain and Diagnostic Criteria (20 Oct 06 New Orleans, LA)

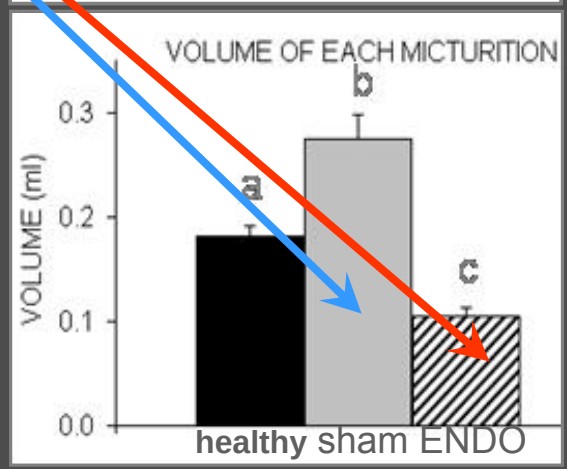
AWAKE RATS (pilot data)

- ENDO induces signs of an overactive bladder.
- shamENDO induces signs of urinary retention.

How do ENDO and shamENDO influence the bladder?







Kaplan S, Martin C, and Berkley KJ, pilot data (Sept 06).

POTENTIAL MECHANISMS?

ENDOMETRIOSIS:

(a) induces vaginal hyperalgesia (greatest in P).

(b) induces vaginal distention to evoke visceromotor and pressor responses (in P).

(c) reduces bladder capacity (in P) and increases urinary frequency and volume.

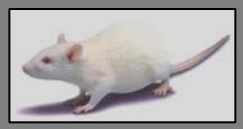
(d) increases pain behaviors and referred muscle hyperalgesia produced by a ureteral stone.

Sham ENDOMETRIOSIS:

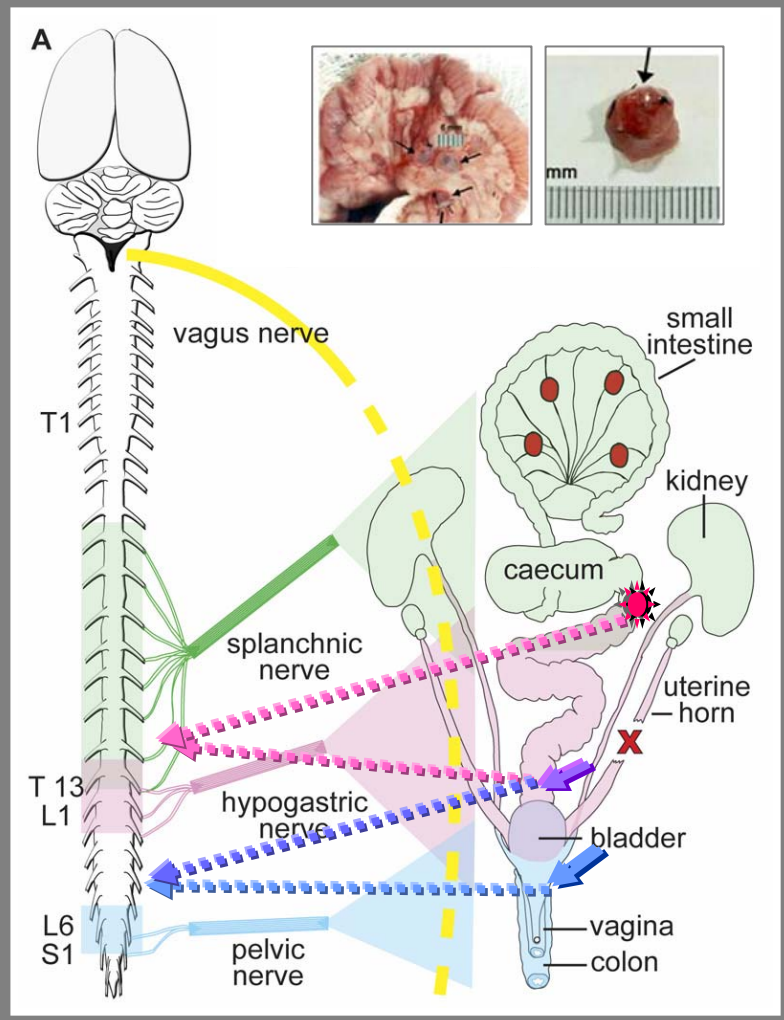
(a) no influence on vaginal nociception.

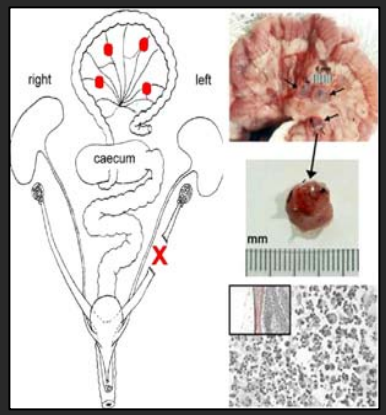
(b) gives rise to signs of urinary retention and prevents bladder inflammation from reducing bladder capacity (in P): "SILENT BLADDER INFLAMMATION."

(c) reduces pain behaviors and referred muscle hyperalgesia from a ureteral stone: "SILENT URETERAL STONE."

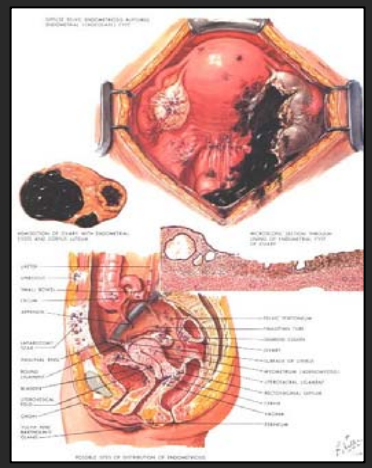


ARE THE ECTOPIC GROWTHS INVOLVED?





IF SO, HOW?



(1) The growths must be vascularized to survive.

(2) Blood vessels are innervated by sensory and sympathetic nerve fibers.

(3) Do these nerves accompany blood vessels as they vascularize the growths?

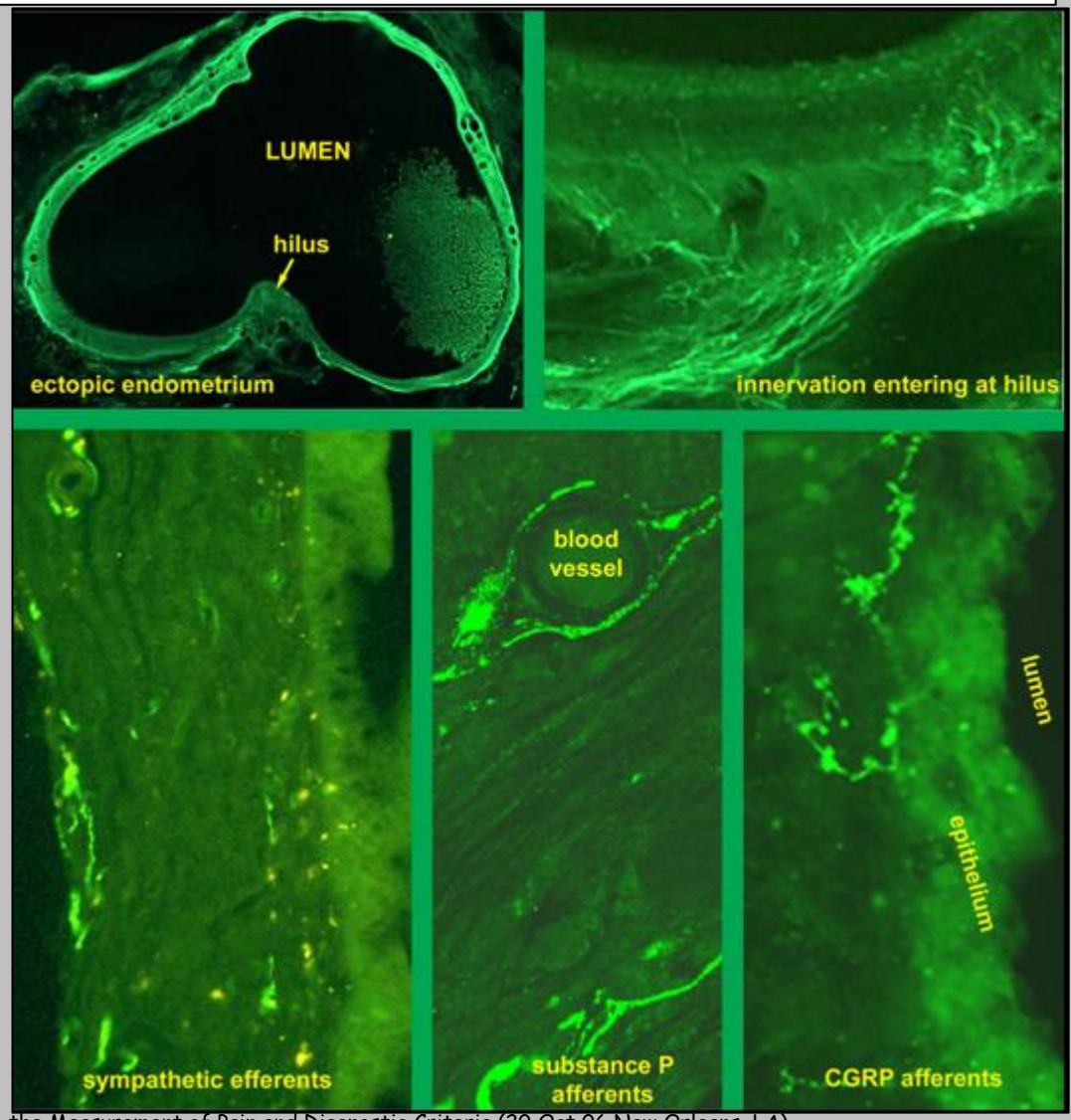
(4) In other words, do the nerve fibers sprout to innervate the growths?

