Ehlers-Danlos Syndrome and its Fellow Traveler, Mast Cell Activation Syndrome

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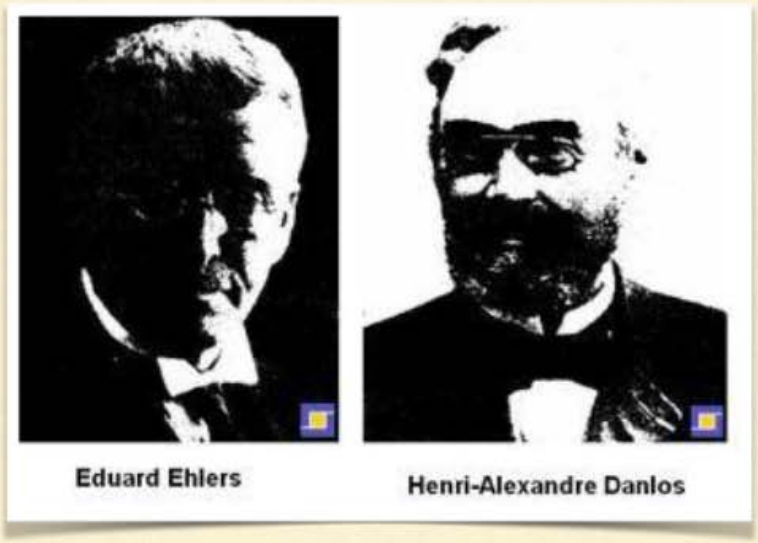
Dr. Ehlers and Dr. Danlos
described a distinct order including lax joints, hyper-extensible, skin and bruising



- 400 B.C.: **Hippocrates'** *Airs, Waters and Places*
- 1657: Dr Job Janszoon **van Meekeren**'s case history of George Albes, a boy with hyperextensible skin
- 1892: Dr A N **Chernogubov**'s detailed association between hypermobile joints and skin findings
- 1901: Dr Edvard **Ehlers**' a case history describing a distinct disorder including lax joints, hyperextensible skin, and bruising
- 1908: Dr Henri-Alexandre **Danlos**' case history describing a disorder much like that described by Ehlers
- 1936: Frederick **Parkes-Weber** suggested "**Ehlers-Danlos Syndrome**"
- 1998: Dr Peter **Beighton *et al***'s publication of the **Villefranche** nosology classifying Ehlers-Danlos Syndromes

Ehlers-Danlos Syndrome is a heritable disorder of connective tissue (HDCT)

Heritable Disorders of Connective Tissue (HDCT) are passed from parent to child

HDCTs affect the "cellular glue" holding tissues of the body together

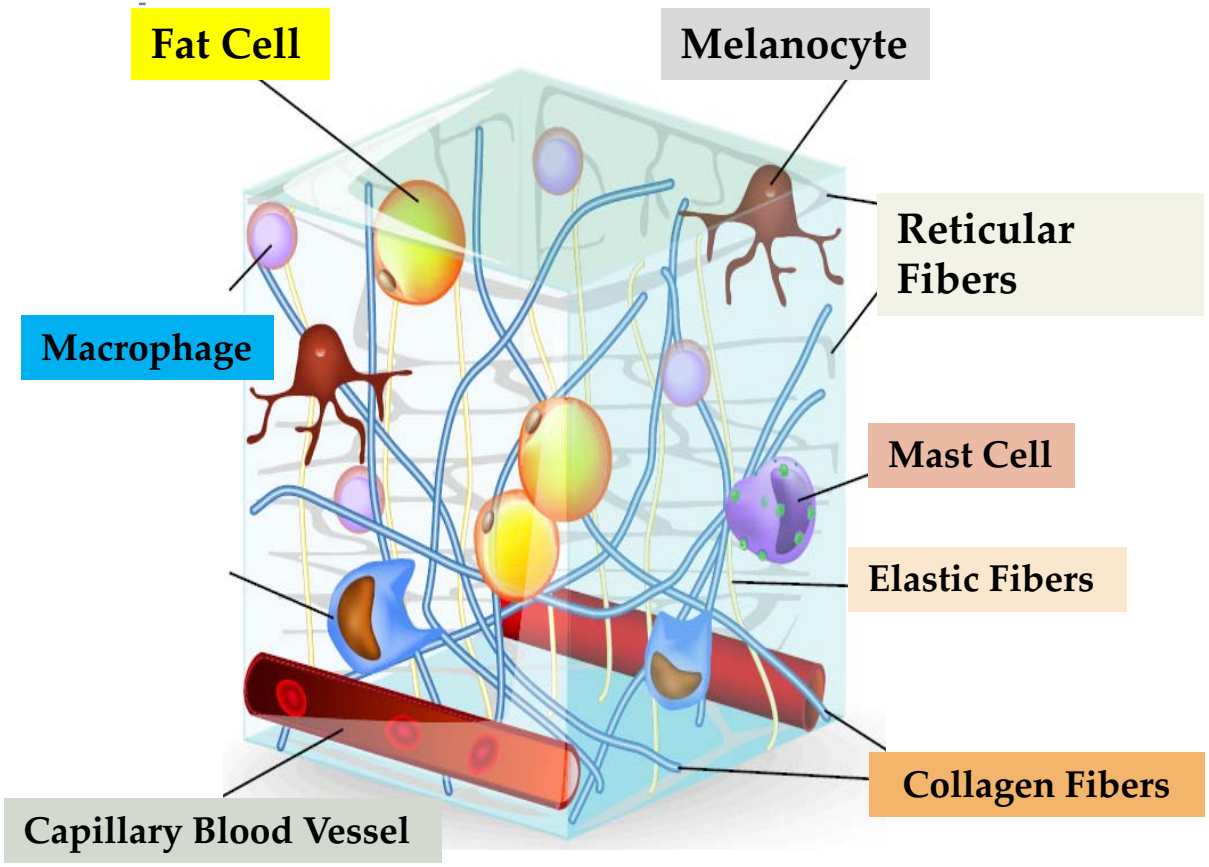
- change the look, growth, or function of tissues such as skin, bones, joints, heart, blood vessels, and numerous other organ systems

There are multiple types of HDCT:

- EDS
- Marfan Syndrome, Osteogenesis Imperfecta, Loeys-Dietz Syndrome, Stickler Syndrome, Alport Syndrome, Beal's Syndrome, Epidermolysis Bullosa, and many, many more.

But... What is Ehlers-Danlos Syndrome (EDS)?

The Structure of Connective Tissue



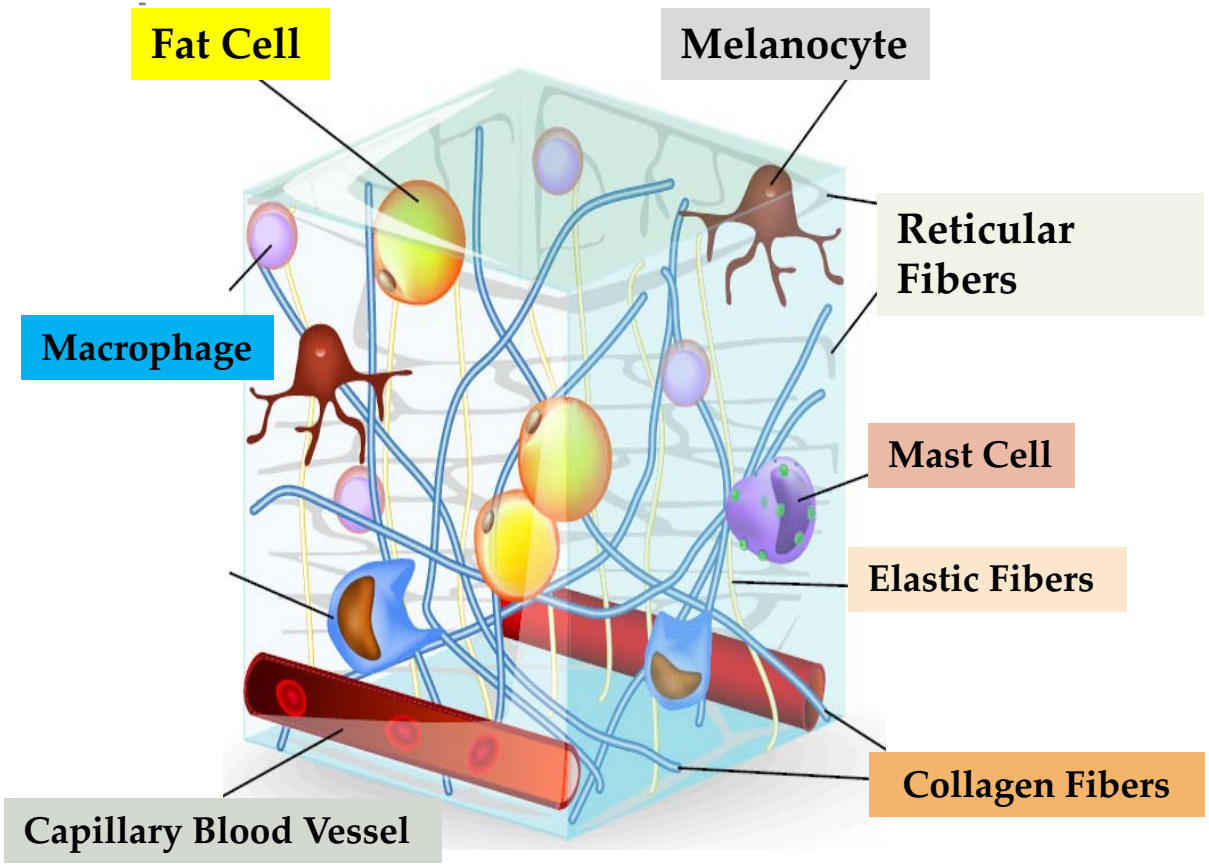
Cells

- Fibroblasts, adipocytes, RBCs, WBCs (Mast Cells), chondroblasts, osteoblasts

Extra-Cellular Matrix

- Ground Substance
- Fibers
- Microfibrils

Factors that Influence the Structure of Connective Tissue



- **genetic factors**
- **environmental triggers**
- **immune dysregulation**

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders

Castori, 2012

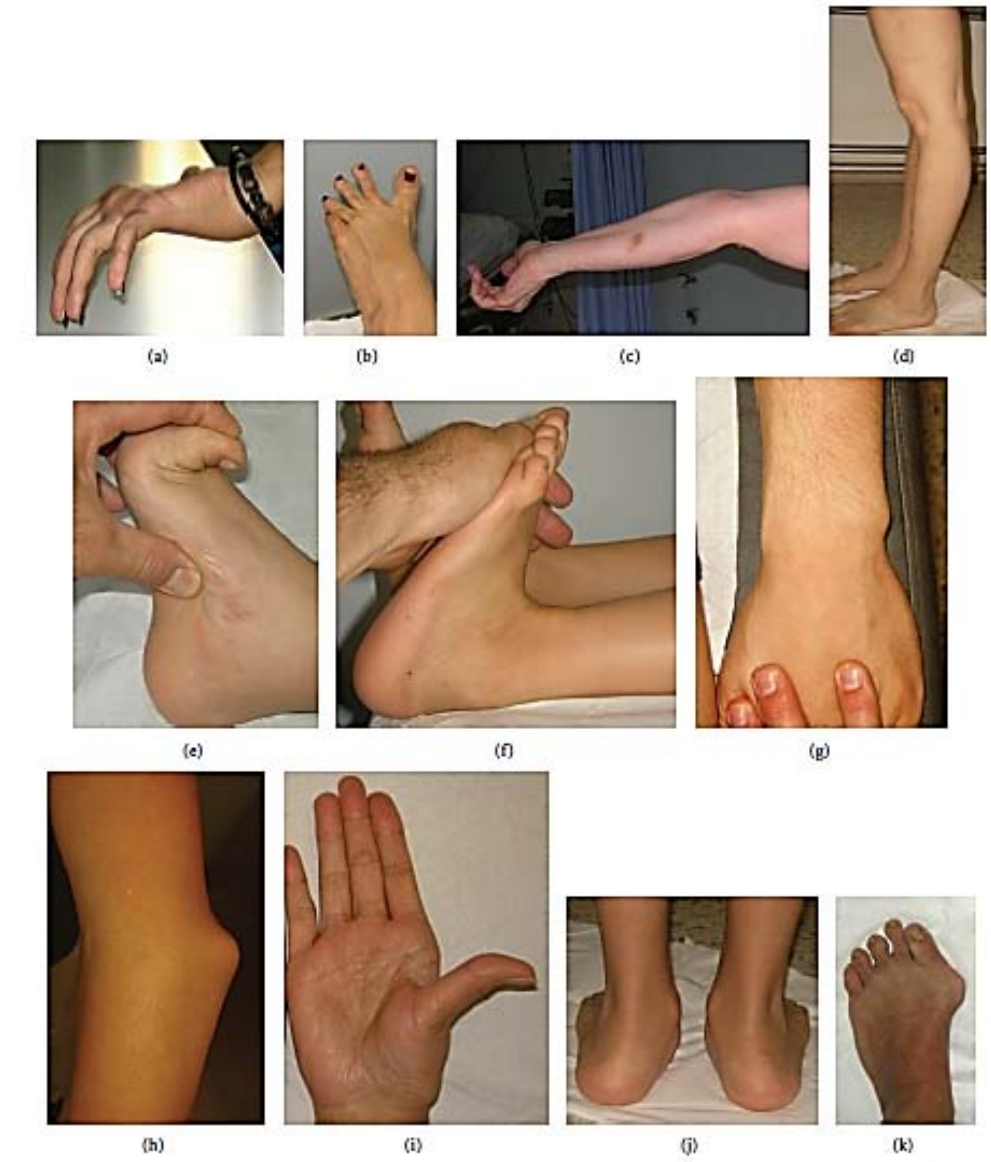
Subtype	Inheritance AD AR XLD	Gene (s)
Classic Skin extensibility, Jt hypermobility	AD	COL5A1 COL5A2
Hypermobility/JHS	**AD???**	**Mostly unknown**
Vascular	AD	COL3A1
Kypho-scoliotic	AR	PLOD1
Arthrochalasia	AD	COL1A1, COL1A2
Dermatosparaxis	AR	ADAMTS2

- Group of inherited connective tissue disorders caused by defect in collagen synthesis
  - structural proteins or
  - proteins/

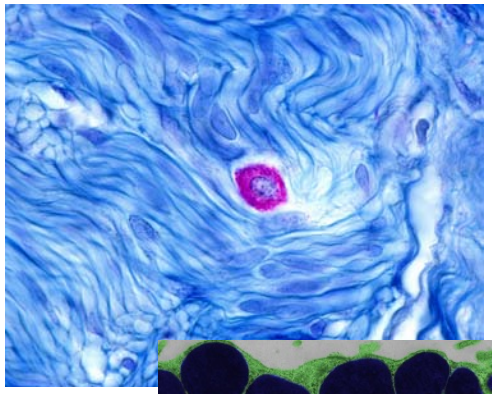
  enzymes involved with collagen biogenesis

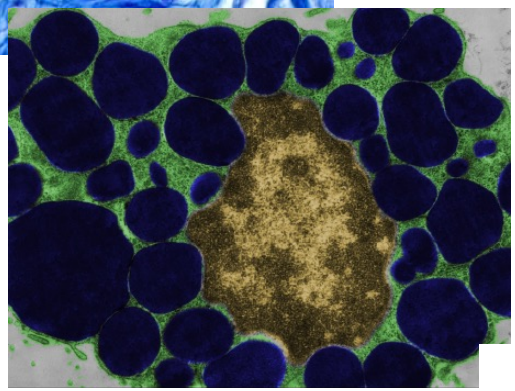
- EDS subtypes can be diagnosed **clinically** or genetically

Orthopedic features of hypermobility Ehlers Danlos Syndrome

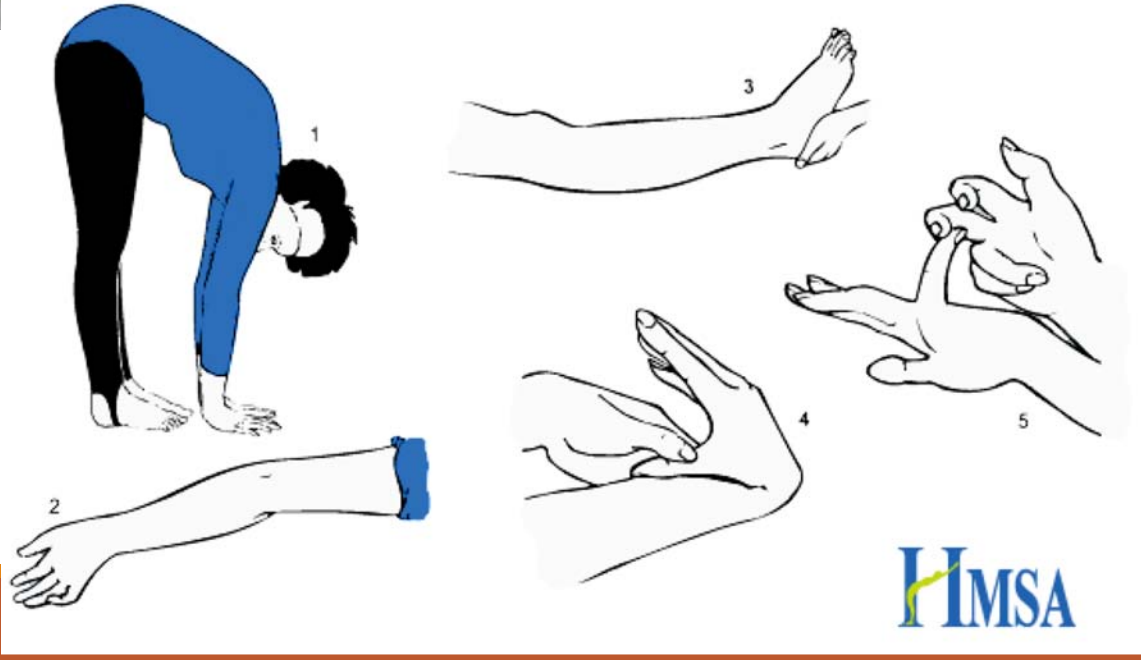


RE 3: Orthopedic features of Ehlers-Danlos syndrome, hypermobility type. Active joint hypermobility at the fingers (a), toes (b), elbow nd knees (genu recurvatum, (d)). Passive hyperextension at great toe (e) and heel (f). Structural changes due to joint instability: fixed xation of the distal ulna (g), asymptomatic fixed subluxation of the elbow (h), fixed subluxation of the first metacarpal (i), hindfoot ation and midfoot eversion in an 11-year-old boy (j), and hallux valgus in a 24-year-old woman (k).

