Mast Cell Activation Disorders and Ehlers Danlos Syndromes, Traveling Together in Modern Times

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Icahn School of Medicine at Mount Sinai
Medical Director, Comprehensive Allergy & Asthma Care, PLLC
Our Journey on mother Earth: “Life on the edge”

(Our) immune systems ... (are) embodied expectations of injury and the corresponding programs of protection and repair.”

- Peter Sloterdijk
The Great Wall of China...
Protection along the Northern Border of China

- A fortification!
- Built for defensive purposes in the 3rd century
- It is
- - 1500 miles along
- - 6 meters wide
In imperial times, the Great Wall of China was easily breached and was not in itself a very effective defense against resolute adversaries.

Rather, it was a communication route and housed, far from the imperial centre, a string of lonely guards who quickly engaged invaders and slowed their progress, while alerting and beckoning more substantial back-up forces.

—Christophe Benoist & Diane Mathis
Mast cells in autoimmune disease Nature, 2002
Innate Immune System Components

Anatomic Barriers
- Skin - 22 square feet
- Mucosa of the
  - Gastrointestinal tract, 25 feet,
  - Respiratory tract, 25 sq. feet,
  - Urogenital tract, 20 sq. feet

Physiologic Barriers
- Temperature, pH, Flow
- Inflammatory Mediators -> redness, swelling, heat, pain

Immune Cells
- NK cells, DCs, Macrophages

Antimicrobial response
- Defensins
- Cathelecidins/
  Psoriasin
- Reactive Oxygen Species

Inflammatory response
- Cytokines,
  Chemokines
- Neuropeptides
- Reactive Oxygen Species

Recruiting the adaptive Immune response
- T cells, B cells
Two important observations are not captured in this common depiction of our innate immune system...
Mast Cells: Beyond Allergy?
Mast Cell Orders

Mast Cell Biology 101
Mast Cell Orders:
Homeostasis: Keeping the Peace

Like a police officer, who strives to serve and protect a neighborhood, “rookie” Mast Cells arrive and learn to meet the needs of local community of cells and tissue.

- Trained and prepared with different tools, each individual police officer must learn how to serve and protect his or her assigned, local neighborhood.

Depending on the nature and severity of the danger, the police officers will respond with a defined, regulated series of actions.
Depending on the nature and severity of the danger, the police officer will respond with a defined, regulated series of actions.

911... what’s your emergency?

Officer Sees This...

And then does this...
Armed with invariant sensors, Mast Cells are hardwired to recognize and then react with a defined set of chemical and physical responses, in order to contain “usual suspects” = harmful substances and microorganisms.

- **TLR 3, 7**
- **CR 3, 4**
- **FcR, FcReI**
- **Enzymes**: Chymase, Tryptase
- **Chemokines**: Tumor Necrosis factor
- **Histamine**, **Heparin**, **Leukotrienes**
- **Cytokines**: NGF
- **IgE, IgG**
- **Mold, Bacteria, Parasites, Worms, Viruses**
Mast Cells act as the local Peace Keepers, maintaining homeostasis in the surrounding microenvironment.

And, through chemical mediators and receptors, will call for...

Depending on the nature and severity of the danger, mast cells will respond with a defined set of mediators, calling for appropriate help.

- Code Blue
- Code Red
- Code Orange
- Parasite
- Virus
- Bacteria
- Insect sting

Vascular leakage -> Serum Proteins -> Swelling, Itch
MAST CELL (MC) 101

- MCs are found in most parts of the body are well known for role in allergic/anaphylactic reactions
- MCs are now recognized to play a role in a number of inflammatory diseases in the skin, respiratory tract, joints, Gastrointestinal tract, nervous system, bladder
- MCs contain > 500 secretory granules and can de novo synthesize and release mediators following stimulation, via degranulation or differential, piecemeal release
Mast Cells = Border Patrol, recognizing and responding to clear and present dangers
Mast Cells = Border Patrol, recognizing and responding to clear and present dangers

“usual suspects”
(1) Infectious, nonself threats, that have as pattern recognition receptors (PRRs) and are recognized by evolutionarily conserved membrane-bound Toll-like receptors (TLRs), on MCs.