YES (!): In rats, the cysts develop their own nerve supply. The nerves send information to and from CNS via the splanchnic & vagus nerves.

Natalia Dmitrieva, PhD

Ray Papka, PhD

Kath Curtis, PhD



--Berkley KJ, Dmitrieva N, Curtis KS, Papka RE. Innervation of ectopic endometrium in a rat model of endometriosis. PNAS 2004;101:11094-8.

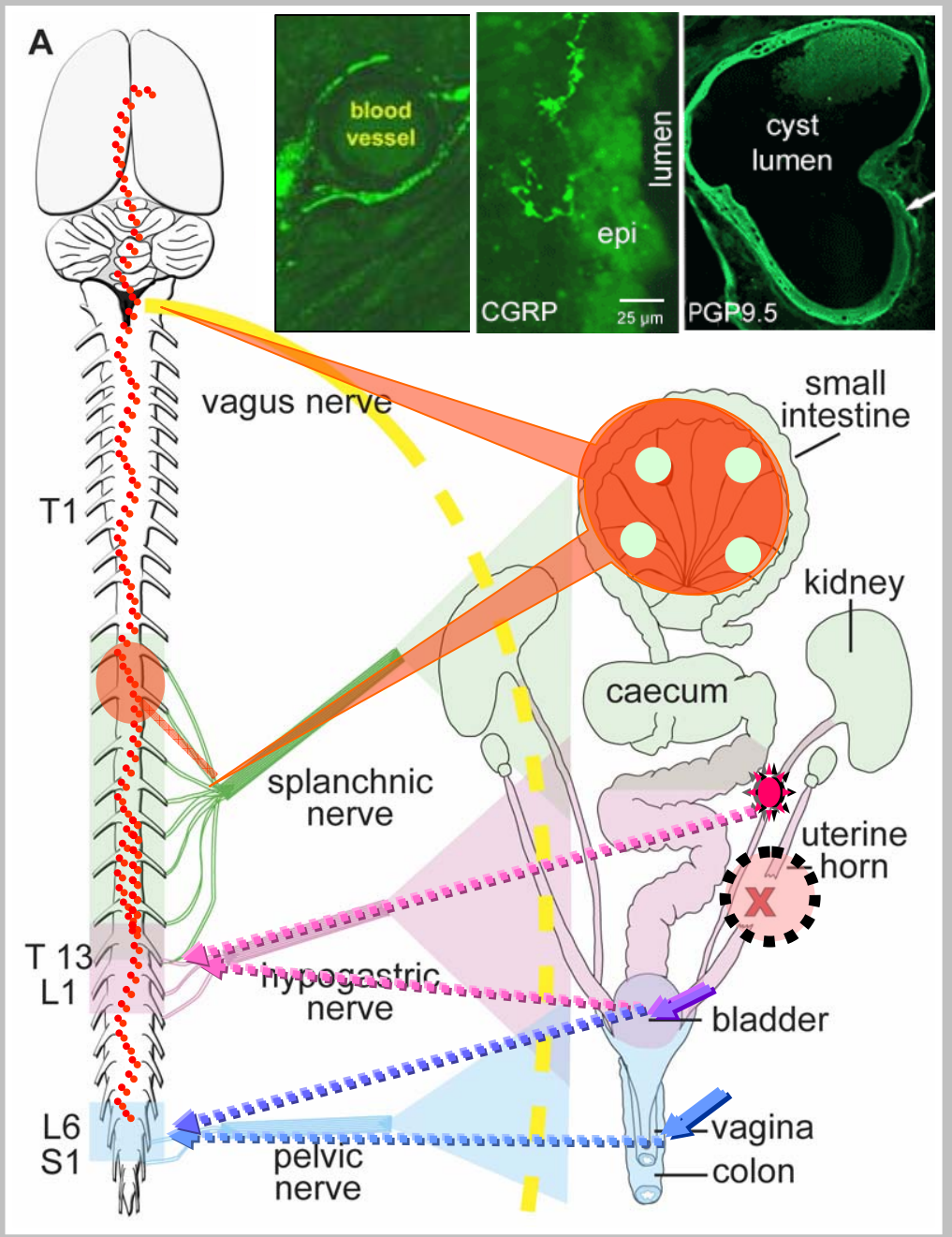
--Berkley, KJ. A life in pelvic pain. Physiol Behav 2005;86:272-80 .

ENDO vs shamENDO

(on vagina, bladder, ureter)

- In ENDO, but not shamENDO, "extra" communication exists between CNS ↔ cysts (plus effects of partial hysterectomy).
- In shamENDO, there is no "extra" communication (only effects of partial hysterectomy).

All effects likely involve excitatory as well as inhibitory interactions within spinal cord & brain.



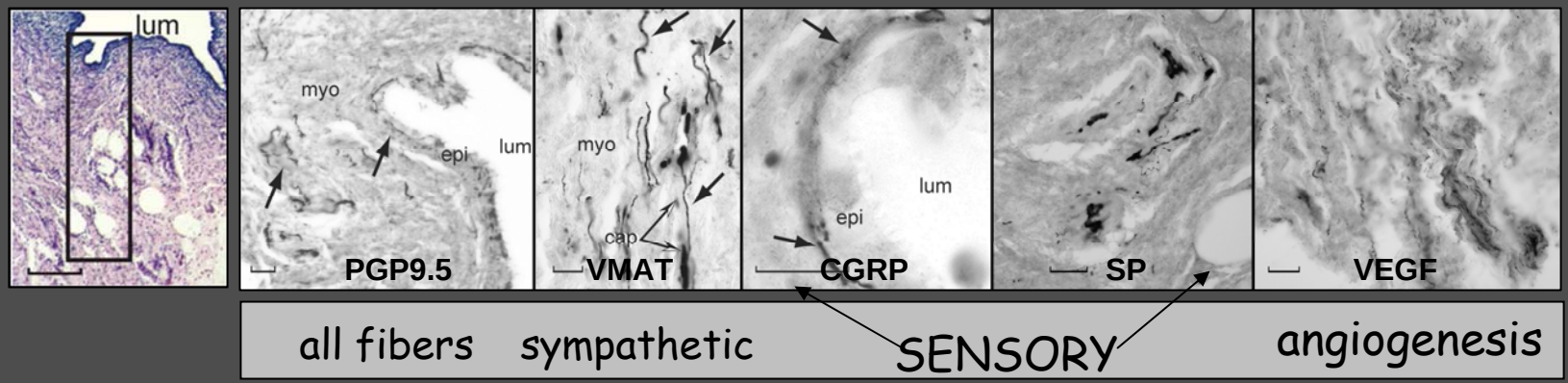
Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. *Science* 2005;306:1587.

Andrea Rapkin, MD

Ray Papka, PhD

What about women? Do their growths develop a nerve supply?

YES! An innervation pattern is found in ectopic endometrial implants from women similar to that seen in cysts in rats.



Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. *Science* 2005;306:1587.

Andrea Rapkin, MD

Ray Papka, Ph.D.

Such results suggest that variations in symptoms associated with ectopic growths may be related to their SENSORY NERVE SUPPLY.

BUT: Is it really all due to the afferents, or are other factors involved?

NEW DATA: 14 patients & 37 samples.

STAINING PATTERNS: WOMEN with PAIN versus NO PAIN

However, note also that there appear to be differences in sympathetic innervation and vascular endothelial growth factor (VEGF)

particularly the sensory ones (CGRP and SP), were less likely to be observed in patients who did not report pain.

PAIN	PGP9.5	VMAT	CGRP	SP	VEGF
YES (n=10)	60%	78%	17%	33%	66%
NO (n=4)	50%	50%	0	0	50%
	all fibers	sympa-thetic	SENSORY		angio-genesis

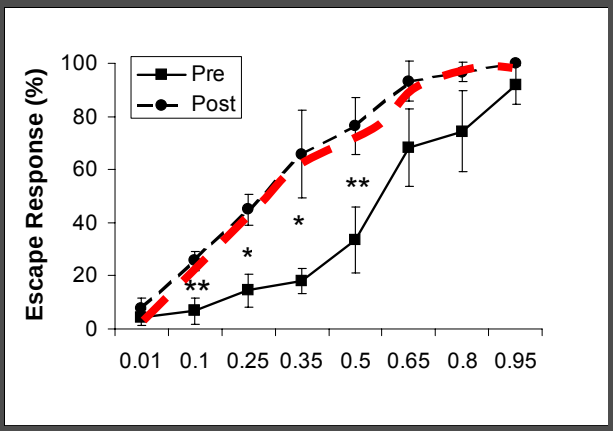
Berkley KJ, Rapkin AJ, Storey-Workley M, Papka RE. Soc Neurosci Abstr. 2005; 2006

BACK TO RATS…

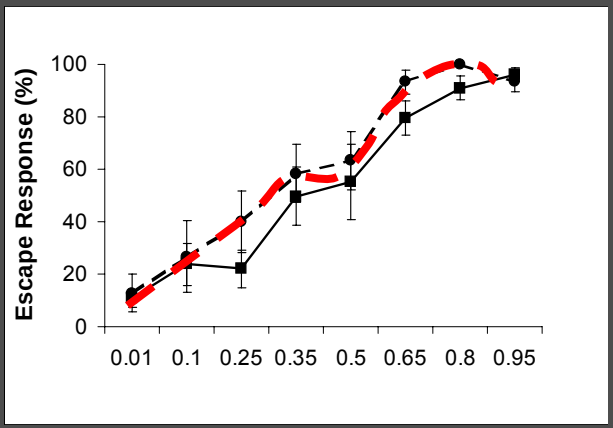
ENDO induces vaginal hyperalgesia that is much greater in PROESTRUS than in ESTRUS.