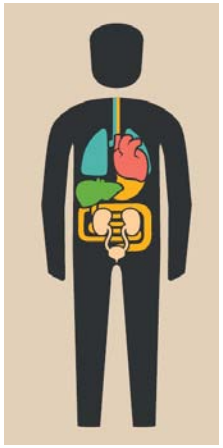


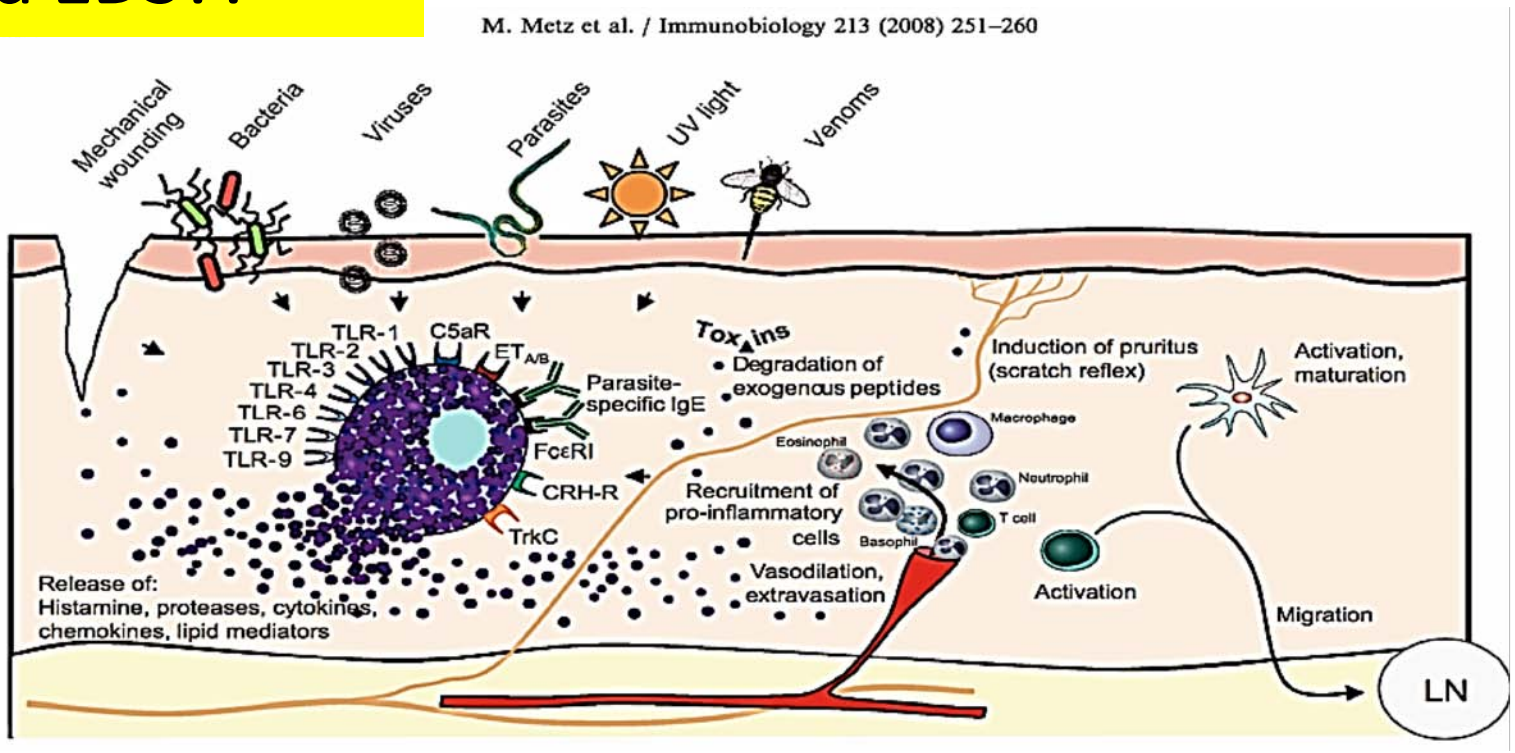


So why is an Allergy/Immunology specialist talking about EDS?



MCAS and EDS?!

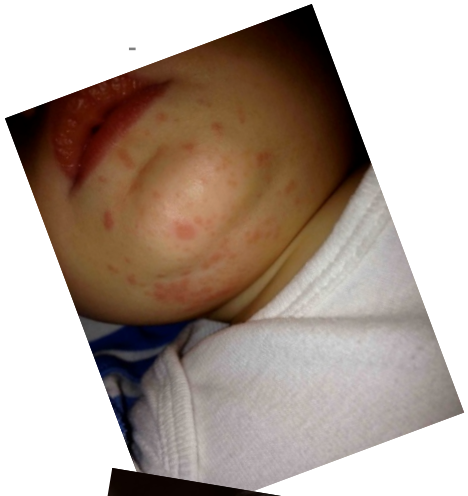


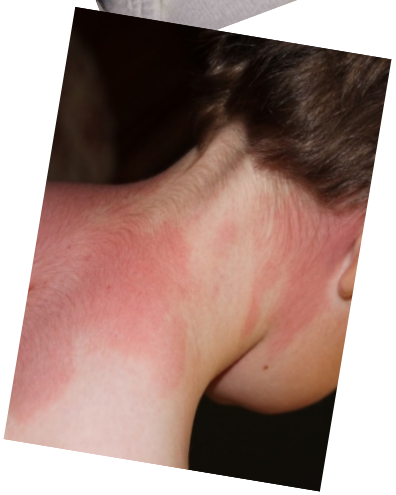


- "many neurologists and cardiologists specializing in [EDS]and POTS have anecdotally observed that the use of antihistamines and other mast cell directed therapies offers benefit to manage symptoms in some patients"
- … patients often describes "allergic-like" reactions to a variety of stimuli, including food, odors and medications. Thus, the allergy/immunology specialists are increasingly requested to evaluate such patients."

Doherty & White, Autonomic Neuroscience, 2018

Meet Sean.
He has been coping with hives, food sensitivities, anaphylaxis, asthma and flushing since birth...





September 2012

To whom It may concern:

I am a mother of a young child suffering from … Mast Cell Activation Syndrome.

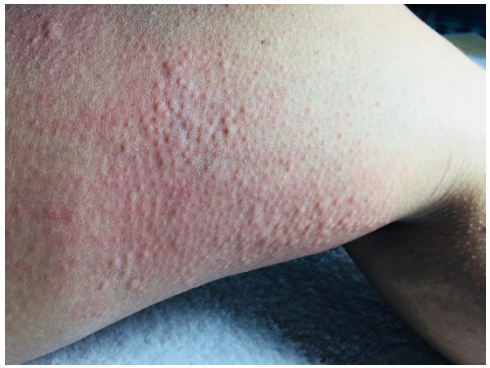
My son's diet consists of 6 safe foods. In his 4 years of life, he's experienced six episodes of anaphylaxis. Our day-to-day living is a constant struggle between pain, fatigue and allergic reactions.

To date, he's seen 10 allergists, 4 orthopedists, 4 gastroenterologists, 3 geneticists, 2 nutritionists, 2 rheumatologists, 2 endocrinologists,, 2 physical therapists, a cardiologist, a neurologist, and a pulmonologist, all to no avail.

My son's "complex case" often leaves doctors bewildered or in disbelief. Only recently have we stumbled upon a doctor who is open minded and dedicated to helping us find answers….

Tina T.

Lessons from Chronic Urticaria: Allergic and Nonallergic Triggers



IgE-mediated reactions from foods, drugs, or other allergens

Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies

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Chronic infections: viral infections- hepatitis B and C, EBV, herpes simplex virus; Helicobacter pylori infections; and helminthic parasitic infections

Complement component deficiencies

Serum sickness or other immune-complex mediated processes

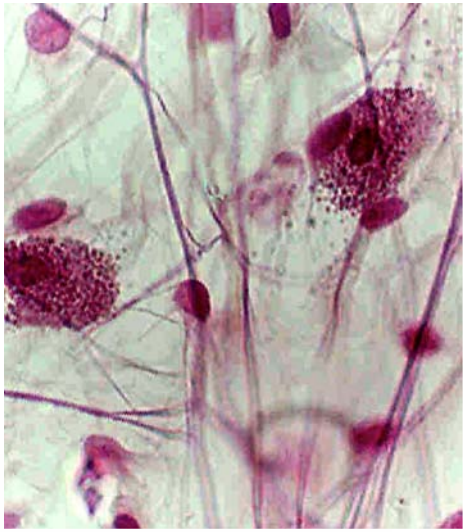
Autoimmune/Connective tissue diseases, systemic lupus erythematosus and rheumatoid arthritis

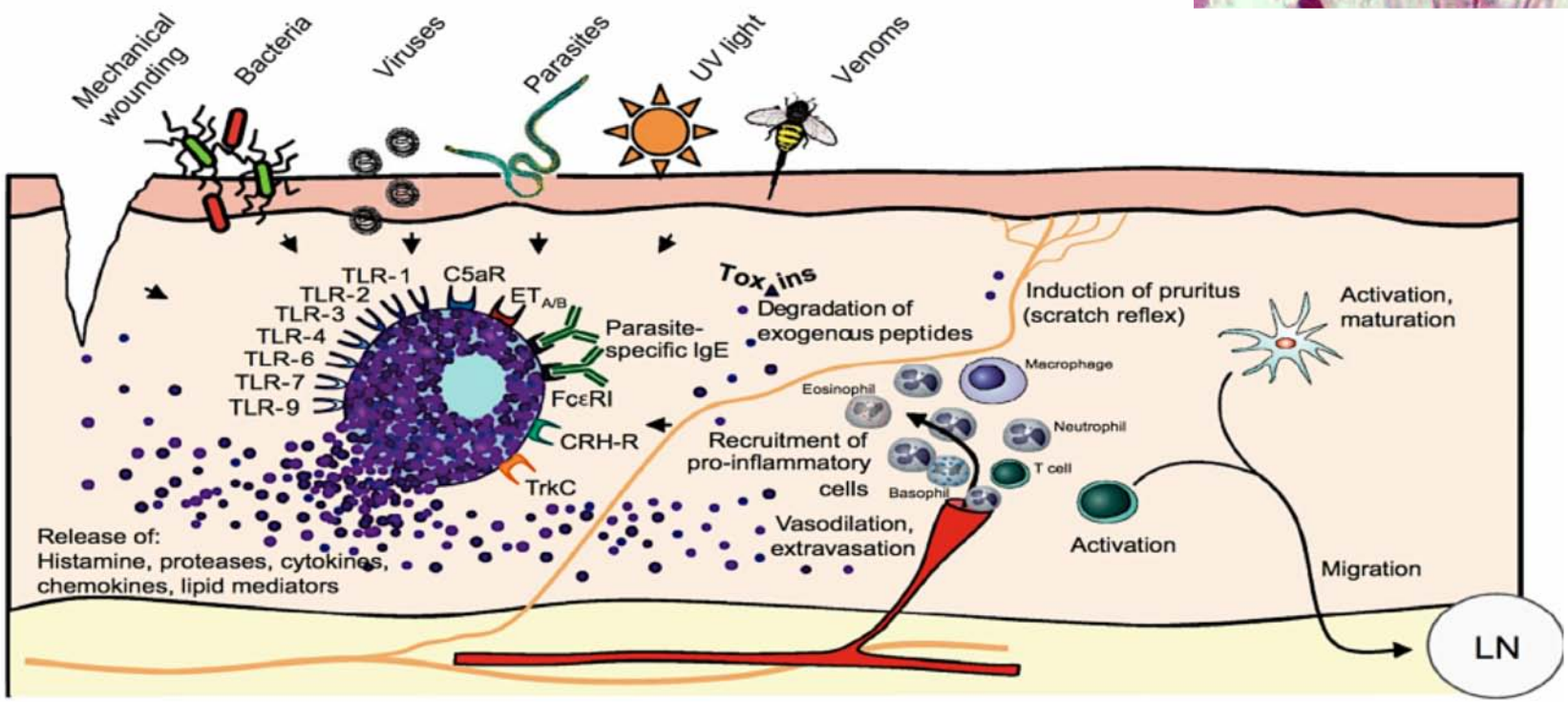
thyroid disease (both hypothyroidism and hyperthyroidism)

neoplasms (particularly lymphoreticular malignancy and lymphoproliferative disorders)

Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies

No allergies, but still reacting!





Can EDS be the key to collagen disorders?

Dr. John B. Symes…..

Have you …. wondered why (some) generally rupture cruciate ligaments during a certain time of their lives, about the same time that (others) are blowing discs, developing heart murmurs, and suffering from immune mediated diseases and that first big wave of cancer?

Haven't you seen patterns that beg answers, like the same (patients) having this happen and even the same time of year? Yes, I had three cruciate ligament injuries come in the same week last month.

Hmmm…"Coincidence"? I don't think so. Why do they rupture those in one leg and then six months or a year, sometimes to the day, they blow the other? That's the pattern we see in almost all immune mediated diseases of tissue, whether it be the eyes, neurological system, and even the kidneys.

…How about the ones that do it the earliest in their lives?

And what dog breeds are involved? It's the dogs that are the most food allergic, isn't it? (Labs, Cockers, Poodles, Rotties, Labs again, English bulldogs, Bichons, Cavaliers…the usual suspects).