(2) Endogenous, self alarm signals, indicating danger:
breakdown products of hyaluron (made when vessels are damaged). mammalian DNA, RNA, heat shock proteins (Hsps), interferon a, interleukin-1beta, CD40-L
Our Immune system: defense against dangers = infectious agents, toxins and trauma...
Immune System Profiles

Good Bacteria:
- Lactococcus
- Lactobacillus
- Lactobacillus rhamnosus

Bad Bacteria:
- Clostridium perfringens
- Staphylococci
- Escherichia coli

Wanted for urinating on fire hydrants and chasing cats.
Profiling by Our Immune system = pro·fil·ing is the practice of attempting to understand an individual or group based on general characteristics or on past behaviors.

http://www.yourdictionary.com/profiling#EtIRjKw4VP5hxzvS.99
Port of Entry, “vetting” process—to allow entry to entities that support and may enhance our existence, survival
Dark Side of Mast Cell Activation

Mast Cells are best known for “Allergies”

Allergen-IGE-IgE Receptor
Mast Cell Activation

Immediate Release
Granule contents: Histamine, TNF-α, Proteases, Heparin

Over Minutes
Lipid mediators: Prostaglandins, Leukotrienes

Over Hours
Cytokine production: Specifically IL-4, IL-13

Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes

Wheezing
Bronchoconstriction

Mucus production
Eosinophil recruitment
CMC Activation after Complement or IGG bound pathogens,

**MC release**
- Tryptase (proteases)
- Histamine

Leukotrienes, Interleukin-1, Interleukin-6, CXCL8, GM-CSF, Tumor Necrosis Factor

TLR-pathogen mediated Mast Cell Activation

- Toll Like Receptors on Mast Cells bind pathogens PRRs for components of bacteria and fungi
  - No Release of Proteases (tryptase)
  - No Histamine Release

Leukotrienes, Interleukin-1, Interleukin-6, CXCL8, GM-CSF, Tumor Necrosis Factor

Mast Cell responses to pathogens. Jean Marshall
Nature Reviews Immunology, 2004 (4): 787-799
Mast Cells as “Local Peace Keepers”

Defense and tissue repair

1. Bacteria and other pathogens enter wound
2. Platelets from blood release blood-clotting proteins at wound site
3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases
4. Neutrophils secrete factors that kill and degrade pathogens
5. Neutrophils and macrophages remove pathogens by phagocytosis
6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair
7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired
Mast Cell Disorders

Mast Cell Activation Disorders 101
Golden age of medicine = Age of immune dysregulation?

Increased Burden of Autoimmune and Allergic Disorders

The middle of the 20th century has often been described as a golden age of medicine: scientific advancement and miraculous medical breakthroughs:

- the bacteriological revolution
- the flowering of scientific research and pharmaceutical development that is associated with World War I
- changes in medical education and public health

Adapted from Bach, NEJM 2002

“Searching for a Golden Age”
University of Pennsylvania
Epidemic of Hypersensitivity Disorders: Role of Mast Cell Dysregulation?

Adapted from Theoharides, NEJM 2015

Adapted from Bach, New Eng J Med 2002

Graph showing trends from 1950 to 2000:
- Crohn’s Disease
- Multiple Sclerosis
- Type 1 Diabetes
- Asthma
Mast Cell Activation Disorders (MCAD): a collection of disorders characterized by...