ENDOMETRIOSIS

PROESTRUS



ESTRUS



Cason A, Samuelson C, Berkley KJ. Horm Behav 2003;44:123-131

SO:

What changes between PROESTRUS AND ESTRUS?


Stacy McAllister


Kristina McGinty


Briane Accius

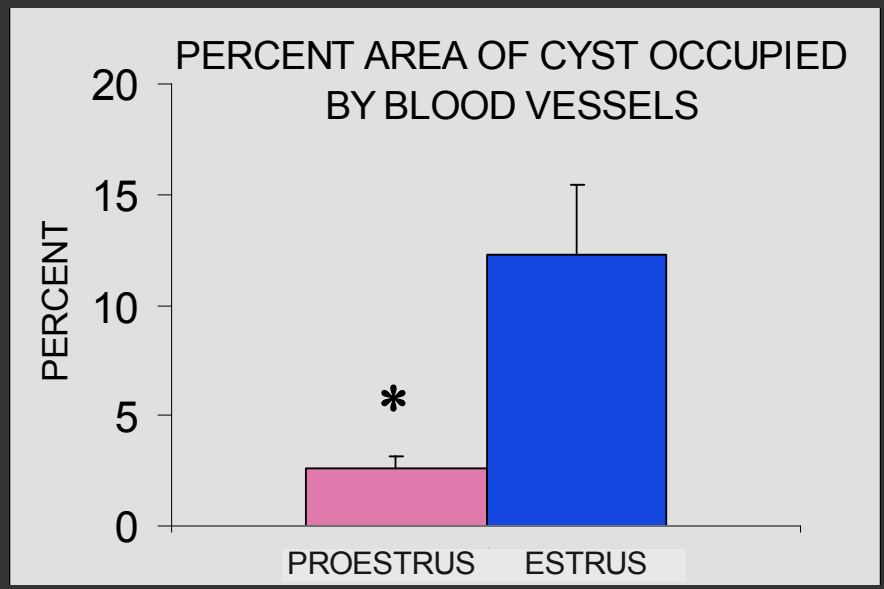

Yan Liu, PhD


Guohua Zhang, PhD


Natalia Dmitrieva, PhD

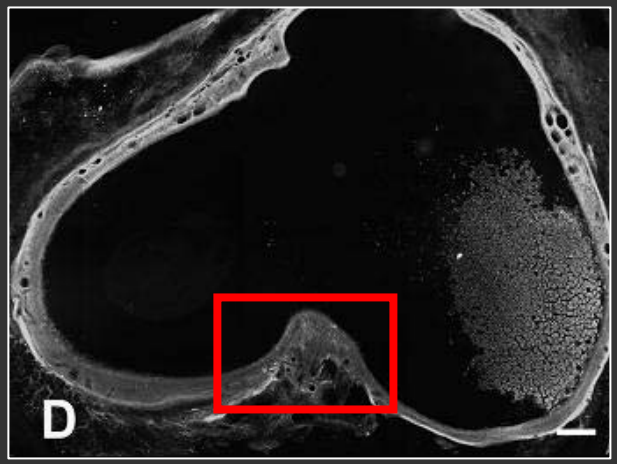

Ken Mackie, MD

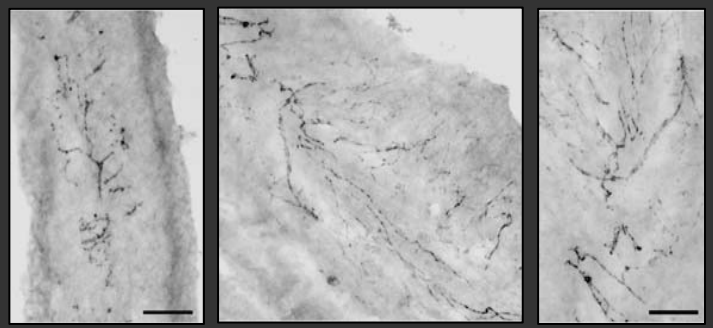
The cysts are significantly less vascularized in PROESTRUS compared with ESTRUS.

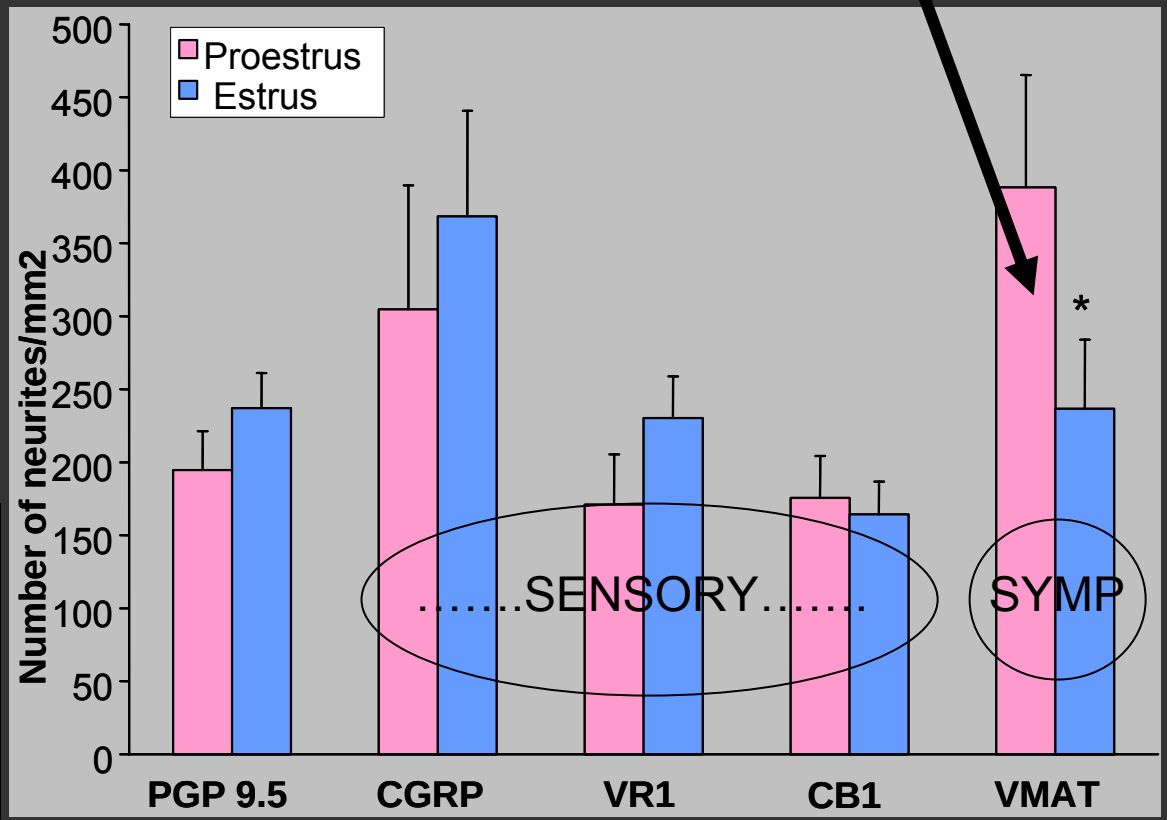


McGinty, Liu, Accius, Dmitrieva, McAllister, & Berkley, 2006 (abstract)

Surprisingly, the density of sensory fibers does not change with estrous. Instead, there are MORE SYMPATHETIC fibers in the cysts in PROESTRUS than in ESTRUS.