Which of these groups (of patients) have the worst

- cruciate ligament ruptures,
- back problems,
- heart valve problems
- combination of gastric
- motility disorders
- weakened supportive ligaments
- food intolerance/allergies are secondary to mucosal damage, a condition known as the "leaky gut syndrome"

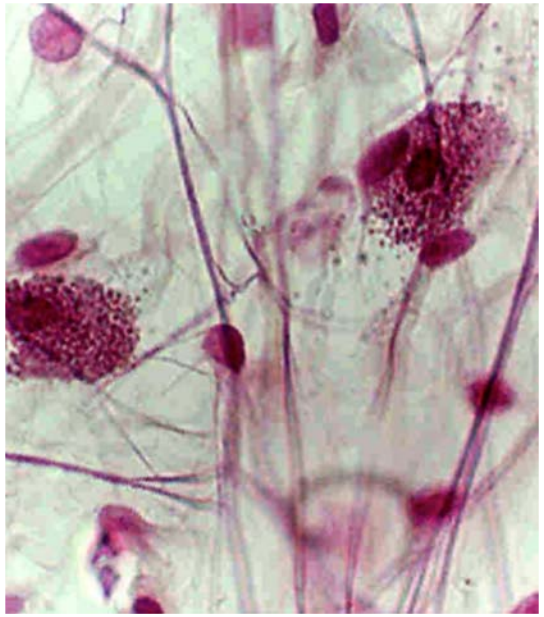
(*these*) patterns we see …should tell us *so* much and can help sort out the cause-and-effect, (*the*) relationships that… often get completely wrong

Clinical Allergy, 1977, Volume 7, page 203

Letter to the Editor

Atopy in Connective Tissue Disorders

An early observation of a possible relationship between connective tissue and mast cells



One Gene Mutation Links Three Mysterious, Debilitating Diseases:

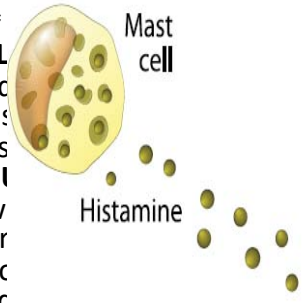
Hypertryptasemia, tryptase > 9 ng/ml

(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."

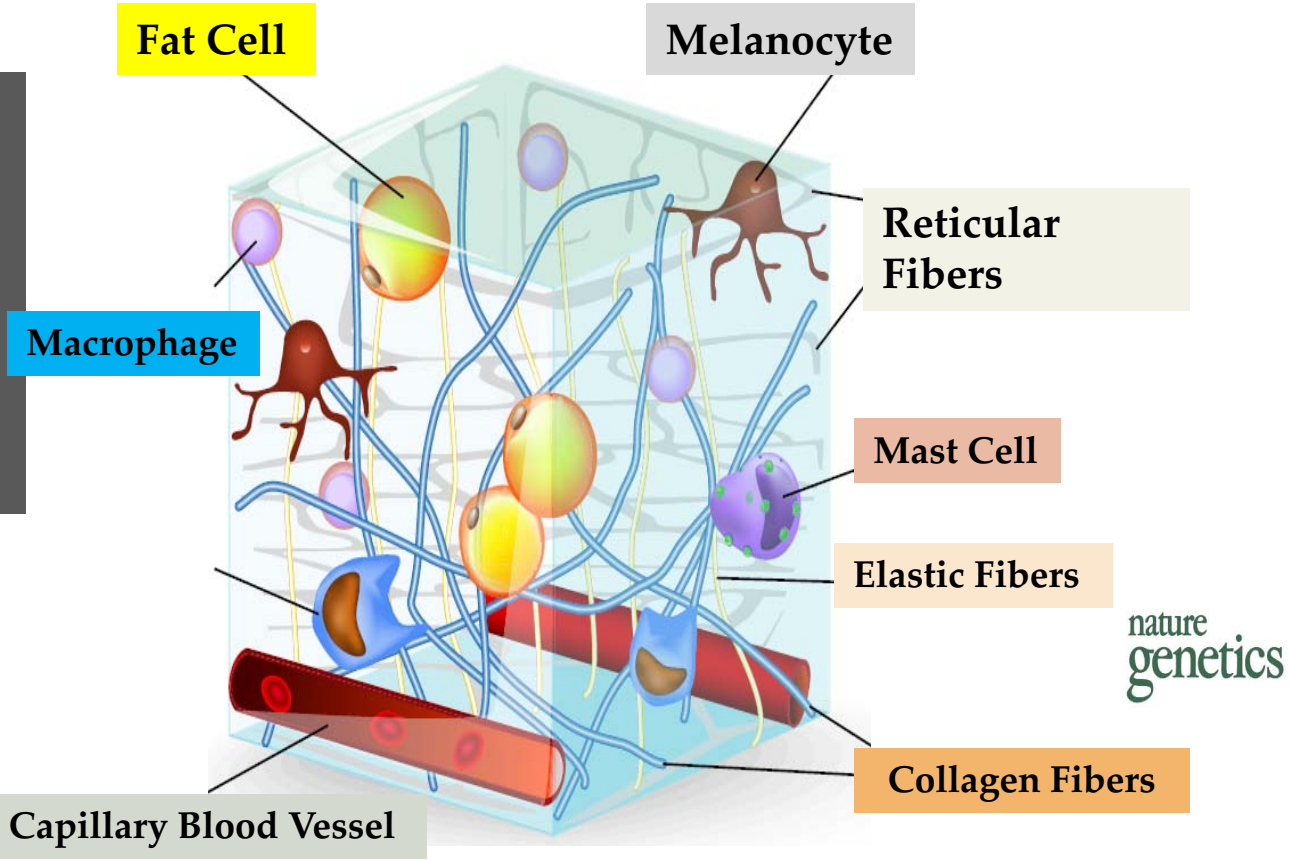
-Kate Horowitz, Mental Floss, October 2016

RHINITIS Sneezing * Congestion * Stuffiness * Itchy Eyes * Runny nose * Post Nasal Drip * **STINGING INSECT ALLERGY** * Wheezing * Shortness of Breath * Throat Tightness * Cough * Hoarse Voice * Chest Pain * Chest Tightness * **ANAPHYLAXIS** Trouble Swallowing * Itchy mouth/throat * Nasal Stuffiness * * Circulation Problems * Pale/Blue color * **FOOD ALL** ness * Breathing Troubles* Lightheaded Blood Pressure * Shock * **ASTHMA** Loss of Cons Hives * Skin swelling * Warm, Red, Fleeting Ras * Nausea * Abdominal Pain/Cramps * Vomiting * **U** nxiety * Feeling of Impending Doom, itchy/red/w **MA** Headacl Uterus * Food Aller g * Multipl **OOD ALLERGY** Lo eathing Trc Lightheaded Blood Press **A** Loss of Consciousness * Itchy Skin * **ALLERGIC ECZE** s * Cough * Food Allergy * Diarrhea/Vomiting * B breath *Wheez ngestic y skin * Noseble ny nose yps* **ANGIOE** Pain/Cr adache * Cramp y * Dia **S** Trouble at * N /Sinus Congest le/Blu **GY** Low Pulse * Light Out, Low Blood Pr ss of Skin * Hives * ting ubles **RHINITI** fines nose * Post Na **LERG** ness of Breath * parse Chest Tightness **Drug Allergies** Headache * **A** **DEMA** * * Trouble Swallowing * Itchy mouth/throat * Nasal Stuffiness sal/Sinus Congestion * Circulation Problems * **ASTHMA*** fatigue ***Pain when Urinating *** Brain Fog * diarrhea * **RHINITIS** Sneezing * Congestion * Stuffiness *



- **Tryptase**
- **Chymase**
- **Cortisol Releasing Hormone**
- **Tumor Necrosis Factor**
- **Heparin**

Derived Enzyme Mutation and EDS/JHS?



Our findings link findings (germline) duplication in TPSAB1 (the alpha-tryptase gene) with

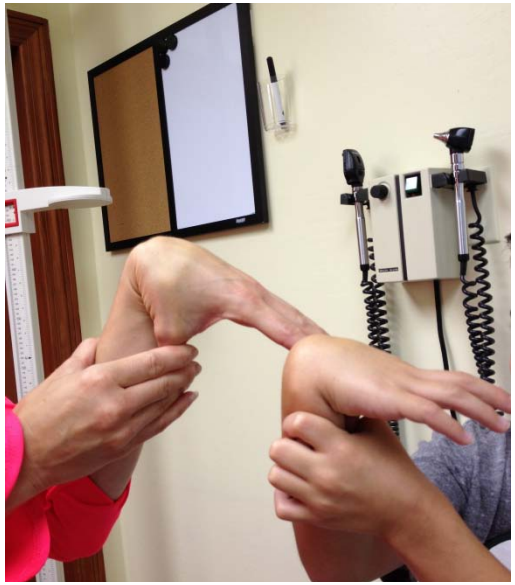
- Irritable bowel syndrome
- Cutaneous complaints
- Connective Tissue Abnormalities
- Dysautonomia

nature genetics

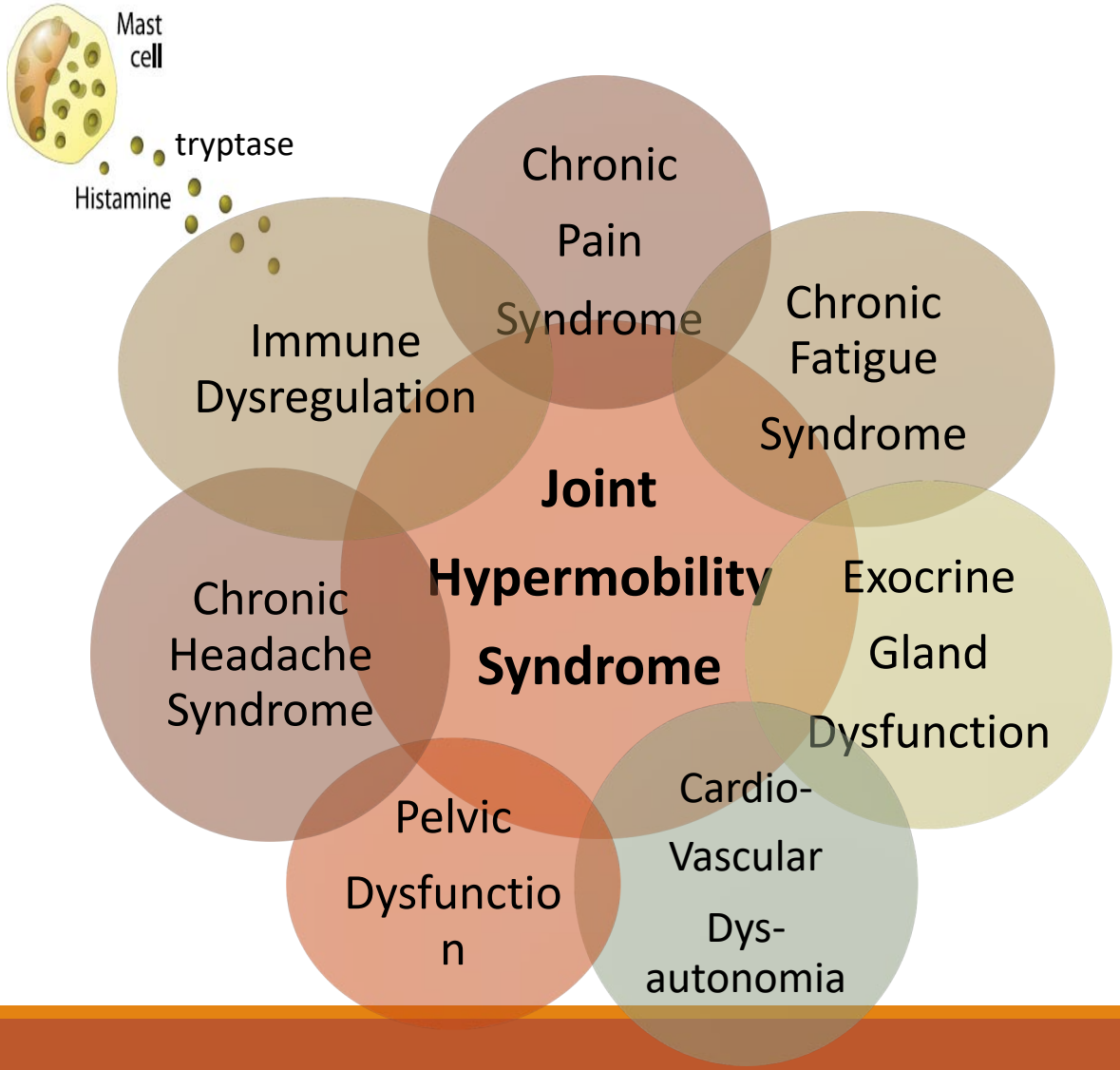
Elevated basal serum tryptase identifies a multisystem disorder associated with increased *TPSAB1* copy number

Jonathan J Lyons[1], Xiaomin Yu[1], Jason D Hughes[2], Quang T Le[3], Ali Jamil[1], Yun Bai[1], Nancy Ho[4], Ming Zhao[5], Yihui Liu[1], Michael P O'Connell[1], Neil N Trivedi[6,7], Celeste Nelson[1], Thomas DiMaggio[1], Nina Jones[8], Helen Matthews[9], Katie L Lewis[10], Andrew J Oler[11], Ryan J Carlson[1], Peter D Arkwright[12], Celine Hong[10], Sherene Agama[1], Todd M Wilson[1], Sofie Tucker[1], Yu Zhang[13], Joshua J McElwee[2], Maryland Pao[14], Sarah C Glover[15], Marc E Rothenberg[16], Robert J Hohman[5], Kelly D Stone[1], George H Caughey[6,7], Theo Heller[4], Dean D Metcalfe[1], Leslie G Biesecker[10], Lawrence B Schwartz[3] & Joshua D Milner[1]

EDS- Hypermobility Syndrome = a hereditary condition with predominant rheumatologic manifestations…

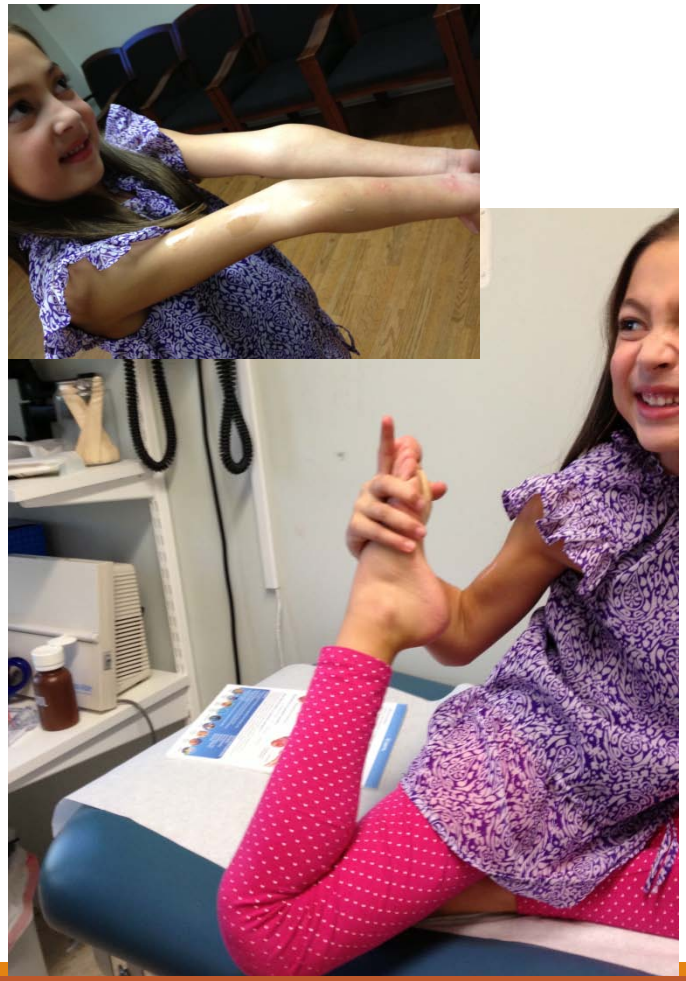


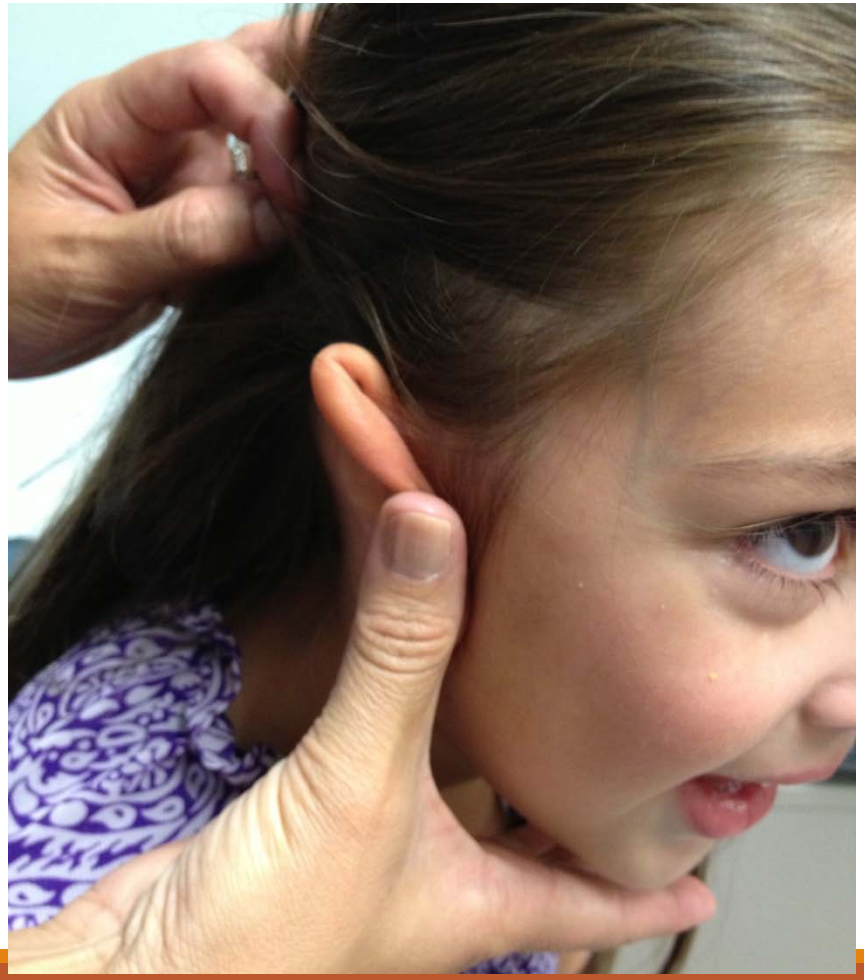
It is now emerging as a multi-systemic disorder with widespread manifestations…