- Accumulation of pathological mast cells in potentially any or all organs and tissues
- Aberrant release of variable subsets of mast cell mediators, leading to one or more symptoms (suggestive of systemic mast cell degranulation)
Proposed Diagnostic Criteria for Mast Cell Activation Disorders

(1) Episodic Signs & Symptoms Consistent with Mast Cell (MC) Activation, affecting 2 or more organ systems

(2) Response to therapy – decrease in frequency, severity or resolution of symptoms with anti-MC mediator therapies or MC stabilizers

(3) Evidence of an increase in validated urinary or serum markers of MC activation; increased burden of tissue mast cells (CD117) or chronically activated mast cells (CD117+ and CD25+/CD2+/CD30+)
Proposed Criteria for MCAS Diagnosis:
Rule out Primary MCAS and Secondary Causes of MC activation, clinical entities that mimic MC activation

**Cardiac conditions:** Coronary hypersensitivity (the Kounis syndrome)* Postural orthostatic tachycardia syndrome

**Endocrine conditions:** Fibromyalgia Parathyroid tumor Pheochromocytoma Carcinoid syndrome

**Digestive conditions** Adverse reaction to food* Eosinophilic esophagitis* Eosinophilic gastroenteritis* Gastroesophageal reflux disease; Gluten enteropathy; Irritable bowel syndrome; Vasoactive intestinal peptide–secreting tumor

**Immunologic conditions:** Autoinflammatory disorders such as deficiency of inter-leukin-1–receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*

**Neurologic and psychiatric conditions** Anxiety; Chronic fatigue syndrome Depression; Headaches; Mixed organic brain syndrome; Somatization disorder; Autonomic dysfunction; Multiple sclerosis

**Skin conditions** : Angioedema* Atopic dermatitis* Chronic urticaria* Scleroderma*
# Mast Cell Activation Disorder: Signs and Symptoms

## Mastocytosis

(Escribano et al, JACI 124:514)

<table>
<thead>
<tr>
<th>Skin Lesions</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritis</td>
<td>82%</td>
</tr>
<tr>
<td>Flushing</td>
<td>56%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35%</td>
</tr>
<tr>
<td>Abdominal Cramping</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Neuropsychiatric Symptoms** 23%

<table>
<thead>
<tr>
<th>Abdominal Pain</th>
<th>94%</th>
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</thead>
<tbody>
<tr>
<td>Dermatographism</td>
<td>89%</td>
</tr>
<tr>
<td>Flushing</td>
<td>89%</td>
</tr>
<tr>
<td>Headache</td>
<td>83%</td>
</tr>
</tbody>
</table>

**Neuropsychiatric** 67%

<table>
<thead>
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<th>Neuropsychiatric</th>
<th>67%</th>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>67%</td>
</tr>
<tr>
<td>Rhinitis (Naso-ocular)</td>
<td>39%</td>
</tr>
<tr>
<td>Asthma</td>
<td>39%</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>17%</td>
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<table>
<thead>
<tr>
<th>Nonclonal Mast cell activation disorders</th>
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<tr>
<td>Hamilton, J Allergy clin Immunol 128;147</td>
</tr>
</tbody>
</table>
- **Mast cells** are found in most parts of the body.

- **Mast cells** have a role in allergic/anaphylactic reactions as well as other inflammatory diseases in the skin, respiratory tract, joints, gastrointestinal tract, nervous system, bladder.

- **Mast cell mediated disorders worsen with stress**
Airway reactions, (70% reactions)
Throat tightening, Throat Swelling
Nasal congestion, Rhinorrhea
Wheezing, Dyspnea, Chest Tightness

Gastrointestinal tract (30-45% reactions)
Nausea, Cramping
Abdominal Pain
Vomiting, Diarrhea

Gastrointestinal tract

Brain (> 20% reactions)
Sense of uneasiness, angst
Headache, Dizziness
Confusion, Tunnel Vision

Heart, Blood Pressure (10-45 % reactions)
Fainting, Chest Pain
Fast Heart Rate, Palpitations (pounding)
Weak pulse, Dizziness

Joint and Muscle Pain

Skin (80-90% reactions)
Hives (Urticaria), Itch
Flushing, Swelling (Angioedema)

Genito-Urinary tract (>10% reactions)
Uterine Cramping
Swelling -labia

Skin
MCAD can be...

