

# CROSSTALK

## Between the CNS and the ANS

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## Goals

- To become acquainted with research over the last 15-20 years which has progressively linked the brain with the immune, endocrine, and intestinal systems.
- To study, in particular, the work of the Venezuelan gastroenterologist Lechin.
- To understand that the sympathetic nervous system actually has two parts, or arms, which can act in opposition to each other.
- To know that two different protocols may address the arms of the sympathetic nervous system thus normalizing both central and peripheral physiologic disorders.

## Crosstalk

- A complex neurocircuitry of crosstalk between the CNS and various nuclei, the immune system, the endocrine and autonomic nervous systems, which are all closely linked and in continuous intercommunication.
- Even on the cellular level, crosstalk occurs:
  - WBC express receptors for neurotransmitters: Fugl, 1995
  - Serotonin induces cytokine release: Laberge, 1996
  - Synthesis of Ach by T-cells; DO, 5-HT, G-mate: Rinner, 1998

## Fuad Lechin MD PhD

- Gastroenterologist, Venezuela
- Post-graduate studies in Paris & Baltimore
- Practice in V. while beginning intensive studies of basic sciences
- Won position at Central Medical School of V.
- Curious about what in the brain controlled the gut.
- Eleven years of psychoanalysis, 5/7 x 11 years with several senior analysts.
- “American physicians are pawns of the drug companies; they should study more of the basic sciences.”

## Methodology

- Started HPLC studies of platelet neurotransmitters in '72
- Added immune and hormones in mid 70's
- Blood studies on monoamines and metabolites, endocrine and immunological studies on normal and diseased patients, before and after supine resting, orthostasis, exercise, glucose load, and different centrally acting drugs on every patient he saw since 1980
- Sleep research lab since 2000
- The only neurochemical lab in the world at a hospital level
- To date 30,000 patients examined.

## Methodology (con't)

- Neither absolute nor isolated nor static values rendered any valuable information about central or peripheral neuroautonomic activities.
- Rather, only global profiles of all parameters responding to physiological and pharmacological stimuli were useful.
- Although NA and Ad plasma values oscillate widely, the normal NA/Ad ratio is 3-5.
- The ratio rises during orthostasis of 1 minute, moderate exercise of 5 minutes, oral glucose ingestion and buspirone, whereas dopamine showed no appreciable change.

## Conclusions

- These and other changes not listed are consistent with two sources, the adrenal glands and the sympathetic nerves, which can function either together or separately: eg associated during exercise and dissociated at orthostasis.
- They function in association during SWS-IV and REM, but are dissociated during SR-2 and SWS-II.
- Both NA and AD increase platelet serotonin stores, but this correlation disappears during exercise, when there is excessive Ad release.
- The positive association of tryptophan and parasympathetic activity is disrupted during exercise, when parasympathetic activity is null.

## Evolution of Thought

- Neural tube buds from neural crest cells (NCC) migrate to abdomen and form neural plexus of intestinal tract
  - Lumsden A et al: Segmental origin and migration of neural crest cells in the hind brain region of chick embryo. Development 1991; 113:1281-1291
- Blood-gut-barrier of intestinal tract similar to BBB
  - Michael Gershon, The Second Brain, HarperCollins 1998
- Lechin becomes convinced that the brain is involved in the cause, or etiology, of all disease.

## Works

- [www.lechin.com](http://www.lechin.com)
- Over 240 publications
- 2001 Nobel Prize in Medicine nomination
  - Asthma & Myasthenia gravis
- 2002 Neurocircuitry & Neuroautonomic Disorders. Karger.
- 2009 Crosstalk between the CNS & ANS: Mechanistic and Therapeutic Considerations for Neuronal, Immune, Vascular, and Somatic-Based Diseases in Maiese, K editor. Neurovascular Medicine. New York: Oxford Univ Press.