Castori, Dermatology 2012

Inherited Connective Tissue Disorders and Mast Cell Activation Syndromes





Diagnostic Criteria: Mast Cell Activation Disorders

Rhinitis

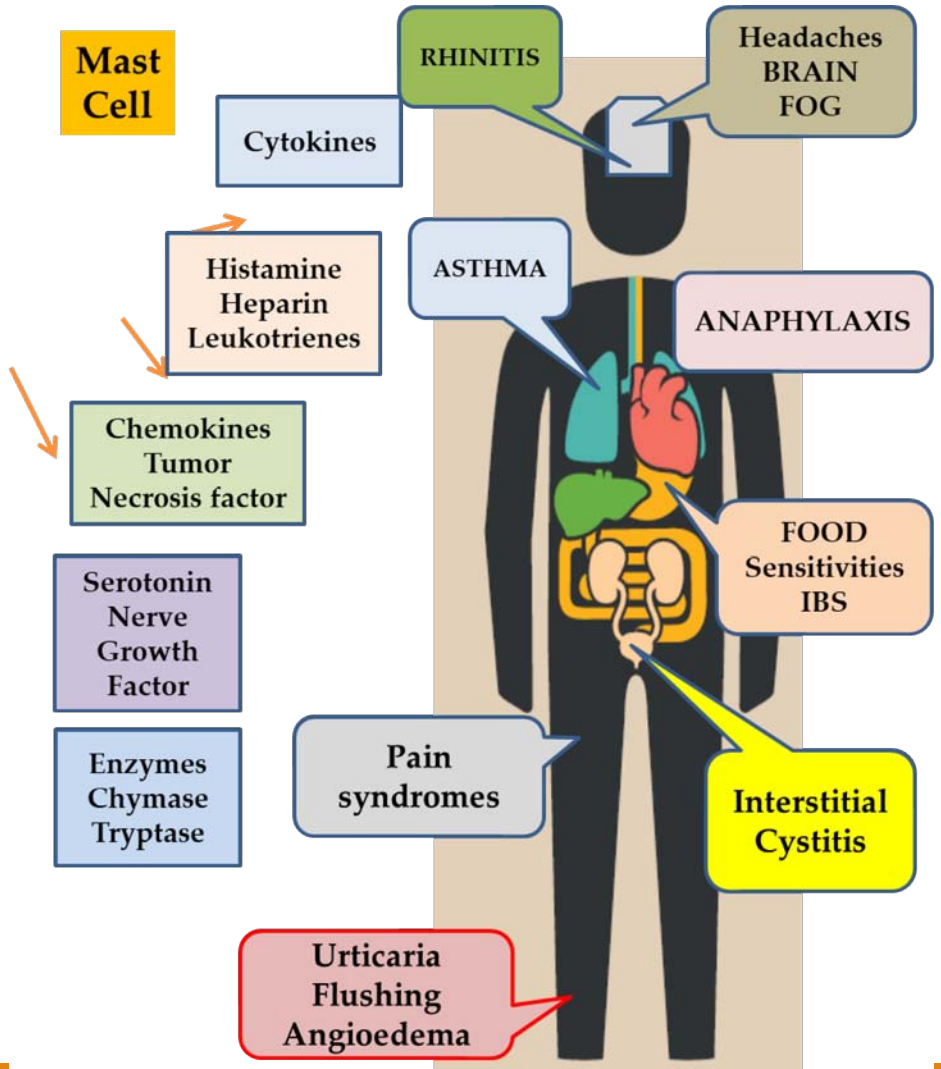
- 7 patients (78%) had chronic rhinitis symptoms, nasal congestion, over the past month.
  - Majority with symptoms severe enough to interfere with sleep.

Itch/Hives

- 100% of patients reported pruritus over past month.
  - Majority (89%) had hives

symptoms that were controlled on anti-mediator therapy:

- Anti-histamine
- Mast cell stabilizer
- Leukotriene modifier



Diagnostic Criteria: Mast Cell Activation Disorders

Asthma

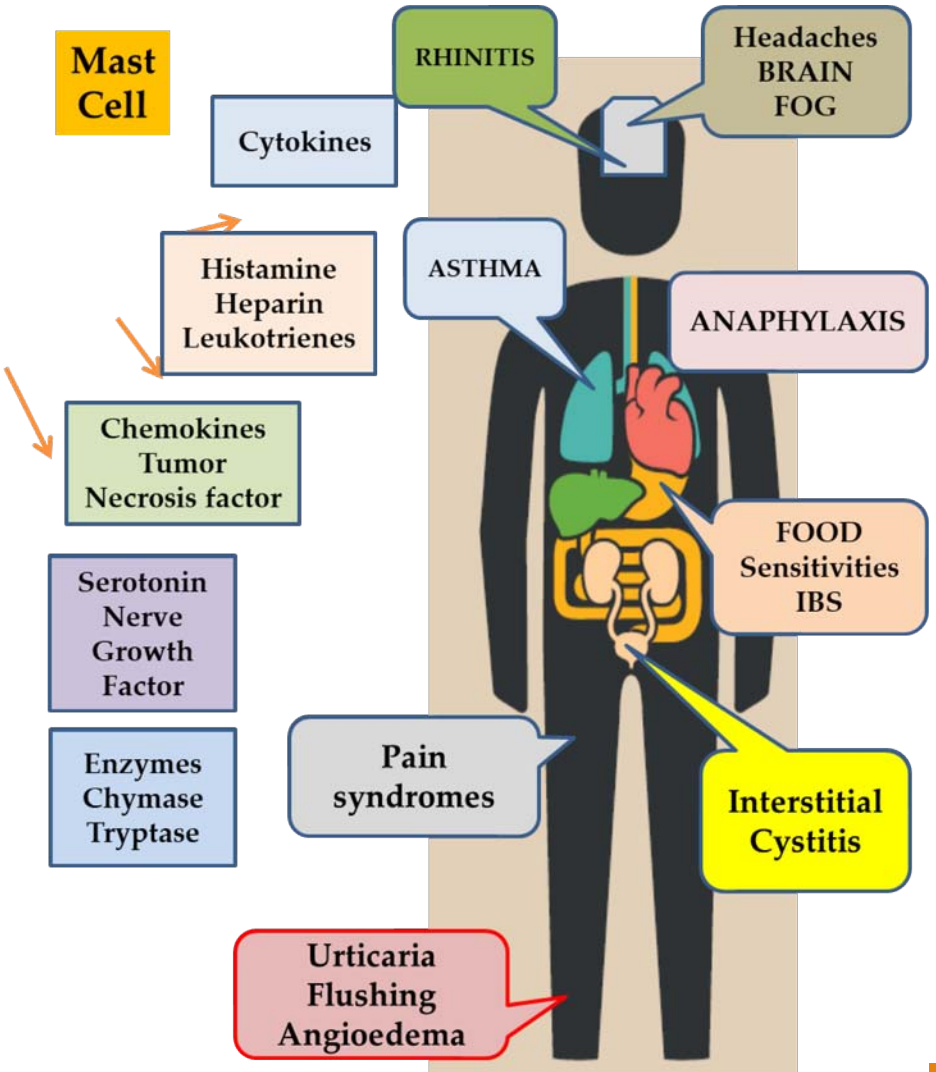
7 patients (78%) had a history of asthma.

- All patients with a history of asthma were treated with a rescue inhaled beta-agonist.
- 44% were on an inhaled corticosteroid, 78% were on a leukotriene modifier.

Anaphylaxis

patients (78%) reported previous symptoms highly likely to be anaphylaxis based on clinical diagnostic criteria:

- acute onset of illness
- either spontaneous or after exposure to common MC triggers
- involving skin, mucosal tissue, hypotension, and respiratory and gastrointestinal symptoms.



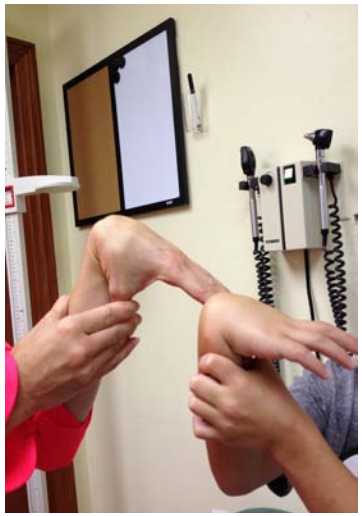
Results: Labs

7 of the 9 patients had no objective signs of IgE-mediated allergy, using in vitro and/or in vivo, percutaneous skin testing.

Among these patients, the total serum serum IGE level ranged from undetectable to 101 KIU/ml (Quest Diagnostics), with the 78% had IGE < 10 KIU/ml

Results: MCAS-ish

	1	2	3	4	5	6	7	8	9
Age (years)	39	6	54	10	7	50	34	43	32
Gender	F	M	F	M	F	M	F	F	F
Episodic Symptoms	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Improved with anti-MC mediators	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
tryptase	1	<10	<10	<10	<10	<10	<10	<10	<10
Other diseases ruled out	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

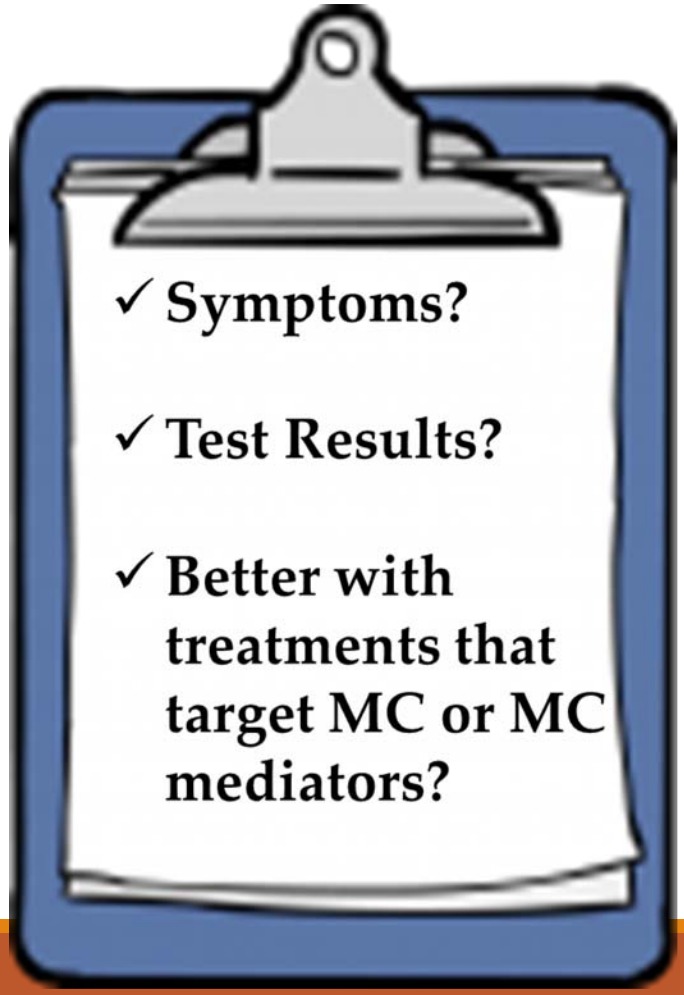


MCAS-ish and EDS: Objective Data

9 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 allergic disease controlled by anti-mediator therapy and avoidance of triggers.



Why PTSD?
Fate of those having symptoms for years but deemed
"Nothing the matter with them",
labeled as a "Malingering", "Somatic", "Conversion Disorder"

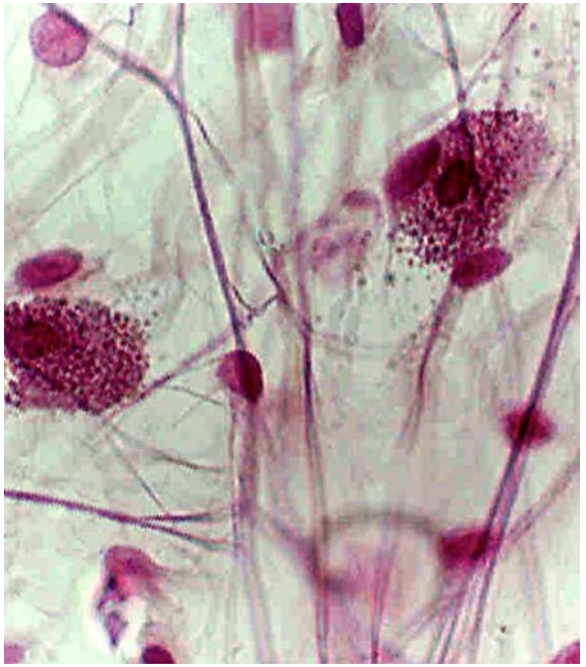
Medically speaking, they are not serious cases as regards prospective death, but they are often extremely serious as regards prospective life.

Their symptoms will rarely prove fatal, but their lives will be long and miserable, and they may end by nearly exhausting their families and friends.