“Aberrant release of variable subsets of mast cell mediators”

- Histamine
- Leukotrienes
- Prostaglandins
- Tumor Necrosis Factor
- Interleukins
Serotonin
Nerve Growth Factor
Enzymes
Chymase Tryptase
Chemokines
Tumor Necrosis factor
Histamine
Heparin Leukotrienes
Cytokines
Chymase
Tryptase
Enzymes

Mast Cell

“I’ll do some tests rather than give you a guess.”
(2) Measuring Mast Cell Activation Markers, Inflammatory Mediators

Immediate Release
Granule contents:
Histamine, TNF-α, Proteases, Heparin

Over Minutes
Lipid mediators:
Prostaglandins, Leukotrienes

Over Hours
Cytokine production:
IL-4, IL-6, IL-13

Pathology - spindle
MC, MC aggregates

CD2, CD25 Expression

Serum, Urine Histamine

Serum Tryptase

Urine PGD2, 11-beta PGF2

IgE

Allergens

FcεRI

CD2, CD25

Expression

Histamine

PGD2, 11-beta PGF2
(3) Response to Treatment: Targeting MC/MC Inflammatory Mediators

**Immediate Release**
Granule contents: Histamine, TNF-α, Proteases, Heparin

- Sneezing
- Nasal congestion
- Itchy, runny nose
- Watery eyes

**Over Minutes**
Lipid mediators: Prostaglandins, Leukotrienes

- Wheezing
- Bronchoconstriction

**Over Hours**
Cytokine production: Specifically IL-4, IL-13

- Mucus production
- Eosinophil recruitment

**Histamine Blockade**
Tricyclic Agents

**Corticosteroids**
MC stabilizers

**Anti-IGE mAb**

**Traditional Chinese (TCM) Herbal Medicine Acupuncture**
Spectrum of Mast Cell Disorders: clonal (c-kit pathway) vs nonclonal
adapted from Akin et al, JACI

1. Typical MC mediated clinical symptoms
2. Increase (transient/sustained) tryptase**
3. Response to anti-MC/MC-mediator treatment(s)

Primary MCAS

MMAS  SM  MCL

Secondary or Idiopathic MCAS

MAST CELL PROLIFERATION

**Decreased likelihood MMAS, SM or MCL by bone marrow MC aggregates diminishes significantly in those with tryptase < 20 ng/mL
<table>
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<tr>
<th>Classification of MCAS</th>
<th>Symptoms Associated with monoclonal mast cell population</th>
</tr>
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| **Primary (c-kit mutation)** | A. Mastocytosis  
B. Monoclonal Mast Cell Activation Syndrome (MMAS) |
| **Secondary** | A. Allergic (IGE mediated) Disorders  
B. MC activation associated with chronic inflammatory/neoplastic disorders  
C. Physical Urticarias  
D. Chronic Autoimmune Urticaria |
| **Idiopathic** | A. Anaphylaxis  
B. Angioedema  
C. Urticaria |

- Mast Cell Activation Syndrome (MCAS)  
  - Hyper-tryptasemia (tryptase mutation-autosomal dominant)
Mast Cell Disorders

Treatment strategies
Mast Cell Activation Disorders
Guidelines to Diagnosis and Treatment

1. Accurate, “Best Working” Diagnosis
2. Assess severity
3. Education for partnership in Care
4. Treatment/Management
5. Return to review and reflect on diagnosis and treatment— are you or are you not better
Mast cell activation syndrome is easily treated, if it's recognized

Last Updated: 2011-06-10 19:15:17 -0400 (Reuters Health)

By Anne Harding

NEW YORK (Reuters Health) - Patients with mast cell activation syndrome (MCAS) frequently go for years without an accurate diagnosis, but once diagnosed and treated, their response is likely to be "excellent," according to a new report.
Who's Holding Up the Queue? Delay in diagnosis and treatment of MCAD

Mast cell mediated allergy (Immune mediated) disorders now cause problems of increased complexity and commonly involves several organ systems, so patients are often referred to a succession of different specialists, resulting only in confusion.