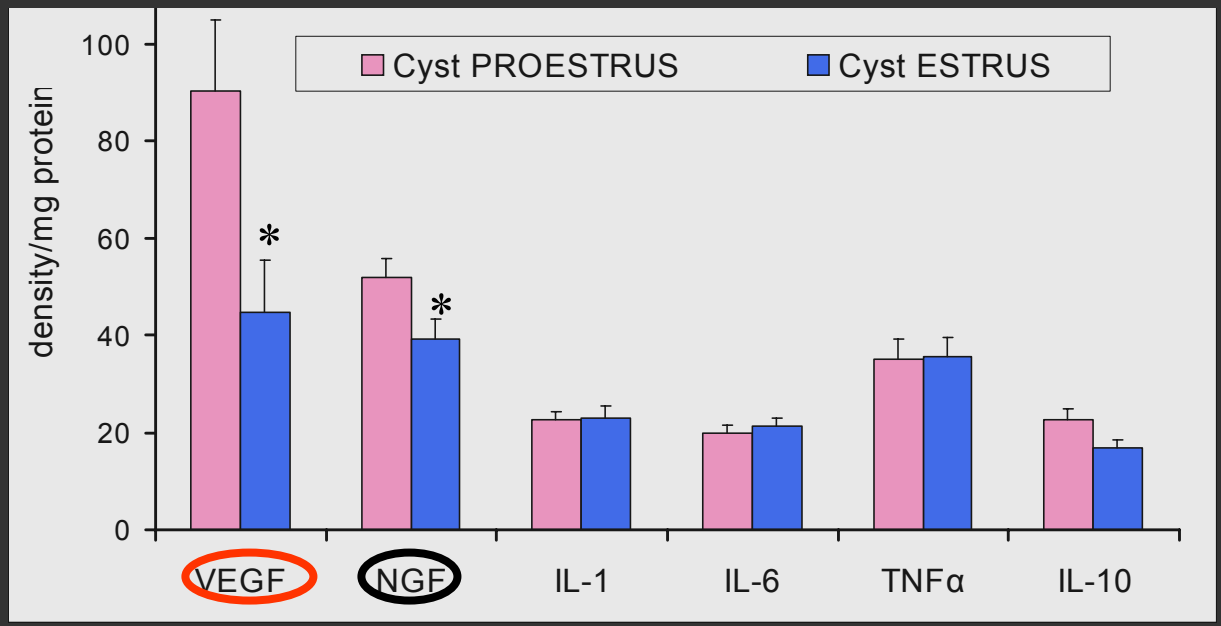


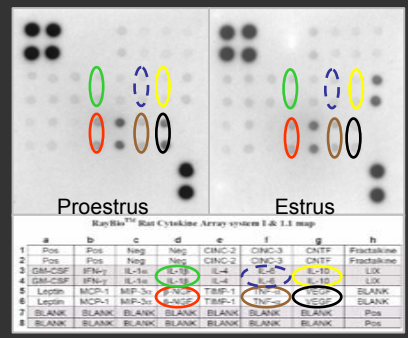




McGinty, Liu, Accius, Dmitrieva, McAllister, Mackie, & Berkley, 2006 (abstract)

Again surprisingly, the cysts' contents of pro- and anti-inflammatory cytokines do not change with estrous. Instead, the cysts contain more VEGF and NGF in PROESTRUS than in ESTRUS.





VEGF=vascular endothelial growth factor
NGF=nerve growth factor

Zhang, Liu, Accius, Dmitrieva, Mackie & Berkley, 2006 (abstract)

In P relative to E, cysts are

- less vascularized
- have more sympathetic fibers
- contain more VEGF and NGF

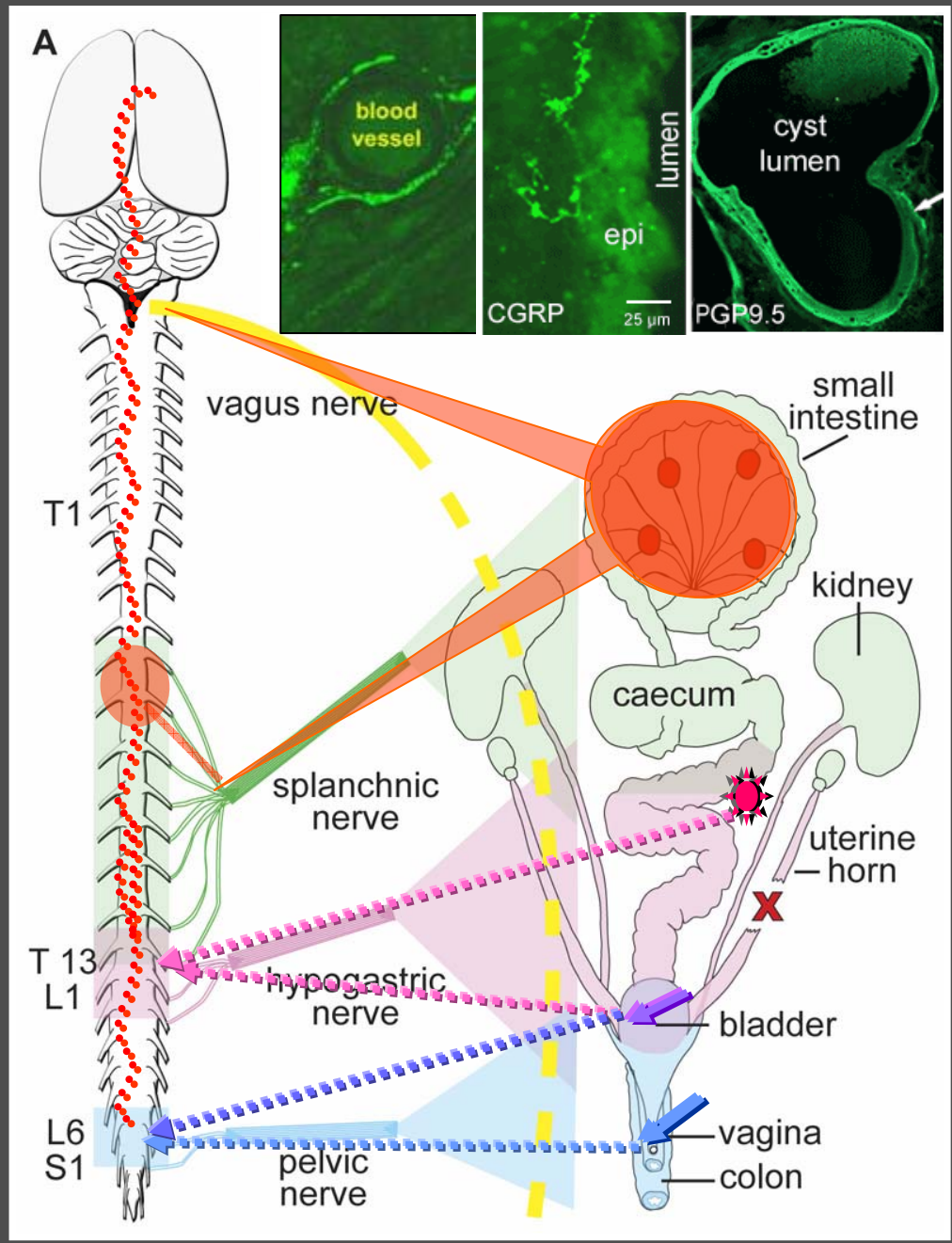
--Surprisingly, there is very little change in sensory input or inflammatory agents.

---Instead, NEURAL OUTPUT to the cysts and their VASCULARIZATION changes.

MECHANISMS of PAIN associated with ENDO?

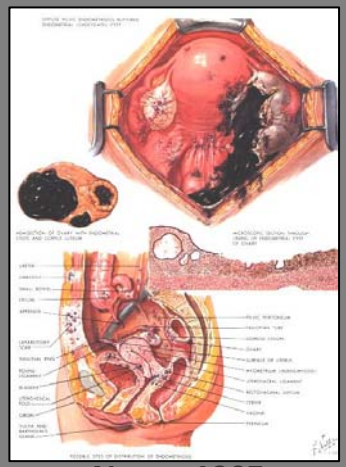
Clearly, in rats, multiple factors are involved:

- Sensory fibers &
- Sympathetic fibers &
- Vascularization of ectopic growths &
- Endocannabinoids &
- Interactions in CNS…



Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. *Science* 2005;306:1587-9.

This conclusion likely also applies to women…



Netter 1965

SYMPTOMS: NONE (!), subfertility, severe dysmenorrhea, dyspareunia (vaginal hyperalgesia), dyschezia, chronic pelvic pain

CO-OCCURRENCE with interstitial cystitis, irritable bowel syndrome, ureteral and kidney stones, temporomandibular disorder, migraine, fibromyalgia, vulvodynia.

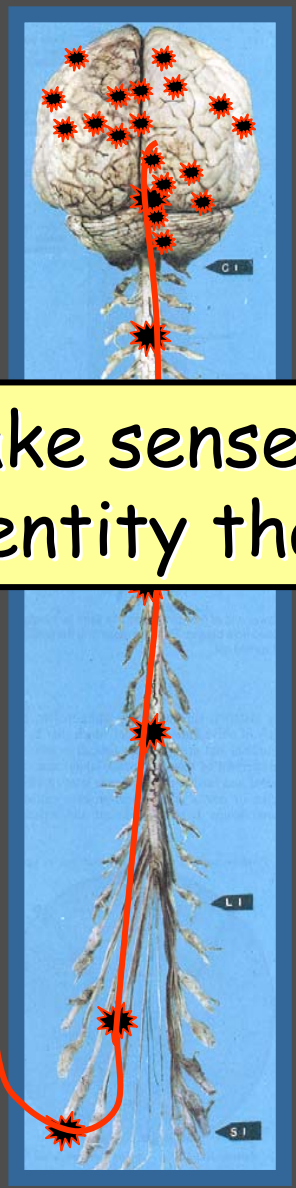
- How are these factors involved?
  - Sensory fibers &
  - Sympathetic fibers &
  - Vascularization of ectopic growths &
  - Interactions in CNS &
  - Endocannabinoids, &?
- And, what about the silencing affects of shamENDO?

Stay tuned..

How can this information be applied now?

What might help is to rethink how we conceptualize pain.