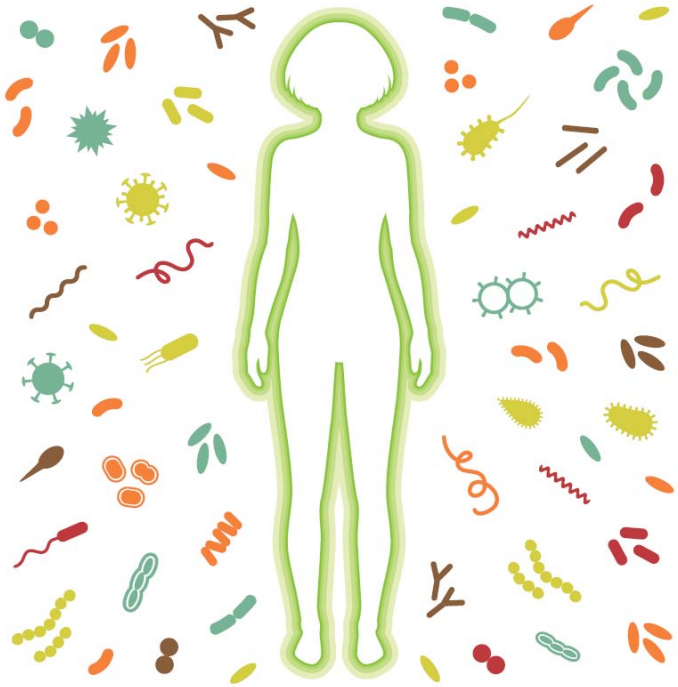
The Care of the Patient,
Francis Peabody, MD JAMA 1927

"MCAS-ish":
Few or No Allergies, but Still Reacting

UNDERSTANDING
MAST CELL ACTIVATION (MCA)
and
MAST CELL ACTIVATION SYNDROME (MCAS)



Our immune systems …



- can be defined a priori as embodied expectations of injury and the corresponding programs of protection and repair

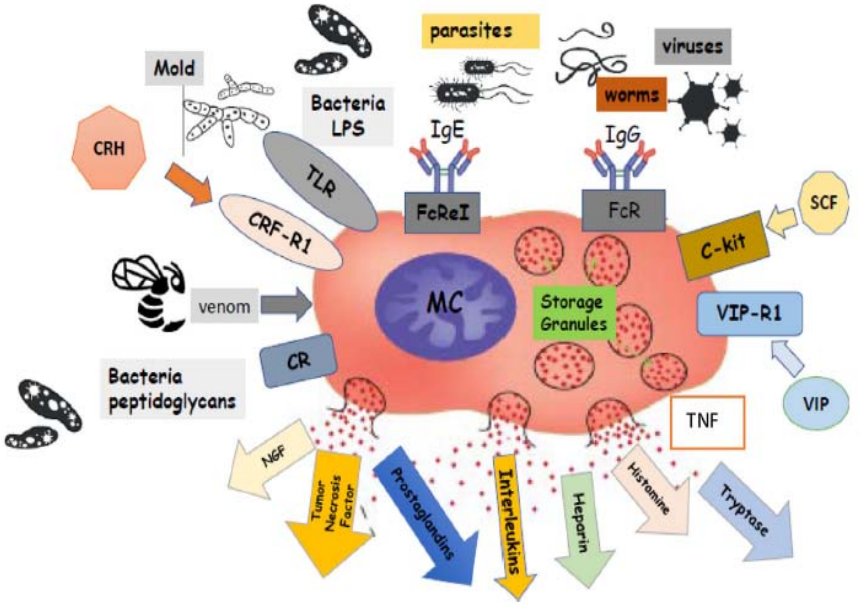
In imperial times, the Great Wall of China was easily breached and was not in itself a very effective defense against resolute adversaries.

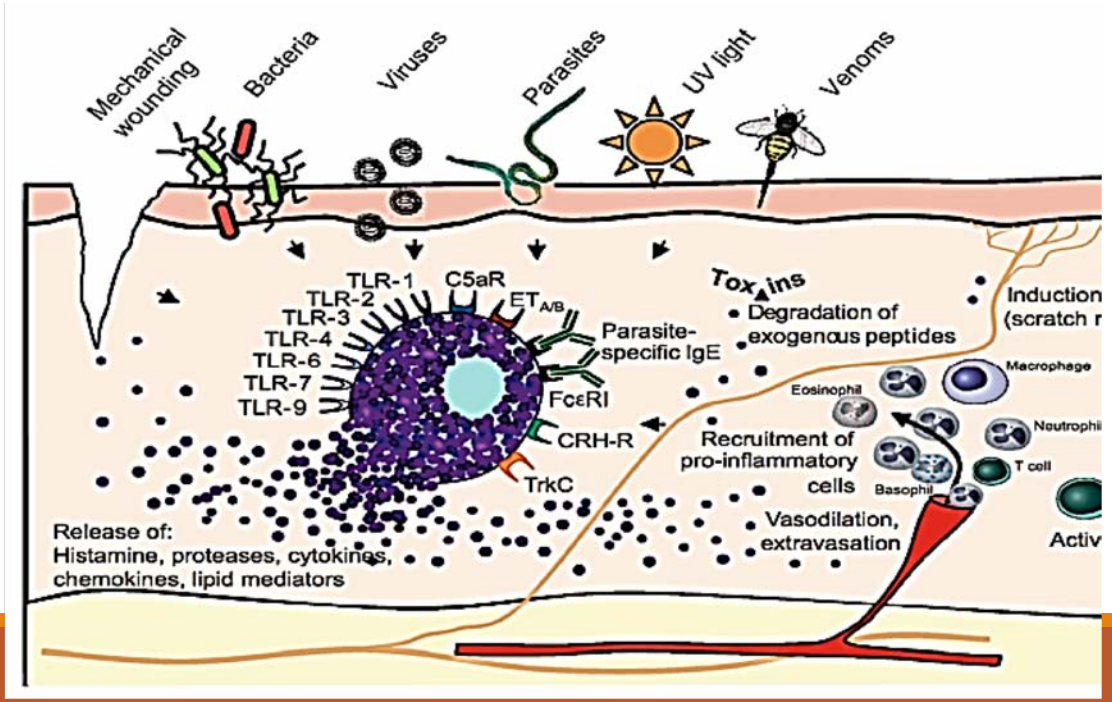
Rather, it was a communication route and housed, far from the imperial centre, a string of lonely guards who quickly engaged invaders and slowed their progress, while alerting and beckoning more substantial back-up forces.

–**Christophe Benoist & Diane Mathis** Mast cells in autoimmune disease Nature, 2002

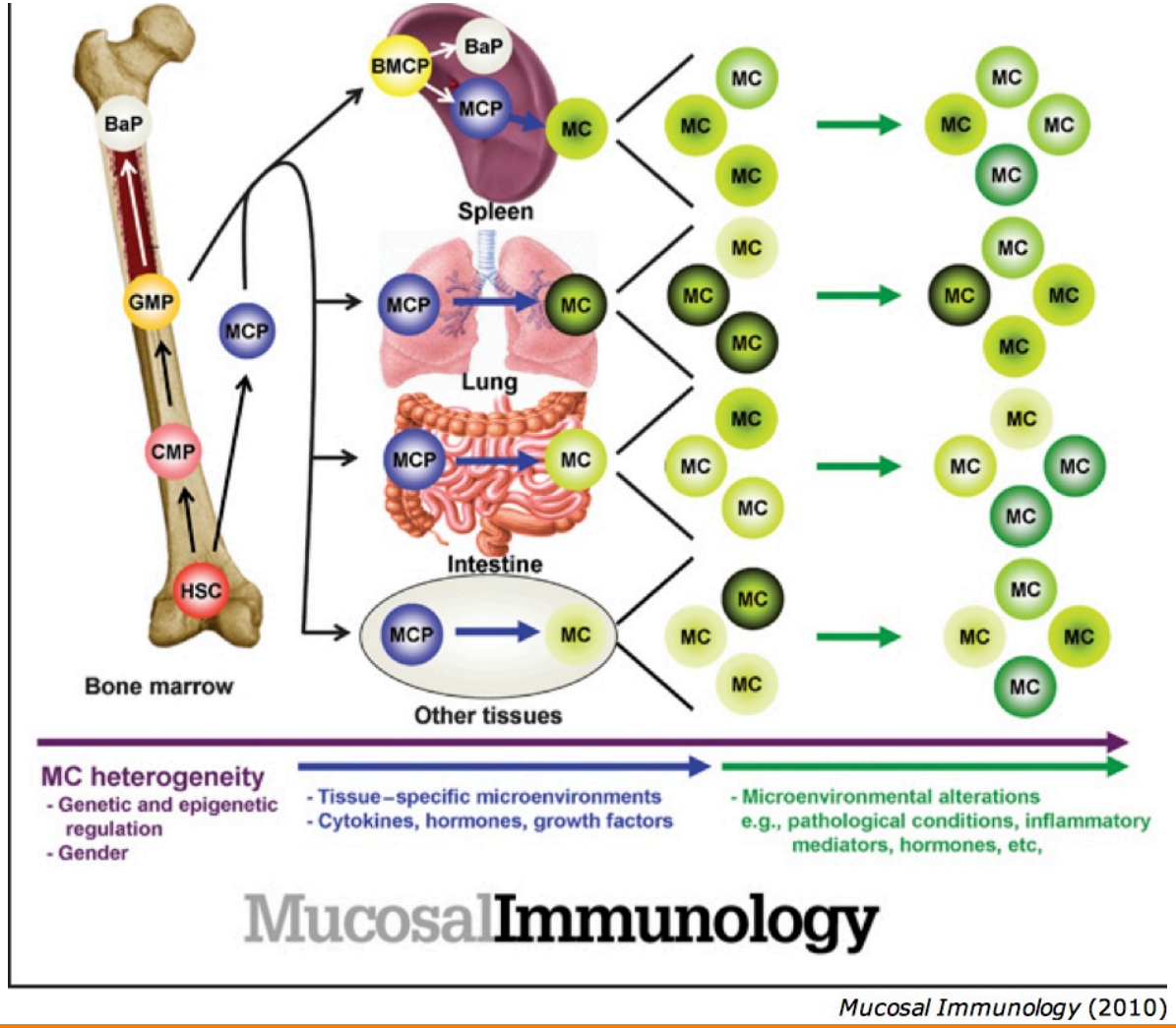
Mast Cell Orders

MAST CELL BIOLOGY 101





Mast Cell Development



Mucosal Immunology (2010)

Bone Marrow:
Pluripotent
CD34+
Progenitors

↓

Blood Stream

↓

SCF-Kit:
*Homing to tissues
*Granule Production
*Local Survival

Homeostasis: Keeping the Peace

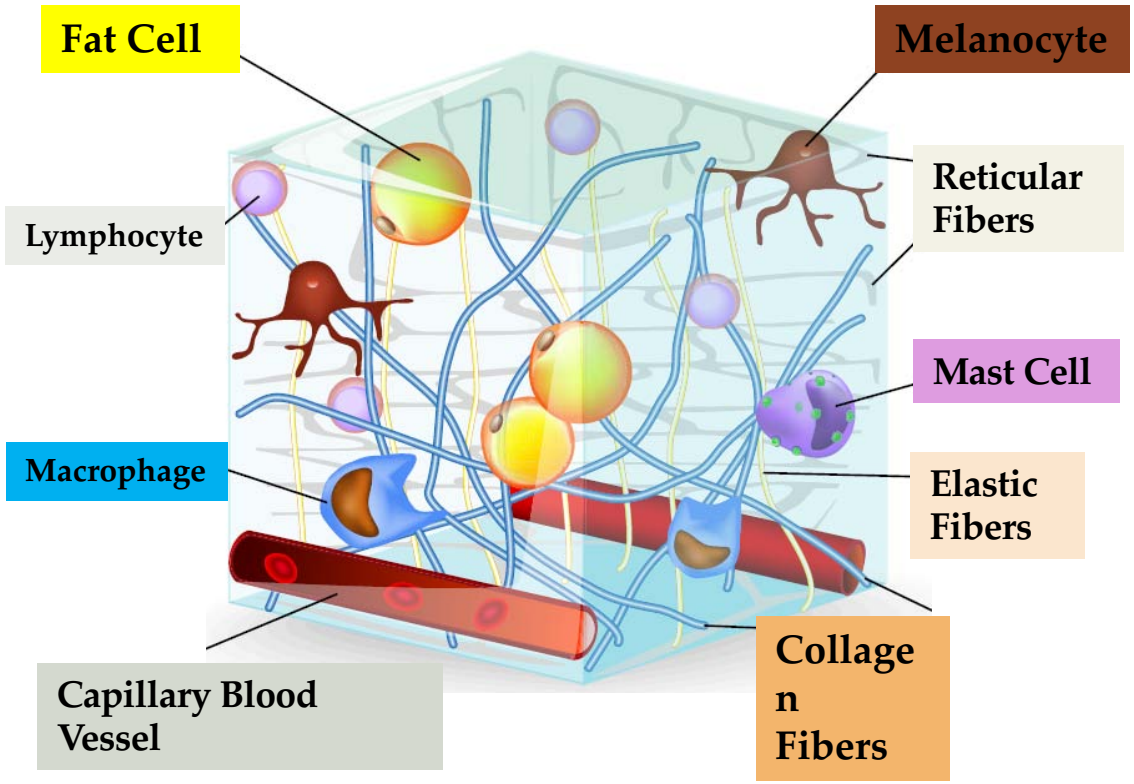
Like a police officer, who strives to serve and protect a neighborhood, "rookie" Mast Cells arrive and learn to meet the needs of local community of cells and tissue.

- **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.

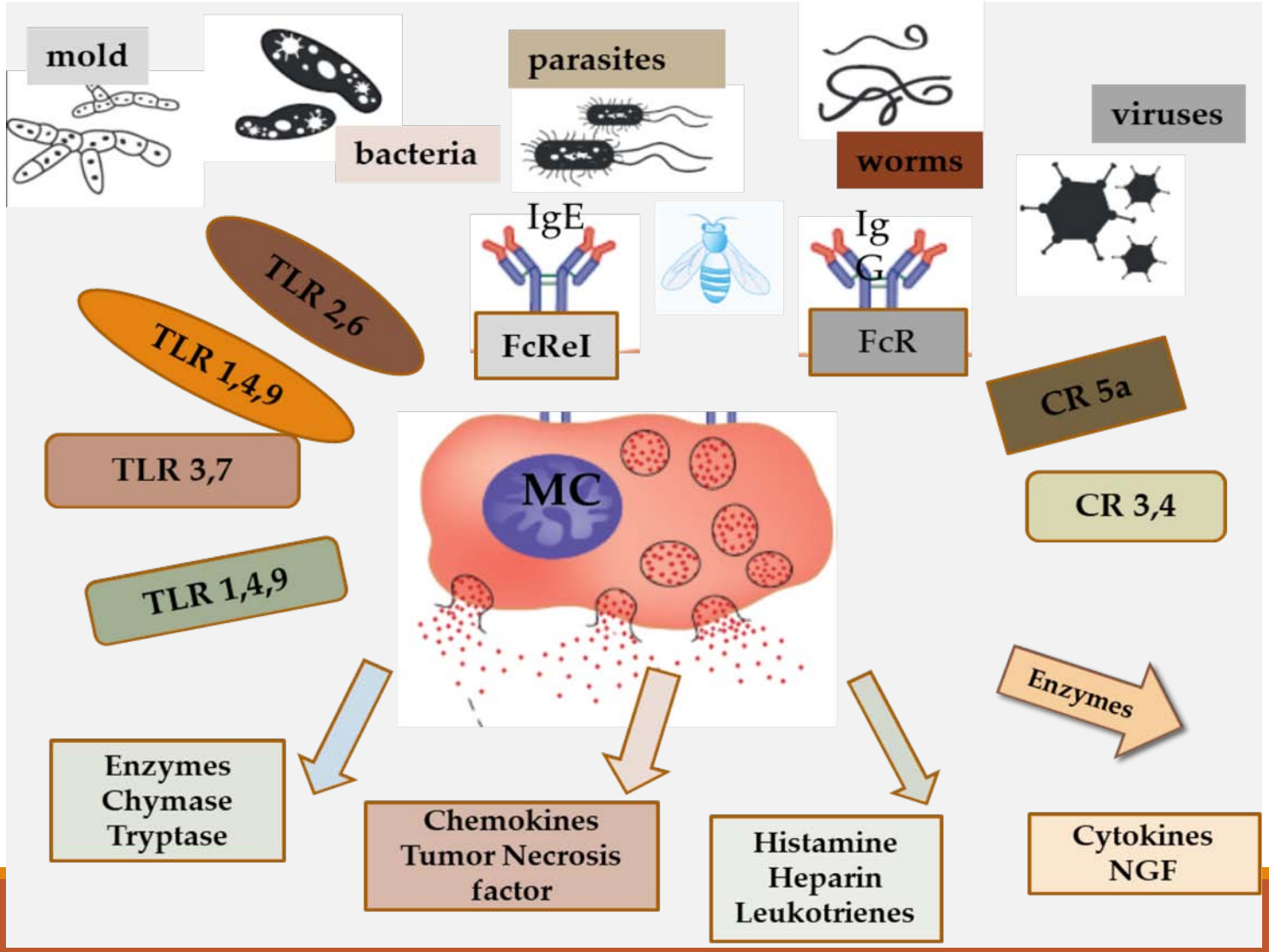
Mast Cell Activation/ Orders: Border Patrol

Surveillance. Protection. Coordinate Response and Repair.



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

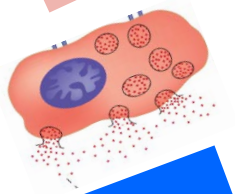
Armed with invariant sensors, Mast Cells are hardwired to recognize and then react with a defined set of chemical and physical responses, in order to contain "usual suspects", pathogens and harmful substances.



911… what's your emergency?

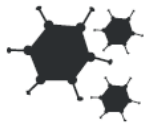
Depending on the nature and severity of the danger, mast cells, will respond with a defined set of mediators, calling for appropriate help.