Allergy: the unmet need, Royal College of Physicians, 2006

Paging ZocDoc for the future of medicine
ZocDoc, turning health care into a one-click experience, upends traditional medical practice.

Knowledge of good allergy management in practice is therefore minimal or non-existent.

Allergy: the unmet need, Royal College of Physicians, 2003

1. **Patient awareness**
   “Do I have a problem that warrants medical care”

2. **General Practitioner Awareness**
   Allergy barely features in the undergraduate medical curriculum
   “Does this patient have an inflammatory disorder that warrants specialist attention”

3. **Specialist Awareness**
   Lack of specialists in academic medical centers and communities means virtually no clinical training is available.

HOMIK, J Rheumatol 2011;38;1225-1227
Mast Cell Activation Disorders
Guidelines to Diagnosis and Treatment

1. Accurate, “Best Working” Diagnosis
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5. Return to review and reflect on diagnosis and treatment- are you or are you not better

- Symptoms?
- Better with treatments that target MC or MC mediators?
- Test Results?
Common MC-Mediated Disorder: Rhinitis

- Sneezing, Itching: Nose, eyes, ears, palate
- Runny nose, Postnasal drip, back drip
- Congestion, Headache, Facial Pain, Dental pain
- Lose sense of smell, taste
- Headache, Earache
- Tearing, Red eyes, Eye swelling
- Fatigue
- Snoring, Poor sleep, Drowsiness, Malaise
- Sore throat, hoarseness. Mouth breathing
- Acute or chronic sinusitis; Otitis media
- Sleep disturbance or apnea
Mast Cell Activation Disorders
Guidelines to Diagnosis and Treatment

1. Accurate, “Best Working” Diagnosis
2. Assess severity
3. Education for partnership in Care

4. Treatment/Management

5. Return to review and reflect on diagnosis and treatment- are you or are you not better
MCAD/MCAS Treatment: Targeting MCs or MC derived Inflammatory Mediators

**Immediate Release**
- Granule contents: Histamine, TNF-α, Proteases, Heparin

**Over Minutes**
- Lipid mediators: Prostaglandins, Leukotrienes

**Over Hours**
- Cytokine production: Specifically IL-4, IL-13

**Histamine Blockade**
- Tricyclic Agents

**Anti-IGE mAb**

**Corticosteroids**
- MC stabilizers
- Cytokine Antagonists

**Leukotriene Blockade**
- Cyclooxygenase Inhibitors

**Nutraceuticals**
- DAO supplement
- Vitamin C
- Quercetin
- Stinging Nettle
- Butterbur

**Traditional Chinese (TCM) Herbal Medicine**
- Acupuncture

Theoharides et al, NEJM 2015; Engler et al, J Allergy Clin Immunol, 2009;
Mast Cells: Defense and Wound Repair
• MCs are common at sites that are in close contact with the external environment (skin, gastrointestinal tract and airways), they are distributed in virtually all organs and vascularized tissues

• Mast cells are found abundant at sites of acupoints
Impact of manual stimulation by an acupuncture needle on anesthesia

Acupuncture:

- Increased the density of mast cells
- Increase in MC degranulation
- Pretreatment of the acupuncture point with disodium chromoglycate not only counteracted the phenomenon of degranulation but also reduced analgesic effect of acupuncture.
Better Health = Mast Cell suppression ???

MCAD/MCAS Treatment: Targeting MCs or MC derived Inflammatory Mediators

Corticosteroids
MC stabilizers
Cytokine Antagonists

Histamine Blockade
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Quercetin
Stinging Nettle
Butterbur

Traditional Chinese (TCM)
Herbal Medicine
Acupuncture

Theoharides et al, NEJM 2015; Engler et al, J Allergy Clin Immunol, 2009;
Like most immunologists, I had thought that immunity is controlled by the cells of the “adaptive” immune system (lymphocytes) or the more ancient “innate” immune system (such as macrophages, dendritic cells, and the complement system).