3 MODERN TRADITIONAL VIEW



Gray's Anatomy

"Pain Matrix"

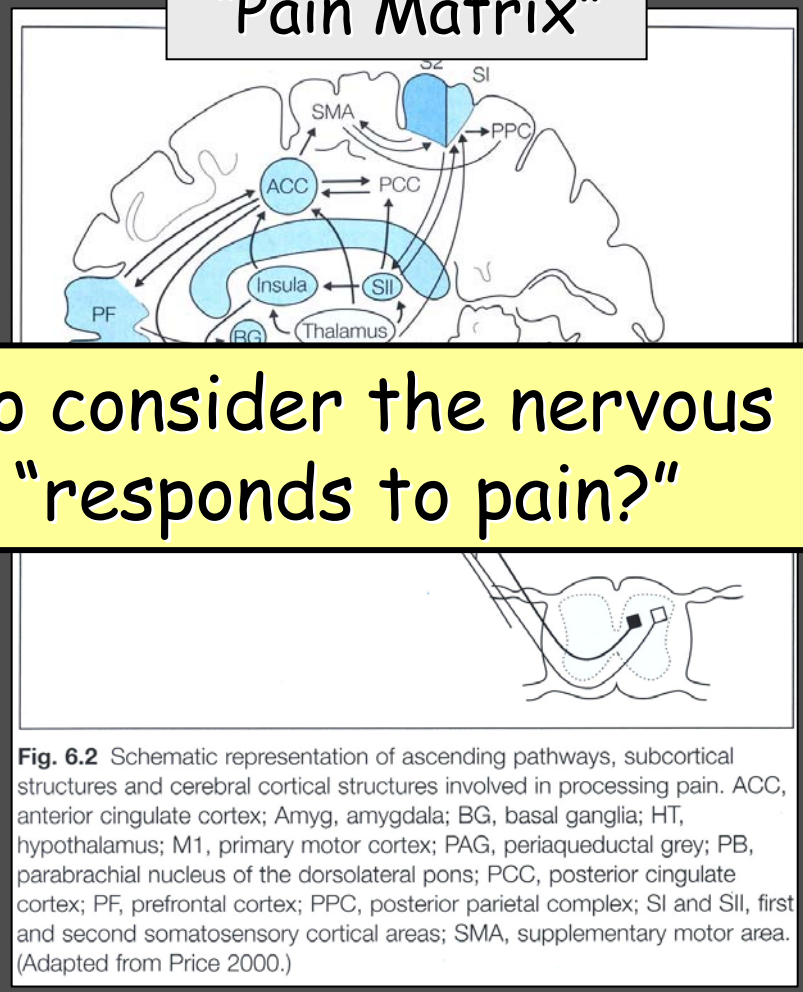
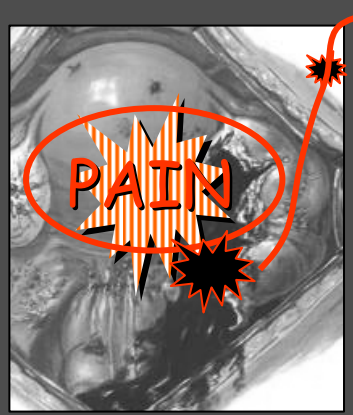


Fig. 6.2 Schematic representation of ascending pathways, subcortical structures and cerebral cortical structures involved in processing pain. ACC, anterior cingulate cortex; Amyg, amygdala; BG, basal ganglia; HT, hypothalamus; M1, primary motor cortex; PAG, periaqueductal grey; PB, parabrachial nucleus of the dorsolateral pons; PCC, posterior cingulate cortex; PF, prefrontal cortex; PPC, posterior parietal complex; SI and SII, first and second somatosensory cortical areas; SMA, supplementary motor area. (Adapted from Price 2000.)

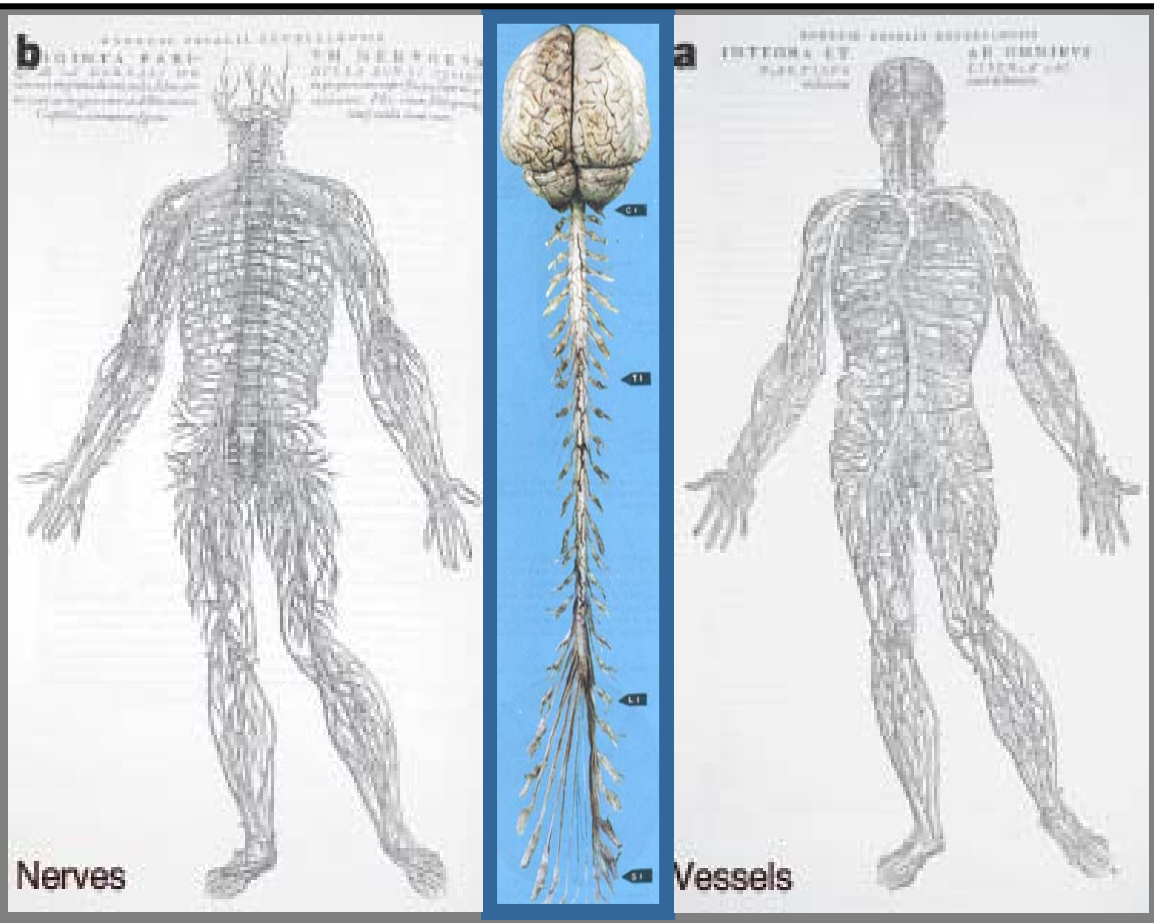
From: Bushnell MC and Apkarian AV. Representation of pain in the brain. In: Wall & Melzack's Textbook of Pain, McMahon S, Koltzenberg M (eds), 5th ed., 2006.

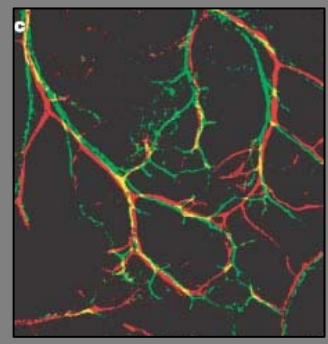
Does it really make sense to consider the nervous system as an entity that "responds to pain?"



What does the nervous system do?

One possibility: an organ that continually integrates information from the entire body, plans, & organizes bodily actions.