Mast Cell Recognizes This…



parasite

virus



bacteria

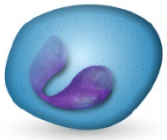
Insect sting

Code Blue

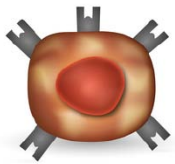
Code Red

Code Orange

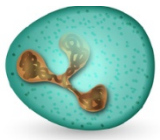
And, through chemical mediators and receptors, will call for…



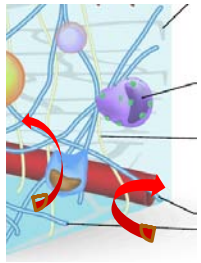
Eosinophil



T Cell



Neutrophil

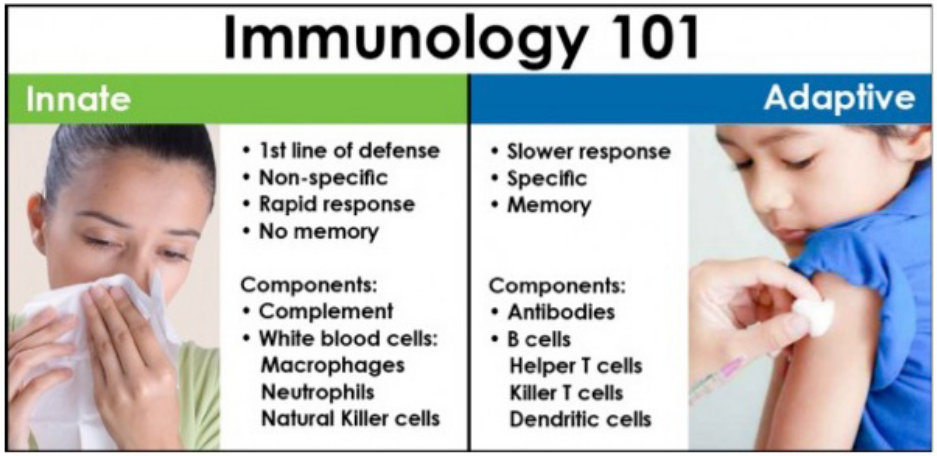


MC

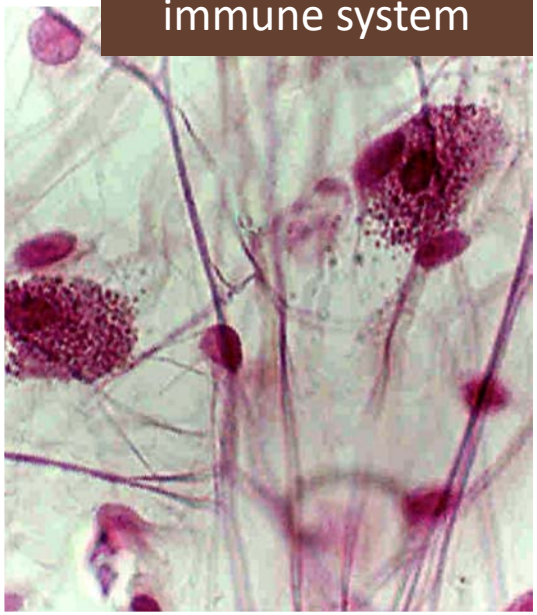
Vascular leakage -> Serum Proteins -> Swelling, Itch

Mast Cells act as the local Peace Keepers, maintaining homeostasis in the surrounding microenvironment.

#Mast Cells?



Part of the innate immune system



Mature MCs are found in the tissue

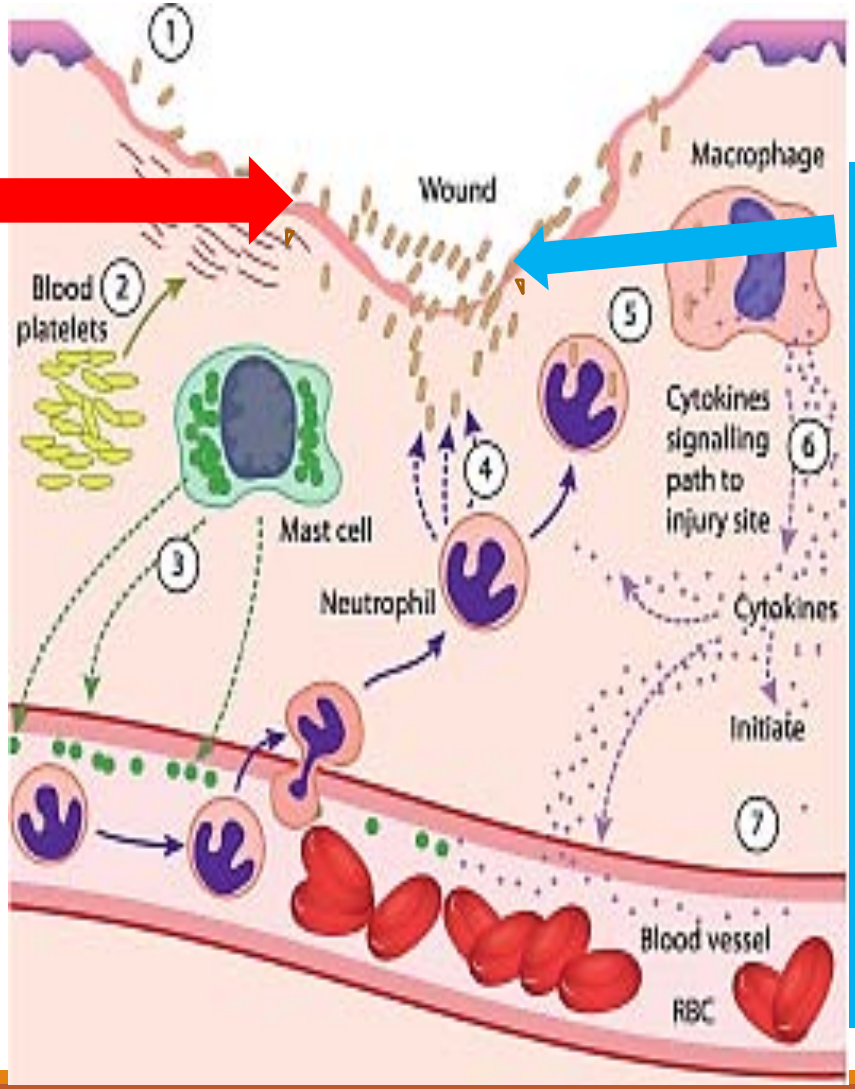
Our Immune system:
Border Patrol:
Not just self or nonself,
but safe vs. danger!

Mast Cell Activation

Danger Signals

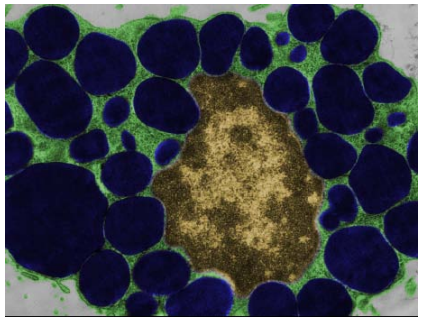
(1)
Damage Alert:
<u>Endogenous, self alarm signals, indicating danger:</u>

breakdown products of hyaluron (made when vessels are damaged).
mammalian DNA, RNA, heat shock proteins (Hsps), interferon a, interleukin-1beta, CD40-L



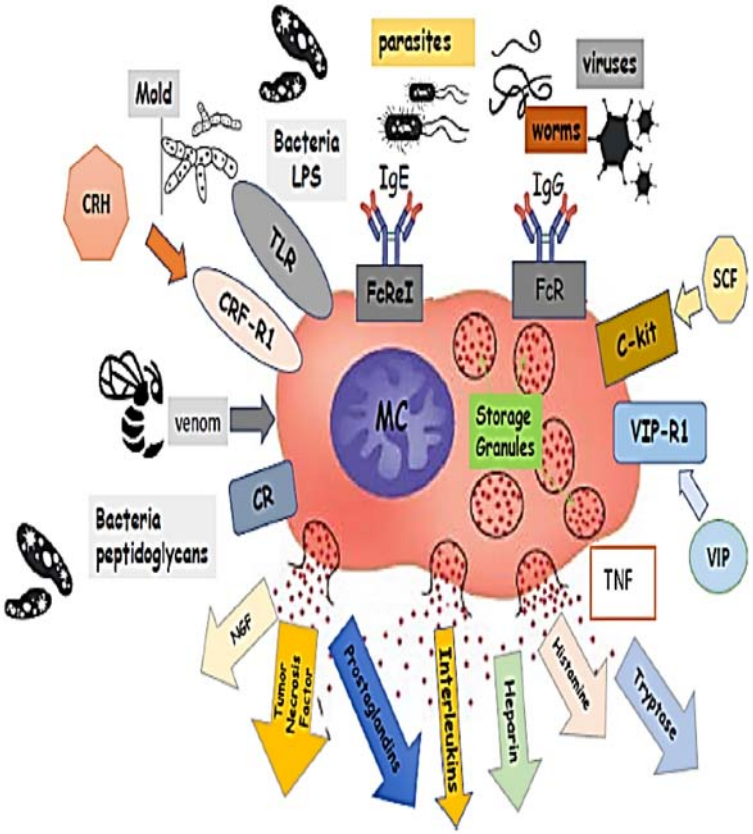
(2)
Threat recognition & Response

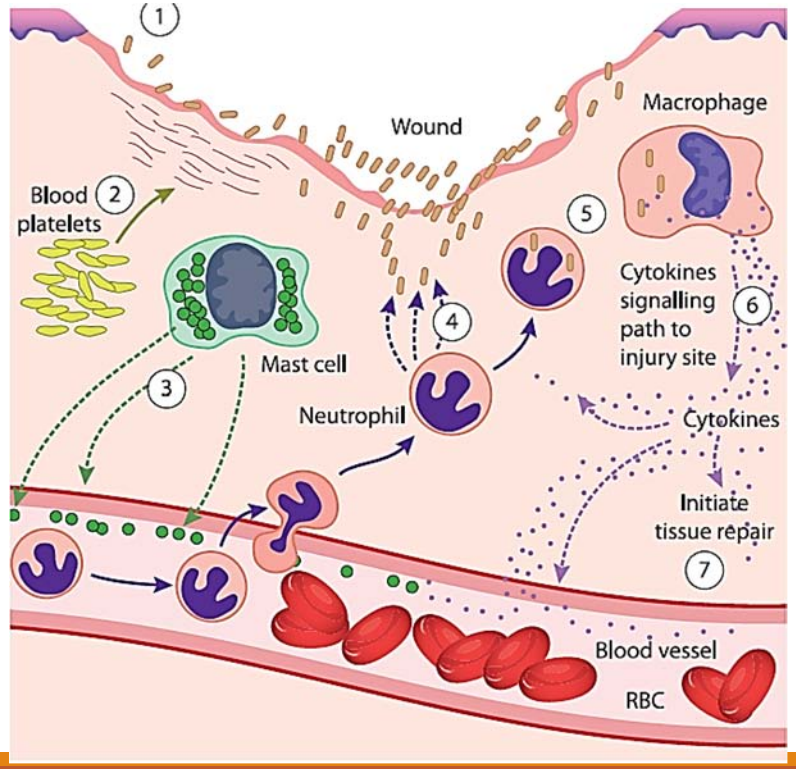
pattern recognition receptors (PRRs) membrane-bound Toll-like receptors (TLRs), Complement receptors, Immunoglobulin Receptors on MCs



Mast Cell Activation: Border Defense and Tissue Repair

COMMUNITY EMERGENCY RESPONSE TEAM

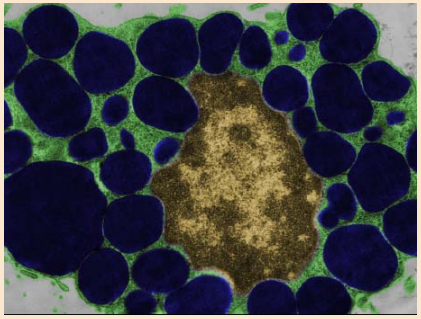




Mast Cell Activation Disorders (including MCAS)

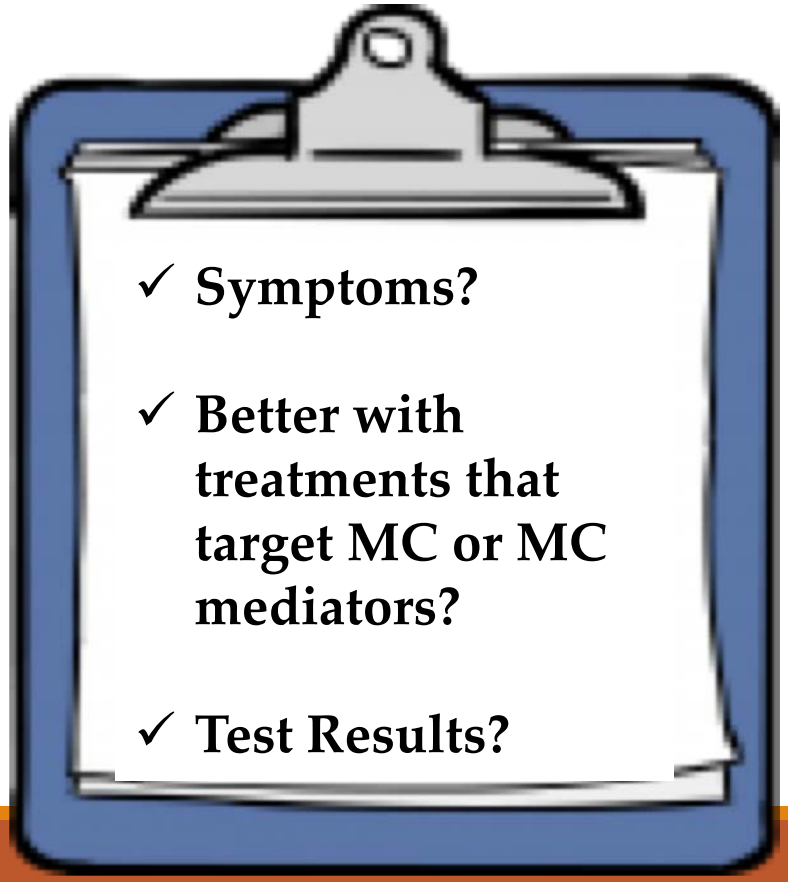
Valent, Allergy 2013

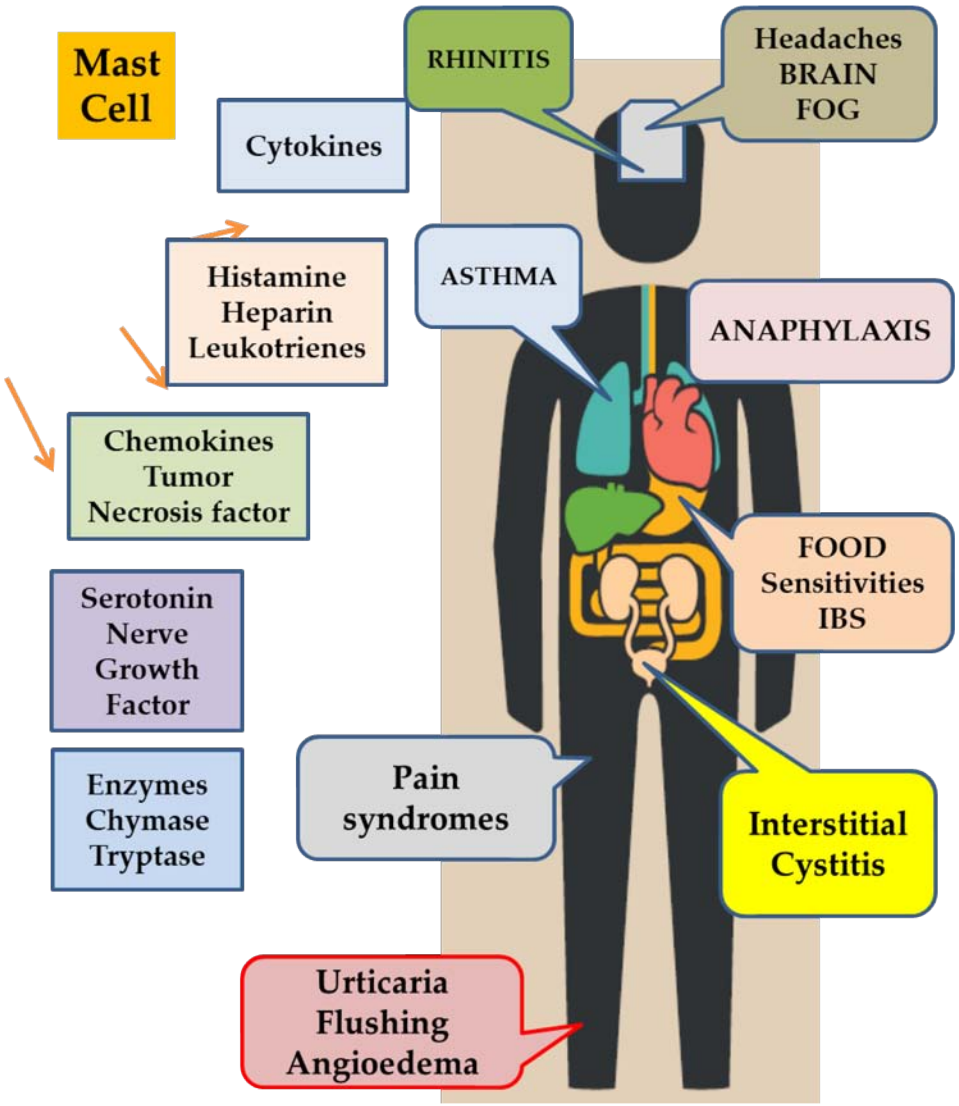
When symptoms are recurrent, are accompanied by an increase in mast cell–derived mediators in biological fluids, and are responsive to treatment with mast cell–stabilizing or mediator-targeting drugs, the diagnosis of mast cell activation syndrome (MCAS) is appropriate.