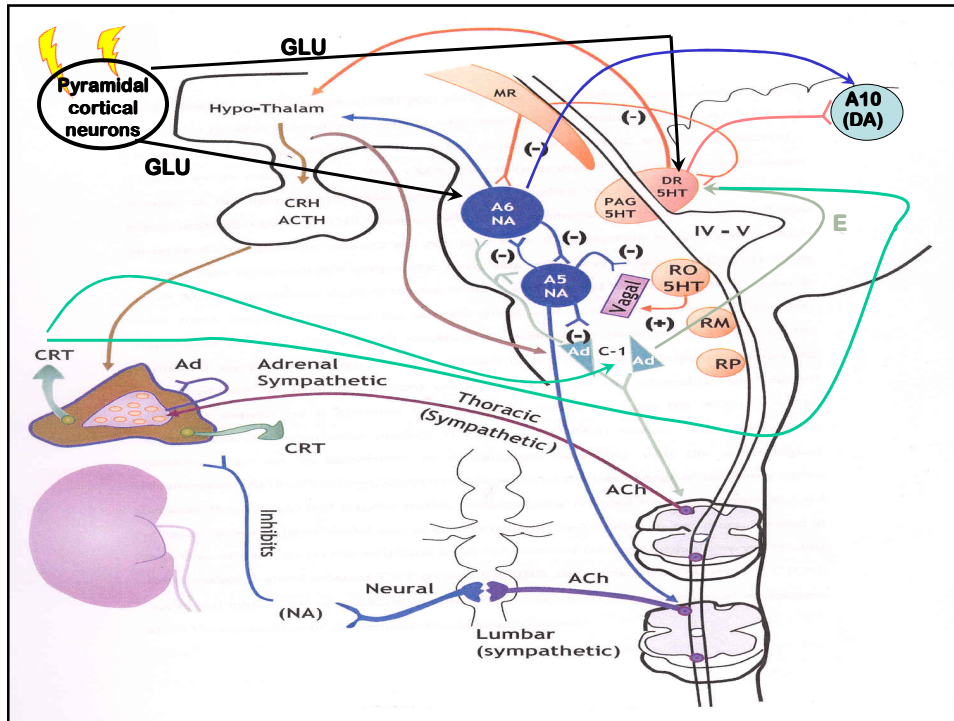
## A6(NA)

locus coeruleus – master controller

Cortical and subcortical connections, so not *directly* reflected in the blood (urine).

Number of neurons increases into adulthood and decreases with age in senescence.

Paralleling this decrease of A-6 is the decline of C-1 (hypoactive adrenals), due to the dominance of A-5; so therapy must be addressed to reducing A-5 dominance, thus restoring A-6 and C-1 activity.



## Neural Sympathetic & A5(NA)

- Arises from the pontomedullary A5 (NA) noradrenergic nucleus.
- Glutaminergic axons for A5 to lateral spinal horns; thence ACh axons to sympathetic chain; then NA axons via sympathetic plexus to organs.
- They release 80-90% of NA and 10-20% dopamine (DA) into the plasma.
- A rigid profile with only slight alternation with the parasympathetic profile.

## Adrenal Sympathetic & C1(Ad)

- Arises from the medullary C1(Ad) adrenergic nucleus.
- Sends glutamatergic axons to the spinal cord, thence ACH axons to the adrenal, which produces 80% Ad, 10% NA, and 10% DA.
- The AS profile presents with abrupt oscillations between the AS and the parasympathetic ANS.

## Serotonin in the PNS

- Emanates from the enterochromaffin cells in the small bowel mucosa; is taken up by the platelets as p-5-HT, and delivered to the liver and lungs, leaving a small amount in the plasma as f-5-HT; does not cross the BBB.
- Via f-5-HT is able to excite the area postrema (a PS-ACH nucleus) outside of the BBB, which in turn is connected to the vagal motor center in positive feedback loop, further enhancing PS drive of the enterochromaffin cells (Bezold-Jarisch reflex) explaining the hyperserotonergic storm of carcinoid patients. This positive feedback loop can be bridled by enhancing A-5 neural sympathetic activity.
- The area postrema is hard-wired to the medullary motor vagal center and to the CNS-5-HT raphe obscurus, which in turn sends motor fibers back to the medullary vagal complex (dorsal motor nucleus and the nucleus ambiguus).