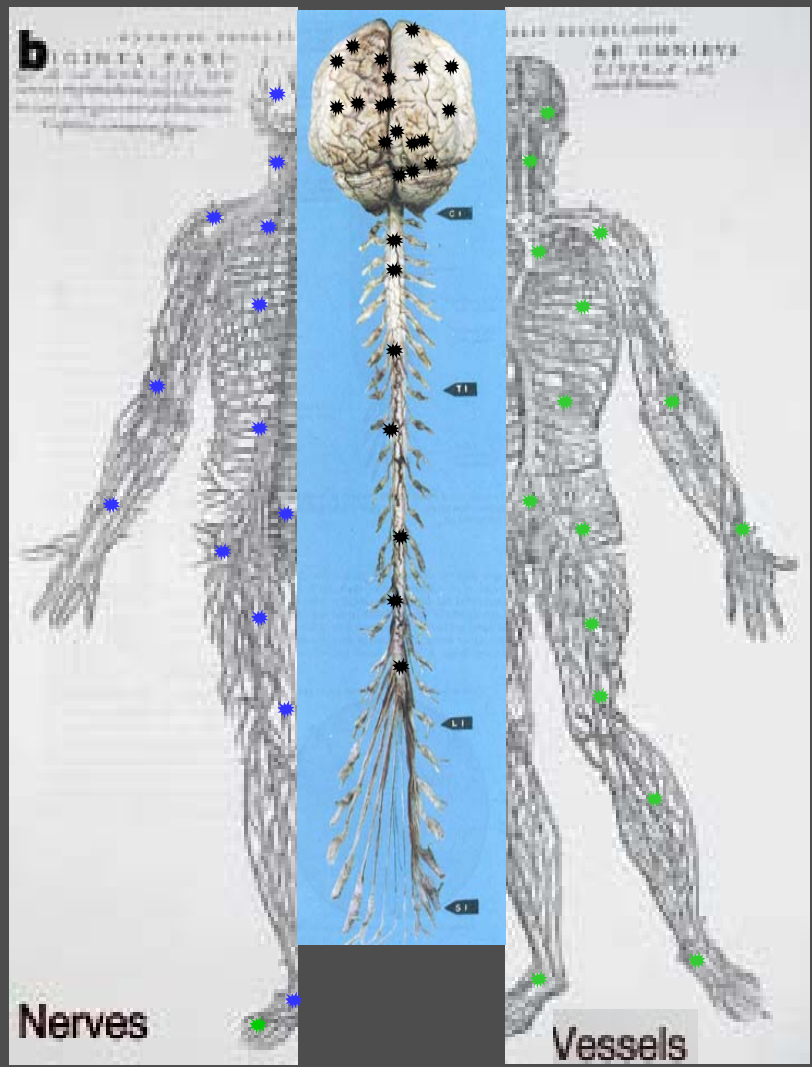




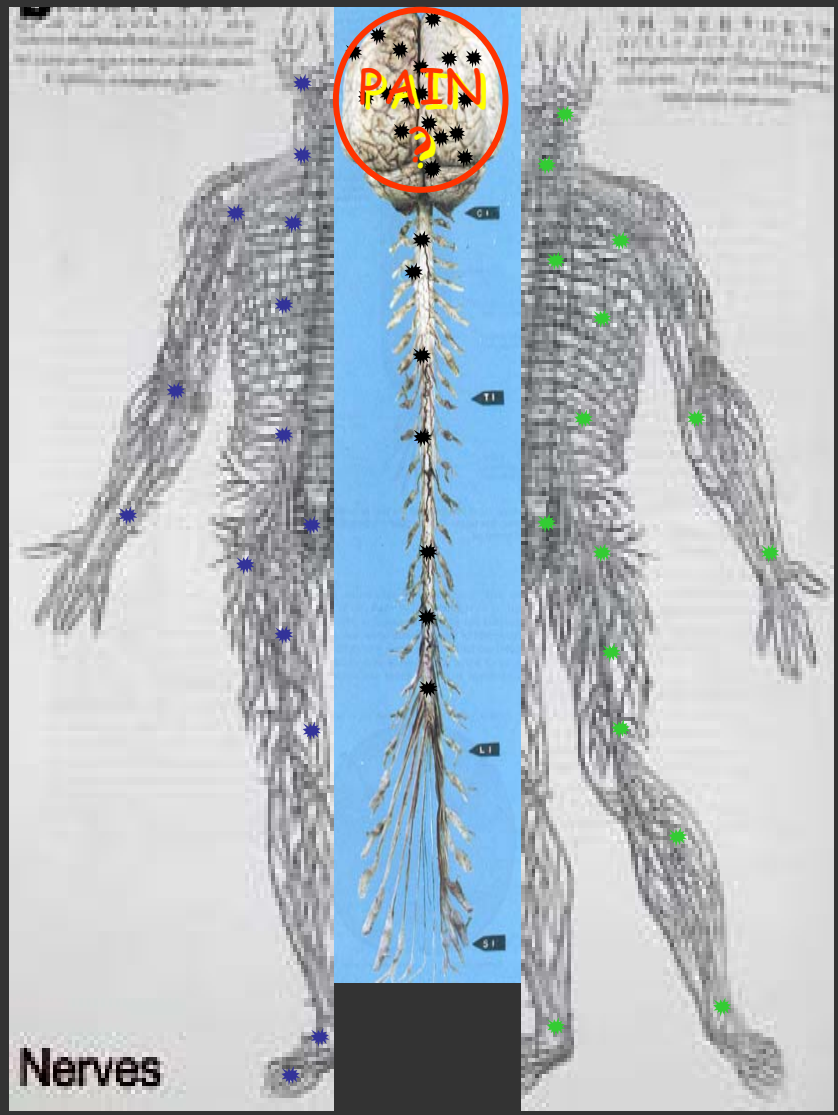
"VESSELS (red) AND NERVES (green) TRACK TOGETHER TOWARDS THEIR TARGETS (2, 4)."

(1) Picture of brain is from: Gray's Anatomy
(2) A, B, and C are from Fig 1 in: **Carmeliet P & Tessier-Lavigne M**. Common mechanisms of nerve and blood vessel wiring. *Nature* 2005;436:193-200.
(3) A is a drawing by Andreas Vesalius in 1543 (!), showing similarities in branching fo vascular and neural networks.
(4) C is from **Mukouyama YS, Shin D, Britsch SA, Taniguchi M, Anderson DJ**. Sensory nerves determine the pattern of arterial differentiation and blood vessel branching in the skin. *Cell* 2002;109:693-705.

One possibility: an organ that continually integrates information from the entire body, plans, & organizes bodily actions.



"Pain," then, becomes a decision, a "call to action," made by a DYNAMIC, DISTRIBUTED SYSTEM in the CNS that is in constant two-way interaction with the body.



Thinking this way--placing the creation of and decision for pain WITHIN a dynamic nervous system --can affect how we develop and test hypotheses.

It can also affect how we assess and diagnose individuals in pain, as well as the strategies we use to treat them (and ourselves).

ASSESSMENT AND DIAGNOSIS?

That's why we are here..

Instead of u THERAPY? her therapy..

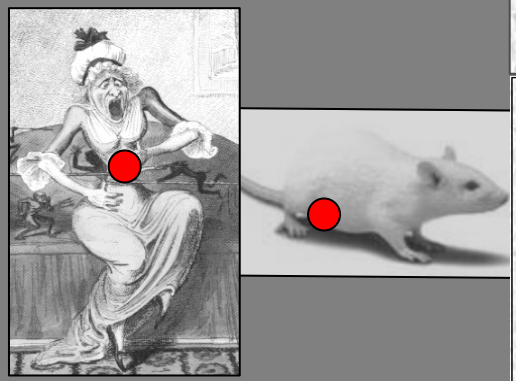
each individual.

DRUGS		SOMATIC		SITUATIONAL	
Primary analgesics	**Adjuvants**	**Simple**	**Invasive**	**Clinician**	**Interactive**
NSAIDS	antihistamines	heat/cold	surgery	education	hypnosis
acetaminophen	laxatives	exercise	radiation Rx	attitude	biofeedback
opioids	neuroleptics	massage	dorsal col. stim.	clinic arrangemt	support groups
Other analgesics	phenothiazines	vibration	nerve blocks	**Self**	advocacy groups
angiogenic inhib.?	**Routes/Timing**	relaxation	neurectomy	education	networking
cannabinoids?	i.v., i.m., i.p.	**Minimally invas.**	local gang. blks	meditation,	self-help groups
corticosteroids, hormones	buccal, sublingual	Physical therapy	sympathectomy	art, poetry	**Structured settings**
anticonvulsants antiarrhythmics	intranasal, oral	traction	rhizotomy	music, theatre	group therapy
β adrenerg.antag.	vaginal, rectal	manipulation	DREZ lesions	virtual reality	family counseling
Ca++ chan. block.	topical	ultrasound	punctate myel.	sports, humor	job counseling
antidepressants	transdermal	TENS	commis. myel.	diet, gardening	cog. / behav.Rx
Cox 2 inhibitors	epidural	acupuncture	cordotomy	aroma therapy	psychotherapy
$GABA_B$ antag	intrathecal	local anes.	brain stim.	religion	multidisipl. clinic
serotonin antag..	slow release		brain lesions	pets	hospice

THANK YOU!!!

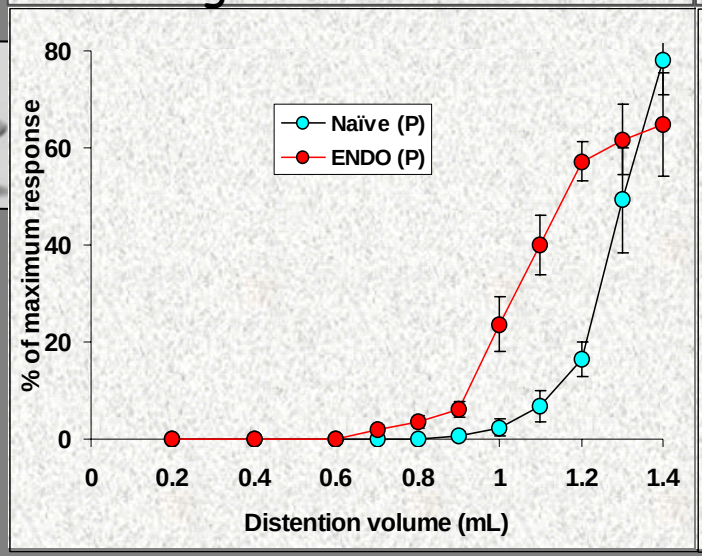
PILOT DATA (2006): "Pseudoaffective Responses"

ENDO also increases abdominal **MUSCLE activity** and PRESSOR responses evoked by vaginal distention (studied in P).