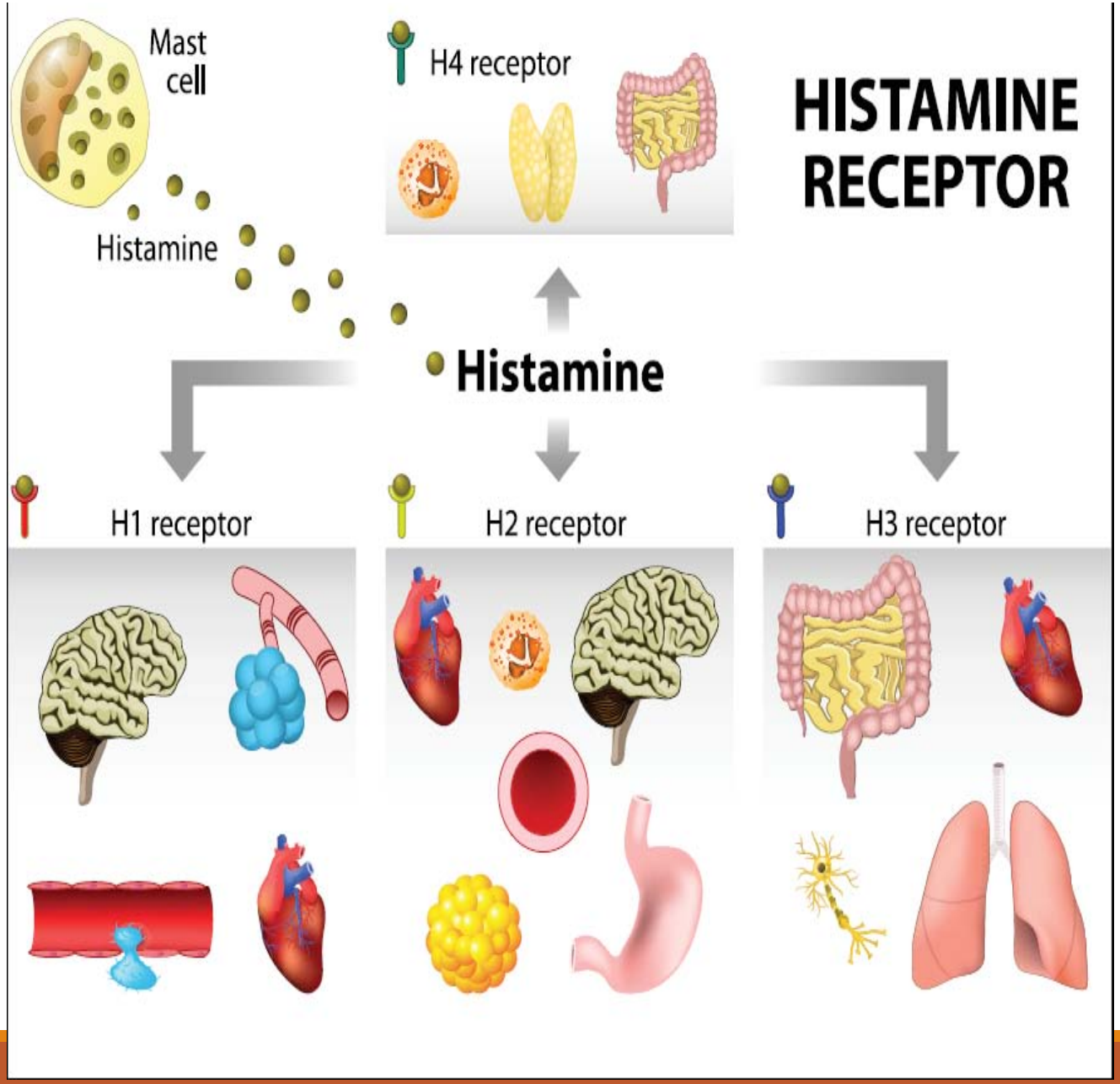


Mast Cell Activation Disorders (including MCAS)

Valent, Allergy 2013







MCAD can is…

"the aberrant release of variable subsets of mast cell mediators"

- Histamine
- Leukotrienes
- Prostaglandins
- Tumor Necrosis Factor
- Interleukins

(1) Mast Cell Activation Disorders: Signs and Symptoms

MASTOCYTOSIS

(ESCRIBANO ET AL, JACI 124:514)

Skin Lesions	90%
Pruritis	82%
Flushing	56%
Diarrhea	35%
Abdominal Cramping	30%
Neuropsychiatric Symptoms	**23%**
Anaphylaxis	23%
Peptic Symptoms	20%
Osteoporosis	18%
Hepatomegaly	12%
Splenomegaly	8%

NONCLONAL MAST CELL ACTIVATION DISORDERS

HAMILTON, J ALLERGY CLIN IMMUNOL 128;147

Abdominal Pain	94%
Dermatographism	89%
Flushing	89%
Headache	83%
Neuropsychiatric	**67%**
Diarrhea	67%
Rhinitis (Naso-ocular)	39%
Asthma	39%
Anaphylaxis	17%

Airway Reactions (ENT/Lungs)
Throat tightening, Throat Swelling
Nasal congestion, Rhinorrhea
Wheezing, Dyspnea, Chest Tightness

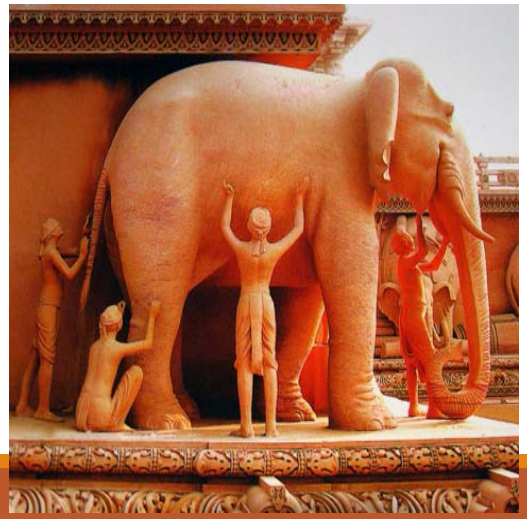
Brain
Sense of uneasiness,
Angst/Anxiety
Headache, Dizziness
Confusion, Tunnel Vision

Gastrointestinal tract
Nausea, Cramping
Abdominal Pain
Vomiting, Diarrhea

Heart, Blood Pressure
Fainting, Chest Pain
Fast Heart Rate,
Palpitations (pounding)
Weak pulse, Dizziness

Genito-Urinary tract
Uterine
Cramping
Swelling -labia

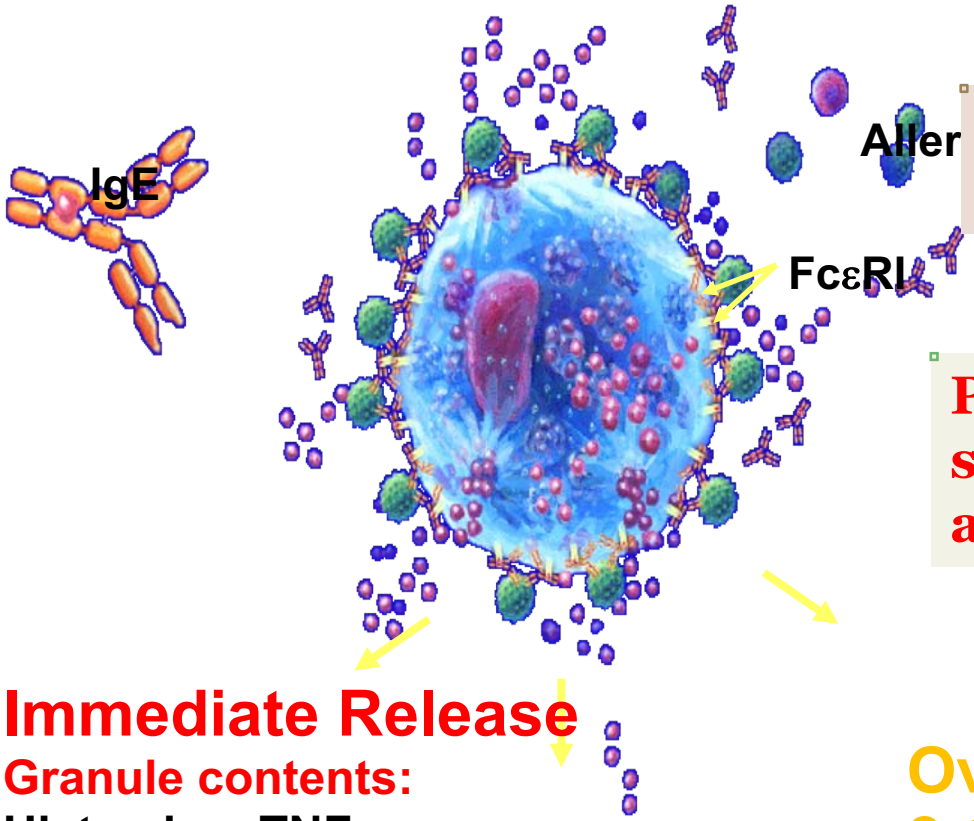
Pain: Joint, Muscle, Nerve



Skin Hives (Urticaria), Itch
Flushing, Swelling
(Angioedema)

(2) Measuring

Mast Cell Activation Markers, Inflammatory Mediators



Serum Tryptase

Serum, Urine Histamine

Pathology- spindle MC, MC aggregates

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

CD2, CD25 Expression

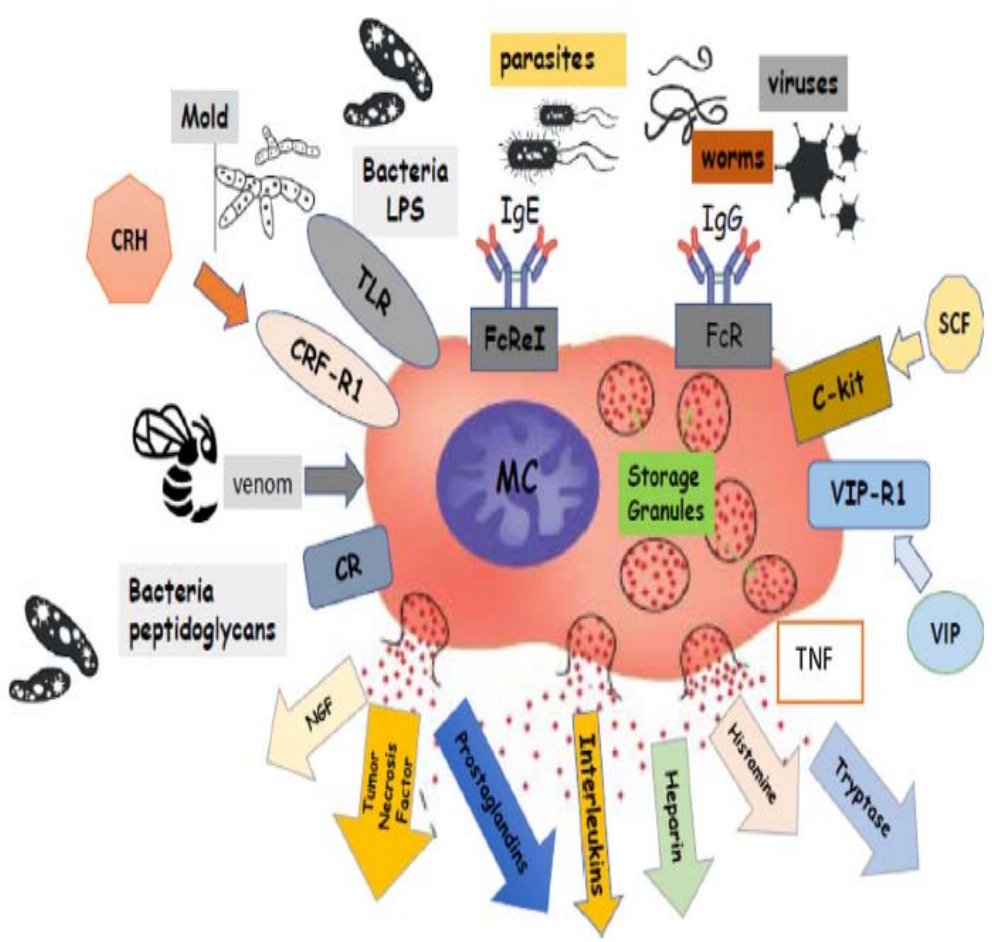
Urine PGD2, 11-beta PGF2

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

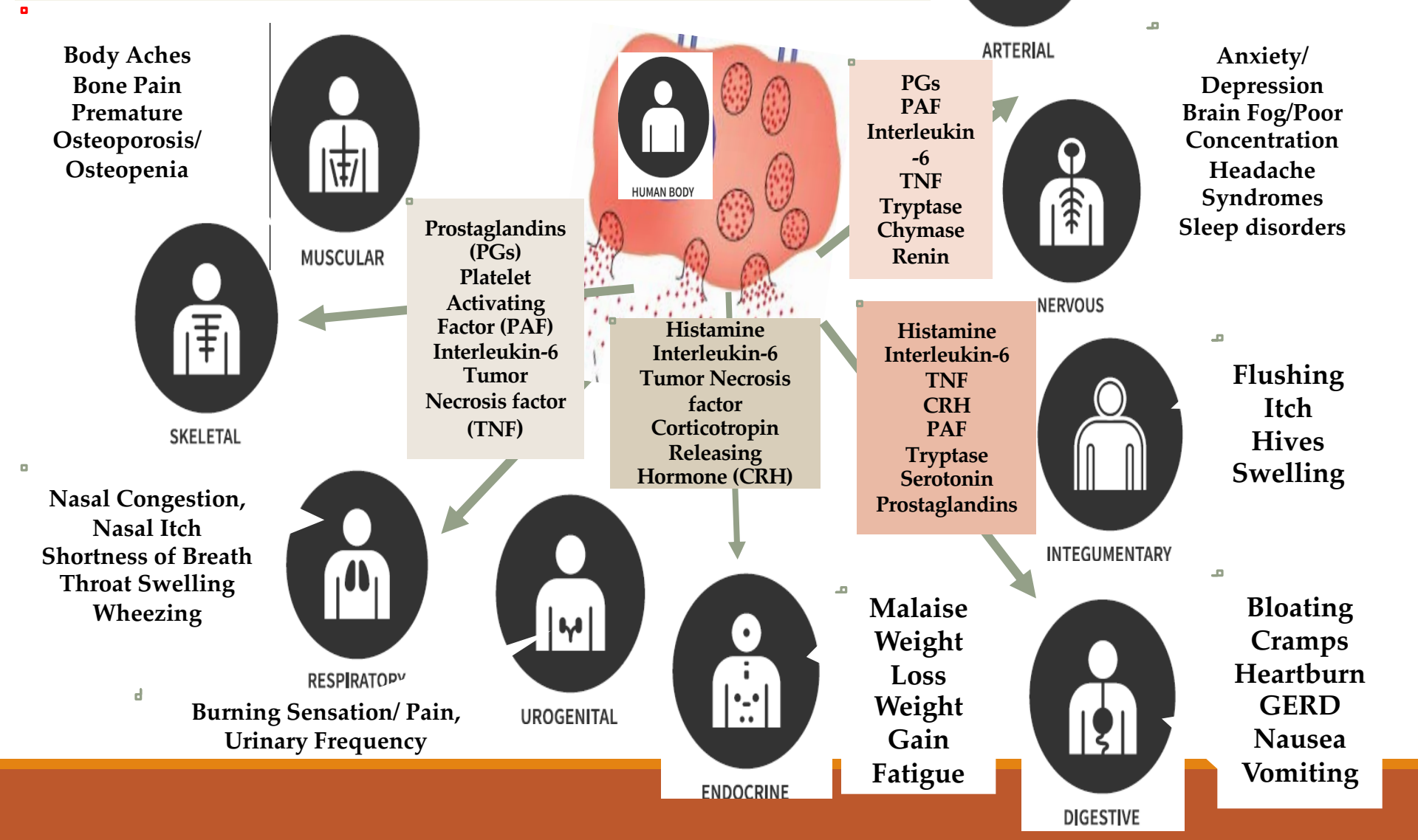
- MCs contain > 500 secretory granules and can de novo synthesize and release mediators following stimulation, via **degranulation or differential, piecemeal release**



arachidonic acid products, biogenic amines, chemo-attractants, cytokines, growth factors, neuropeptides, proteoglycans, and proteolytic enzymes