- Polly Matzinger, Science 2002
(1) Infectious, non-self threats, that have as pattern recognition receptors (PRRs) and are recognized by evolutionarily conserved membrane-bound Toll-like receptors (TLRs), on MCs.

(2) Endogenous, self alarm signals, indicating danger: breakdown products of hyaluron (made when vessels are damaged), mammalian DNA, RNA, heat shock proteins (Hsps), interferon a, (an inducible protein often made by virus-infected cells), interleukin-1beta, CD40-L (a surface molecule on activated platelets and activated T cells), and
| Primary (c-kit mutation) | A. Mastocytosis  
B. Monoclonal Mast Cell Activation Syndrome (MMAS) |
|-------------------------|-------------------------------------------------|
| Secondary               | A. Allergic (IGE mediated) Disorders  
B. MC activation associated with chronic inflammatory/neoplastic disorders  
C. Physical Urticarias  
D. Chronic Autoimmune Urticaria |
| Mast Cell Activation Syndrome (MCAS) |  
- Hyper-tryptasemia (tryptase mutation-autosomal dominant) |
| Idiopathic              | A. Anaphylaxis  
B. Angioedema  
C. Urticaria |
Allergic Reactions

Allergen-IGE-IGE receptor triggered Mast Cell Activation

First exposure to a sensitizing antigen causes B-cells to make IgE antibodies

IgE binds to mast cells

Subsequent exposure to antigen causes mast cell action, releasing allergenic mediators

Allergy: e.g. hives, hay fever, asthma, food allergy
While the cause of the condition isn't clear... "we have some clues that it might be something to do with the signaling that goes on at the mast cell surface." - Dr. Matthew J. Hamilton of Brigham and Women's Hospital, Boston, 2011
| Primary (c-kit mutation) | A. Mastocytosis  
B. Monoclonal Mast Cell Activation Syndrome (MMAS) |
|-------------------------|--------------------------------------------------|
| Secondary               | A. Allergic (IGE mediated) Disorders  
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**Mast Cell Activation Syndrome (MCAS)**
- Hyper-tryptasemia (tryptase mutation-autosomal dominant)

| Idiopathic               | A. Anaphylaxis  
B. Angioedema  
C. Urticaria |

**Mast Cell Activation Syndrome (MCAS) Endotypes:**
- from  
- Clinical Phenotypes to Molecular Approaches
Inherited Connective Tissue Disorders and Mast Cell Activation Syndromes
EDS- Hypermobility Syndrome = a hereditary condition with predominantly musculoskeletal / rheumatologic manifestations...

It is now emerging as a multi-systemic disorder with widespread manifestations...

Castori, Dermatology 2012
It is now emerging as a multi-systemic disorder with widespread manifestations...

Castori, Dermatology 2012
Sir,
The atopic status and total serum IgE levels have been determined in thirty-three scoliotics. Prick tests to twenty-three common allergens and a control solution were performed in each subject. The subjects were regarded as atopic if one or more solutions produced a weal 3 mm or more in diameter. The total IgE concentration was determined in ten patients by a radioimmunoassay technique. A value of 800 units/ml was taken as the upper limit of normal (Gleich, 1971; Johansson, Bennich & Berg, 1972).

Only five (23%) of the twenty-two patients with congenital, idiopathic, or postpoliomyelitis scoliosis were atopic. The total IgE was normal in four of the non-atopics and one atopic. However, six (86%) of the seven subjects with Marfan’s syndrome were atopic, and the total IgE was raised in the four of them in whom it was measured. In the single non-atopic individual it was normal. Three of the remaining four subjects had neurofibromatosis and were atopic; the fourth had fragilitas ossium, was atopic, and had a total IgE concentration of 4000 units/ml.