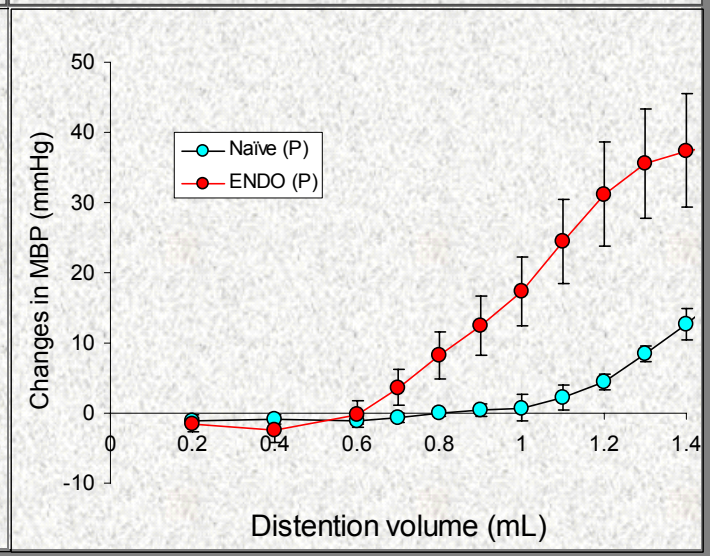


Hiroshi Nagabukuro, PhD

Visceromotor response to vaginal distention



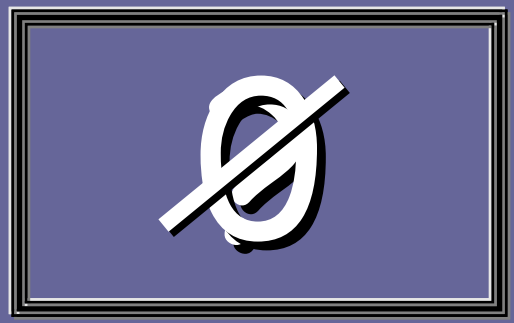
Pressor response to vaginal distention



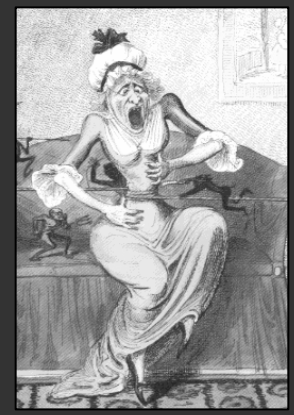
Ness TJ and Gebhart GF. Colorectal distention as a noxious visceral stimulus: Physiologic and pharmacologic characterization of pseudoaffective reflexes in the rat. Brain Res 1988;450:153-169.

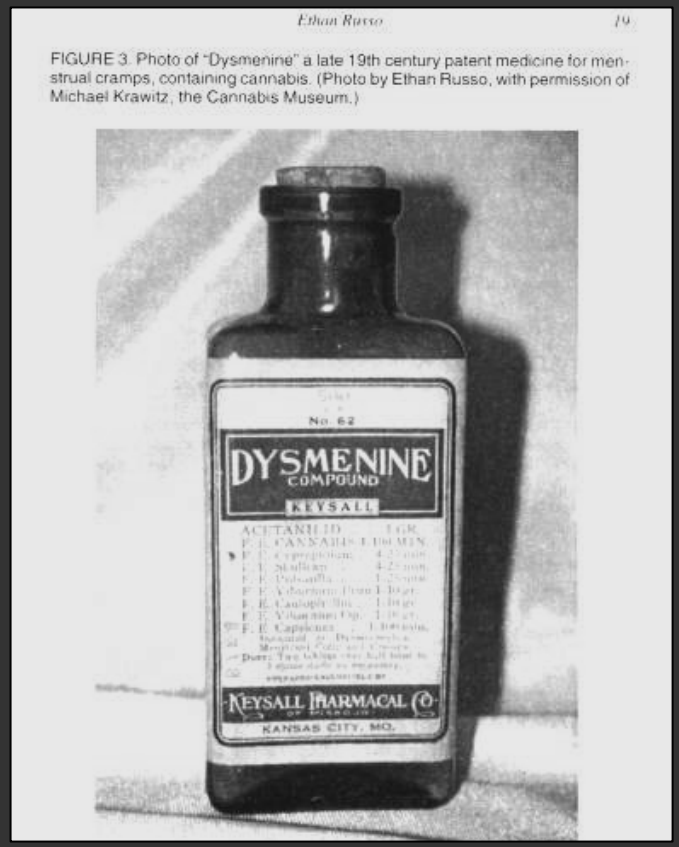
Nagabukuro & Berkley, 2006 (abstract)

Fundamental Pain Mechanisms in Endometriosis



CENTURIES-OLD TREATMENT FOR DYSMENORRHEA (endometriosis?): CANNABINOIDS



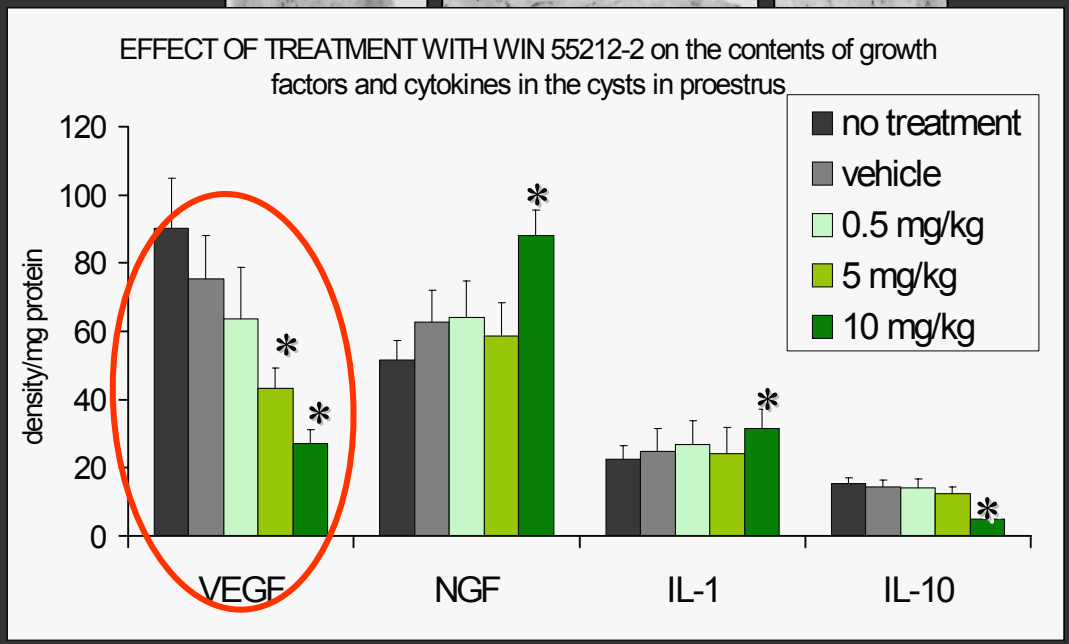


Ethan Russo 19

FIGURE 3. Photo of "Dysmenine" a late 19th century patent medicine for menstrual cramps, containing cannabis. (Photo by Ethan Russo, with permission of Michael Krawitz, the Cannabis Museum.)

From: Russo E. Cannabis treatments in obstetrics and gynecology: an historical review. In: Russo E, Dreher M, Mathre ML. Women and Cannabis: Medicine, Science, and Sociology. Haworth Press: New York, 2002, pp.5-35.

Confusingly, treatment with a cannabinoid CB1/CB2 agonist dose-dependently reduces VEGF and increased NGF in the cysts, but has very little effect on cysts' contents of cytokines, except at the highest dose, where the effect is opposite to what we expect..




Yan Liu, PhD


Natalia Dmitrieva PhD


Guohua Zhang, PhD


Ken Mackie, MD

Zhang, Liu, Dmitrieva, Mackie, & Berkley, 2006 (abstract)

If we agree on that idea, then the nervous system can be conceptualized as a dynamic organ that..

(1) …coordinates components of each individual's body so it functions as a working whole,

(2) …in the context of present circumstances and past learning.

(3) The nervous system thereby provides a framework by which pathophysiology in one organ can influence the healthy physiology or response to pathology of other bodily organs.

VASCULARIZATION & AXON SPROUTING

Not surprisingly, therefore, anti-angiogenic agents (that may also affect nerve fibers), appear to represent a promising new treatment direction.

Hull ML, Charnock-Jones DS, Chan CL, Bruner-Tran KL, Osteen KG, Tom BD, Fan TP, Smith SK. Antiangiogenic agents are effective inhibitors of endometriosis. J Clin Endocrinol Metab 2003;88:2889-99.