## Endogenous Depression Th-1 autoimmunity

- Absolute predominance of neural over adrenal sympathetic activity (N.S.)
- A5(NA) nucleus exerts maximal inhibition of both the C1(Ad) and vagal medullary nuclei (serotonin stim.)
- Responsible for disappearance of both adrenal and parasympathetic peripheral activities.
- Inhibition of the adrenal glands disinhibits thymus (or the spleen) which redounds in the Th-1 profile.
- NA 80-90% and DA 10-20%
- A5(NA) + MR(5HT) dominance (> A6(NA) + DR(5HT))
- Prolactin chronic and sustained rise

## Example

- One of many cases of multiple sclerosis was an MD ophthalmologist who had lost his vision. He recovered his sight completely (he is now performing eye surgery) with therapy for the Th-1 profile diseases. All types of therapy had previously failed with this patient including steroids,  $\beta$ -interferon, etc. Dermatomyositis, muscular dystrophy, hemolytic anemia, rheumatoid arthritis, Sjogren disease, psoriasis, scleroderma, Raynaud disease, Crohn's enteritis, pemphigus and other Th-1 autoimmune diseases have likewise been successfully treated with this therapy.



## Example of Depression in Urine

	Feb 06	Mar 06	Apr 06	May 08
Ad	5.3	2.0	5.8	7.8
NA	61.6	44.9	34.9	46.6
n/a	11.6	22.45	6.02	5.97
Ser	48.7	120.3	121	126
G-mate	23.9	10.4	22.4	32.1

## Th-2 autoimmunity

- Many other patients have been treated with a Th-2 immune profile. To date (2002) he has successfully treated patients suffering from myasthenia gravis (over 800 cases), thrombocytopenic purpura, Guillan-Barre, atopic dermatitis, stress associated female infertility, gastric malthoma, and non-Hodgkin lymphoma.
- Malignant diseases are included in this group, with the exception of Hodgkin's lymphoma and pancreatic adenocarcinoma.
- Therapy is oriented to increasing noradrenergic dominance.

## Uncoping Stress

- Adrenal gland predominates over neural sympathetic
- Overactivity of C1(Ad) nuclei triggers excitation of vagal medullary nuclei→peripheral parasympathetic nerves activity
- These two branches may alternate
- Ad 80% + NA 10% + DA 10%
- Predominance of Ad and cortisol→TH-2
- f-5HT > p-5HT

## Example of Uncoping Stress in Urine

recent diagnosis of GB cancer M

	May 06	Aug 06	Mar 07
Ad	7.9	4.2	5.6
Nor	9.9	43.3	44.8
n/a	1.3	10.2	8.0
Ser	183	109.3	395.7
G-mate	365.4	18.1	44.9

## Cancer

- Up to the present (2002) he has treated some 3000 advanced cancer patients. Most come to his institution when all conventional therapies had failed. He has presented results in the most important cancer hospitals of the US (including MD Anderson in Houston). They were greatly impressed, but asked for a package treatment like chemotherapy and radiotherapy. They could not accept treatments based on neuropharmacological, neuroendocrinological, or neuroimmunological manipulations. Nor were their hospitals equipped with neurochemical laboratories.

## Steroids

- suppress thymus hyperactivity and the MR(5HT) predominance short term.
- excite the DR(5HT) but not the MR(5HT) neurons.
- suppress neural sympathetic activity, which is enhanced in all TH-1 patients.
- wear out and provoke the exhaustion of both the DR(5HT) and the adrenal gland

## Sleep Disorders

- Short REM latency (no SWS + frequent awakenings) is attributed to the exhaustion of A6(NA) and DR(5HT)
- Prolongation of SWS parallels clinical improvement
- Use NA + 5HT uptake-inhibitor like doxepin 25mg or imipramine 25mg before supper along with NA and 5HT releasing agent like mirtazapine ( $\alpha$ -2 + 5HT-2 antagonist) 15-30mg HS
- In psychotics, may use olanzapine HS which excites A6(NA) neurons (in addition to DA and 5HT effects)
- In elderly clomipramine 25mg before supper and clonidine 0.15mg HS

## Clonidine & Psychosis

- An  $\alpha$ 2-agonist, centrally acting.
- Works on C1-Ad > LC-NA & A5
- Psychosis: over-activity of the adrenal glands.
- deficiency of LC-NA, DR-5HT, & mesocortical DA
- predominance of mesolimbic DA, MR-5HT, & C1-AD
- increased activity of medullary serotonergic nuclei
- reduction of both DR-5HT and LC-NA favors disinhibition of the serotonergic PAG system (responsible for panic in psychotic patients).
- Low ACH (hypoparasyspathetic) permits higher platelet uptake, so elevated p5HT.