Thus the eleven subjects with Marfan’s syndrome, neurofibromatosis, and fragilitas ossium were more frequently atopic ($P < 0.01$) and showed higher total IgE levels than the ‘control’ group of the other twenty-two scoliotics. The three conditions in question are usually transmitted by autosomal dominant genes and it is therefore possible that these are linked to the genes responsible for atopy. Study of the HL-A types in these connective tissue disorders may throw further light on these relationships.

J. M. SHNEERSON
Cardiothoracic Institute,
Brompton Hospital,
London SW3 6HP

References
GLEICH, G.J. (1971) Journal of Laboratory and Clinical Medicine, 77, 690.
• 10 patients were tested for objective evidence of mast cell activation, including
  • serum tryptase levels were normal
  • Serum IGE < 20 kiu/ml (3-20)
  • 24 hour urine histamine collections were unremarkable.

• All Ehlers Danlos Syndrome patients appear to display non-IgE mediated MC Activation and symptoms = partly or well controlled by anti-mediator therapy and avoidance of triggers.
  • Silverman, Louisias and Maitland, ACAAI, 2013
Got M.C.A.S.?

• Symptoms?
  • Rhinitis, Asthma
  • IBS
  • Urticaria
  • Anaphylaxis

• Better with anti-MC treatments?
  • Partial response

• Test Results? Urine, blood
  • – biopsies CD117, CD25 +ve
MCAS and EDS: Objective Data

- Blood markers (histamine, tryptase)
- Urine Markers (histamine, Prostaglandins, Leukotrienes)
- Tissue Biopsy - Mast Cell Pathology
The Curse of a ‘None of the Above’ Disease

Undark 07.24.2017 / BY Ed Cara

• Millions of Americans languish with elusive or poorly understood diseases. New genetic research — and some humility from doctors — might help.

• “The whole culture of medicine is set up very badly to treat people who are unusual.”

• “A good number of them cry, because they’ve been told it’s nothing for such a long time.”

Allergic To Everything: Woman With Mast Cell Disease Gets Diagnosed After A Lifetime Of Allergic Reactions

• May 3, 2015 5:23 PM By Samantha Olson


When flexible becomes too flexible
Facing a life of loose limbs
https://www.washingtonpost.com/national/health-science/when-flexible-becomes-too-flexible/2014/03/07/4d669e30-69c5-11e3-ae56-22de072140a2_story.html?utm_term=.afc5c5891eb1
One Gene Mutation Links Three Mysterious, Debilitating Diseases: Hypertryptasemia, tryptase > 9 ng/ml (personal communication with J. Milner, MD, PhD)

• “On a good day, my shoulders, knees, and hips will dislocate two to five times apiece. The slightest bump into a table or door will bloom new bruises on my arms and legs or tear a gash in the thin skin on my hands. My blood pressure will plummet each time I stand, making me feel woozy, nauseated, and weak. I’ll have trouble focusing and remembering words. I’ll run my errands from underneath an umbrella to prevent an allergic reaction to the Sun.”

• -Kate Horowitz, Mental Floss, October 2016
Mast Cell Derived Enzyme Mutation and EDS/JHS?

- Our findings link findings (germline) duplication in TPSAB1 (the alpha-tryptase gene) with:
  - Irritable bowel syndrome
  - Cutaneous complaints
  - Connective Tissue Abnormalities
  - Dysautonomia

Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number
An "endotype" is a subtype of a condition defined by a distinct pathophysiological mechanism.

Criteria for defining MCAS endotypes on the basis of their phenotypes and putative pathophysiology.

Using these criteria...
Mast cells

- are found in most parts of the body
- have a role in allergic/anaphylactic reactions and other inflammatory diseases in the skin, respiratory tract, joints, gastrointestinal tract, nervous system, bladder
- *worsen with stress*

MCAD Diagnosis: (1) Symptoms, (2) Data, (3) Response to MC medications
Key to MCAD treatment: Early Diagnosis, Education to reduce stress

You're fine, take the lollipop!
I now believe that the ultimate power lies with the tissues. When healthy, tissues induce tolerance. When distressed, they stimulate immunity, and (continuing down this path) they may also determine the effector class of a response.