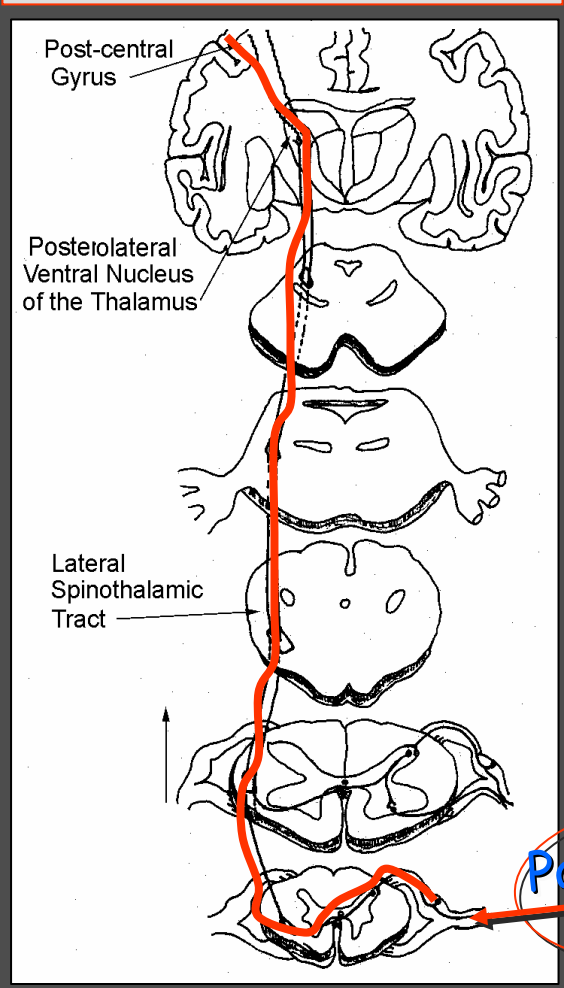
Becker CM, Sampson DA, Rupnick MA, Rohan RM, Efstathiou JA, Short SM, Taylor GA, Folkman J, D'Amato RJ. Endostatin inhibits the growth of endometriotic lesions but does not affect fertility. Fertil Steril 2005;84 Suppl 2:1144-55.

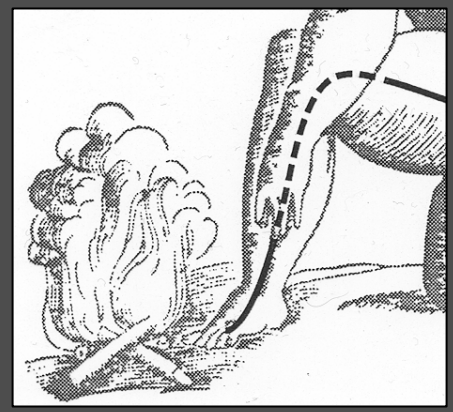
Becker CM, Sampson DA, Short SM, Javaherian K, Folkman J, D'Amato RJ. Short synthetic endostatin peptides inhibit endothelial migration in vitro and endometriosis in a mouse model. Fertil Steril 2006;85:71-7.

Jin K, Mao XO, Greenberg DA. Vascular endothelial growth factor stimulates neurite outgrowth from cerebral cortical neurons via Rho kinase signaling. J Neurobio. 2006;66:236-42.

Does it really make sense to consider the nervous system as an entity that "responds to pain?"

PAIN PATHWAY



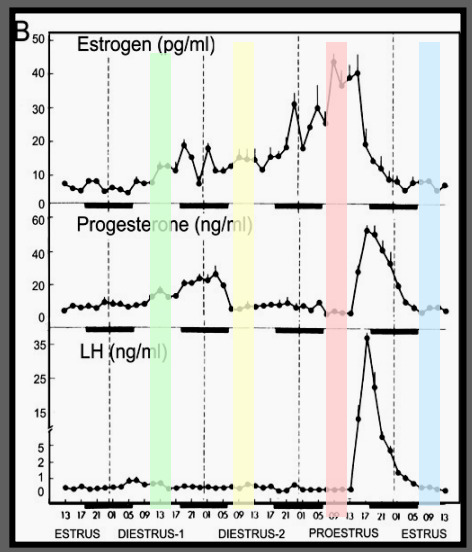


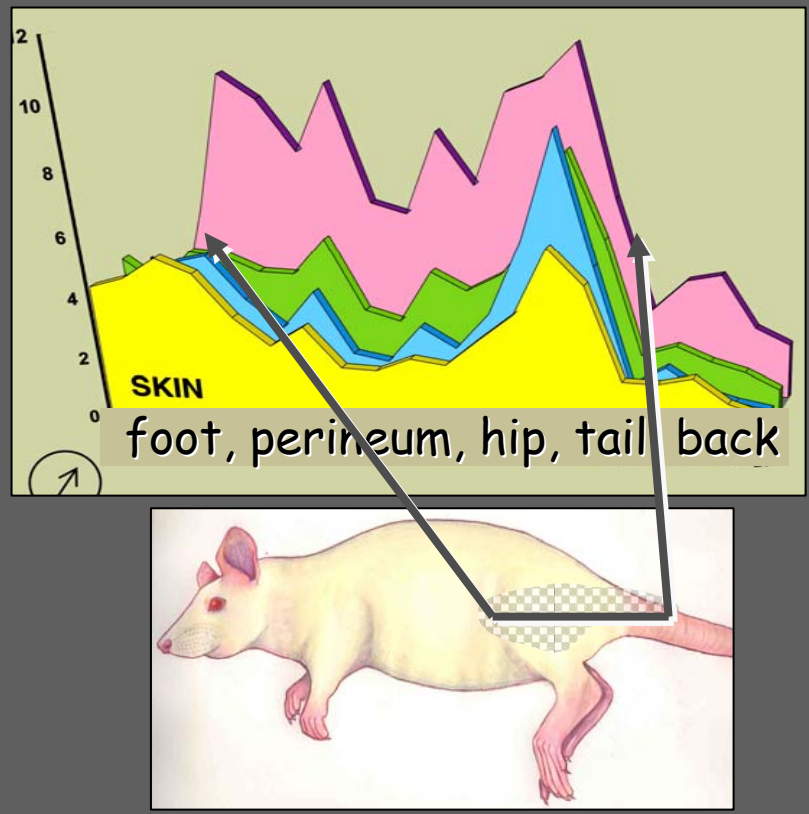
SO???

#5a PLASTICITY… Furthermore the responses can change dramatically during the ovarian cycle (a natural, non-pathophysiological process).

Response magnitudes to gentle brushing of the skin of perineum, hip, and tail, but not foot and back were greater in proestrus (■) than other stages.

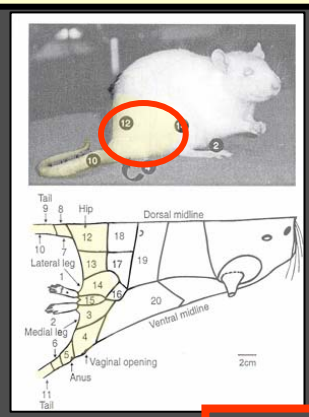
Heather Bradshaw, PhD

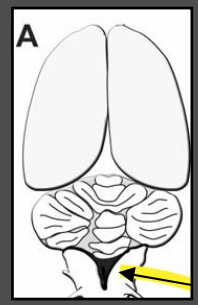




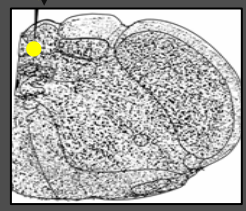
Bradshaw HB, Berkley KJ. J Neurosci 2000;20:7722-7727.

#5a This neuron in the GRACILE NUCLEUS responds to stimulation of skin, bladder, cervix, uterus, colon and vagina in a complex way (i.e., with combination of inhibition and excitation).



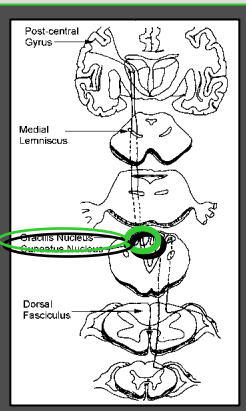


Gracile n.

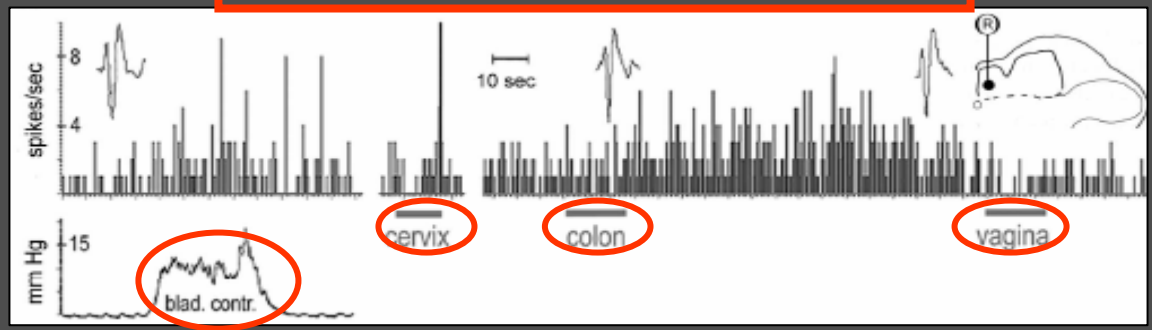


skin: +
bladder: +
cervix: -/+
uterus: ∅
colon: + [delay]
vagina: -

TOUCH PATHWAY



RESPONSES OF ONE NEURON



- Berkley KJ, Hubscher CH. Nature Med 1995;1:766-73.
- Bradshaw HB & Berkley KJ J Neurosci 2000;20:7722-7.
- Peng W, Dmitrieva N, Berkley KJ. 2002

Charles Hubscher

Weimin Peng
Natalia Dmitrieva

Heather Bradshaw