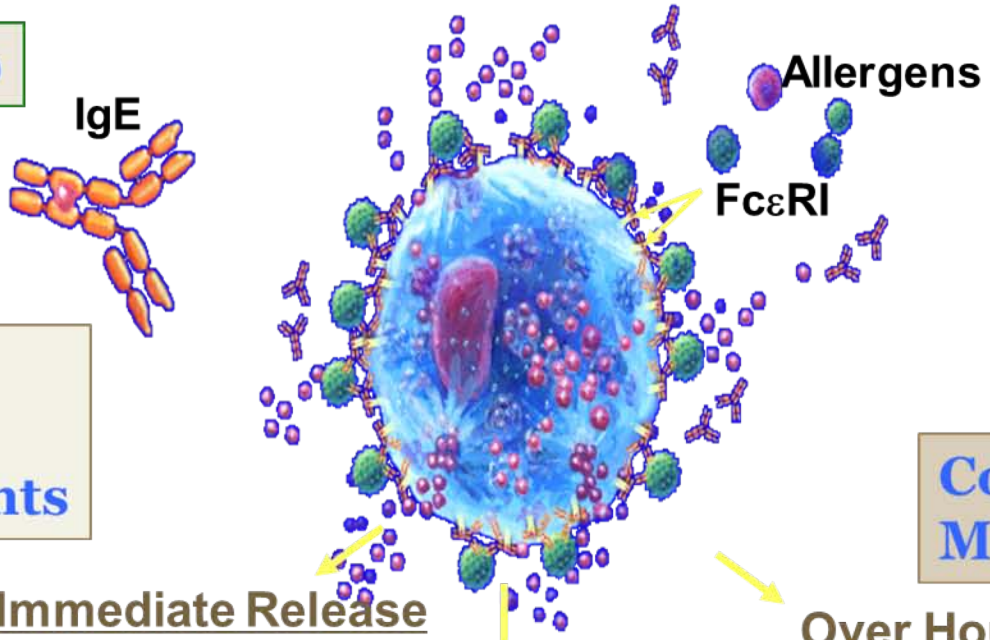
Theoharides, & Bielory, Annals Allergy, Asthma & Immunology, 2003

- Mast Cells are situated in every organ system and have various sensors to detect different "dangers."
- The kind of trigger and the site of encounter will determine which chemical mediators are released, and consequently, the MCAD associated symptoms.



(3) Response to Treatment:
Targeting MC/MC Inflammatory Mediators

Anti-IGE mAb



Traditional Chinese (TCM) Herbal Medicine Acupuncture

Histamine Blockade Tricyclic Agents

Corticosteroids MC stabilizers

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

Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes

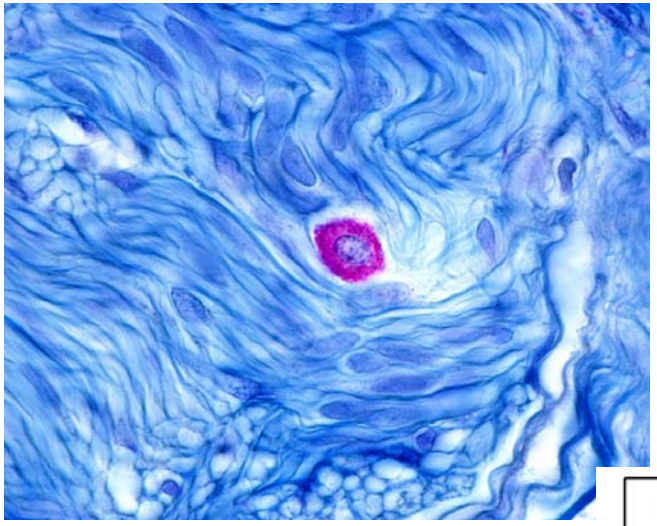
Over Hours
Cytokine production:
Specifically IL-4, IL-13

Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes

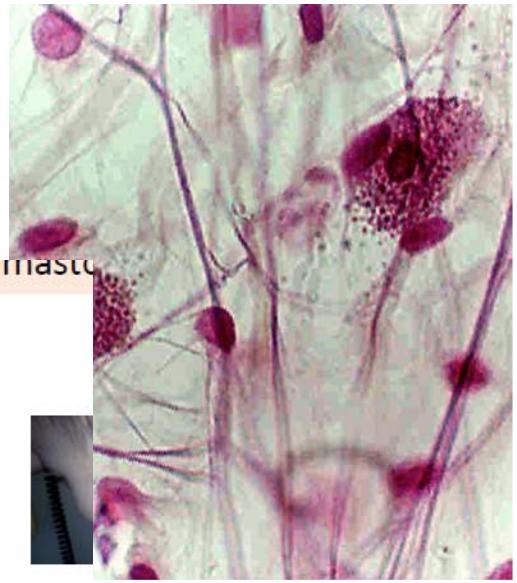
Wheezing
Bronchoconstriction

Mucus production
Eosinophil recruitment

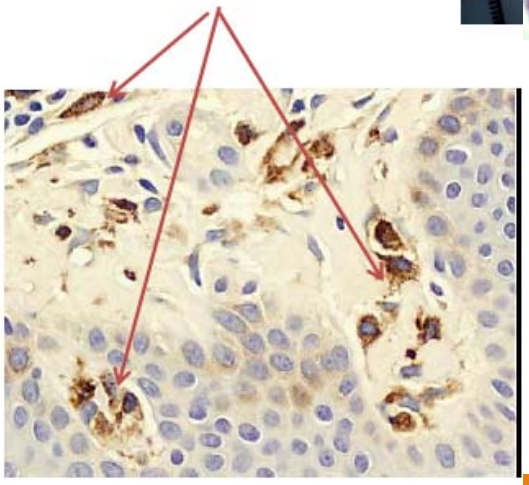
Leukotriene Blockade



Looking for Mast Cells?



Under the Microscope:
A sign of mastocytosis: Mast cells, that are spindled shaped (no longer round) and are clustered.



- **Ask the pathologist:**

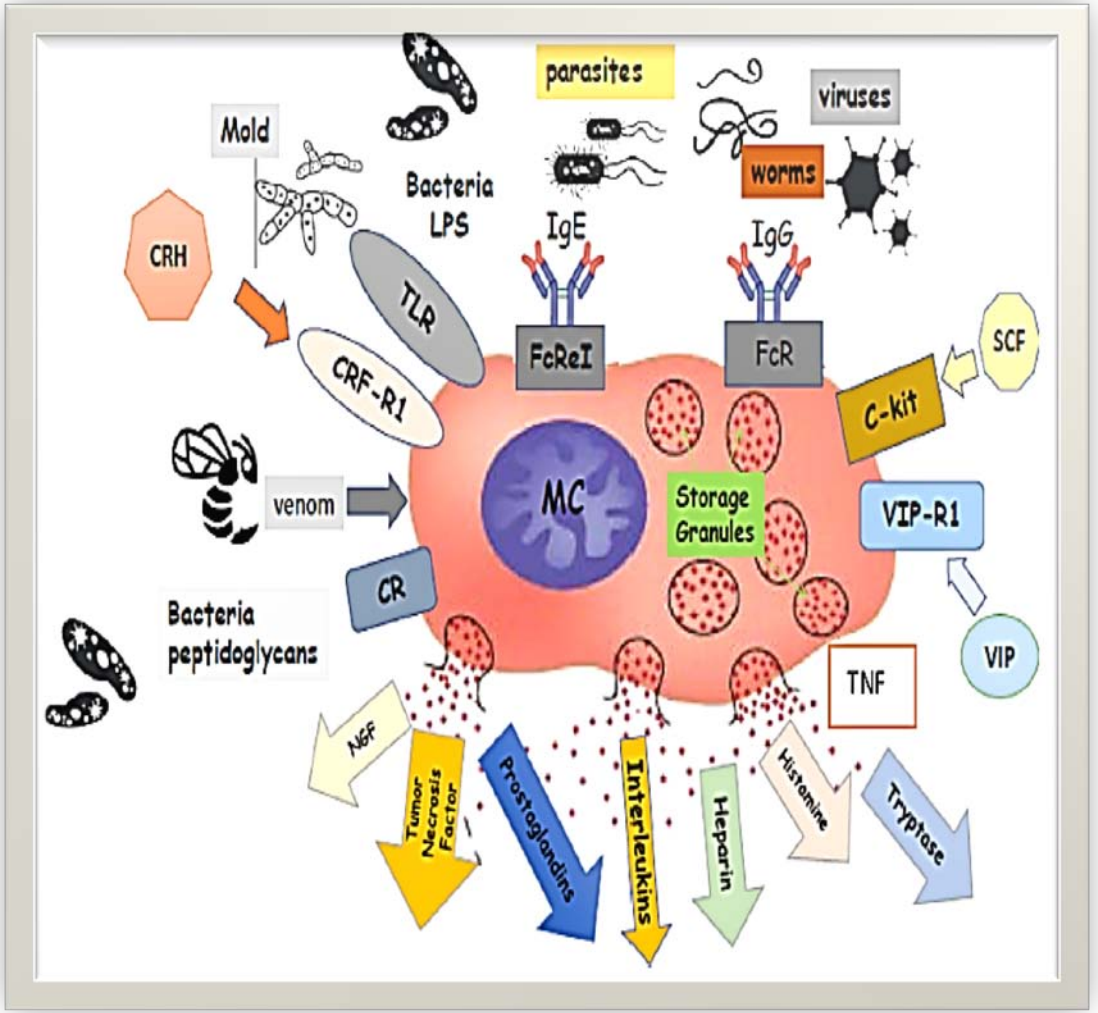
MCs: CD117, anti-tryptase

MC activation markers: CD2, CD25, CD30 Expression

What's tickling the MCs?

While the cause (s) of MCAS 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."

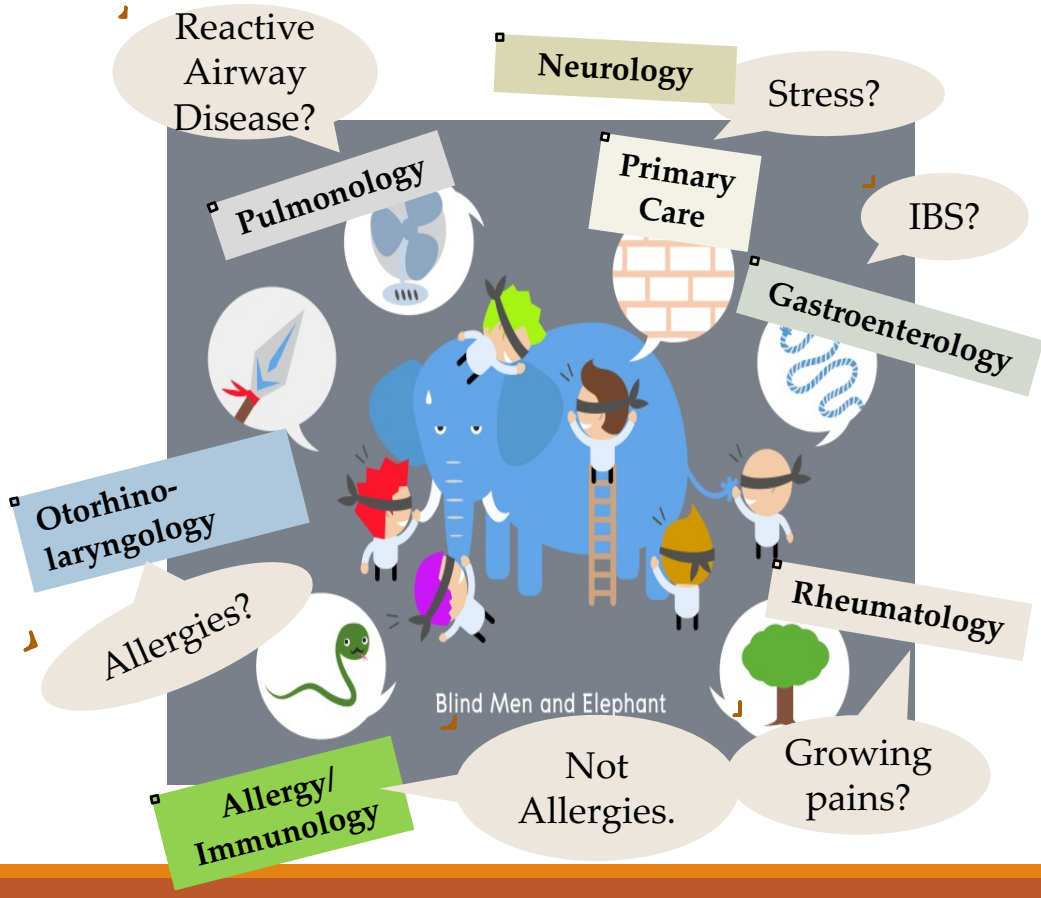
- Dr. Matthew J. Hamilton of Brigham and Women's Hospital, Boston, 2011



Roadblock #1
Delay in diagnosis of MCAD

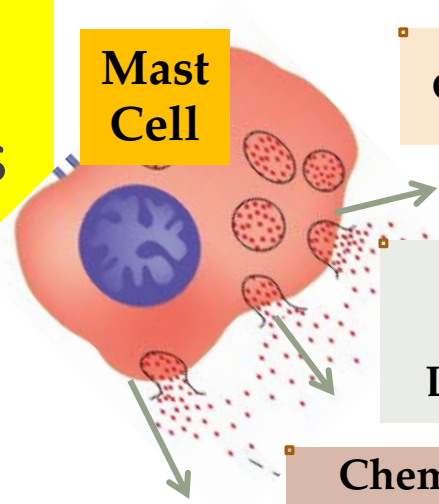
(Mast Cell) disorders now cause problems of increased complexity and commonly involves several organ systems, so patients are often referred to a succession of different specialists, resulting only in confusion.

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



Roadblock #2
Delay in diagnosis of MCAD

"I'll do some tests rather than give you a guess."



Cytokines

Histamine
Heparin
Leukotrienes

Chemokines
Tumor Necrosis factor

Serotonin
Nerve Growth Factor

Enzymes
Chymase
Tryptase

Few commercial tests available to detect MCA

Not all mediators are MC specific (only tryptase)

Failure to inform pathologists to stain for mast cells (anti- CD117 or anti-tryptase Antibodies)

Not enough data on number or morphology of mast cells = worrisome for MCAD?

Mast Cell Suppression –> Symptoms – No Better or Worse with Histamine Blockers??

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

Corticosteroids
MC stabilizers
Cytokine Antagonists

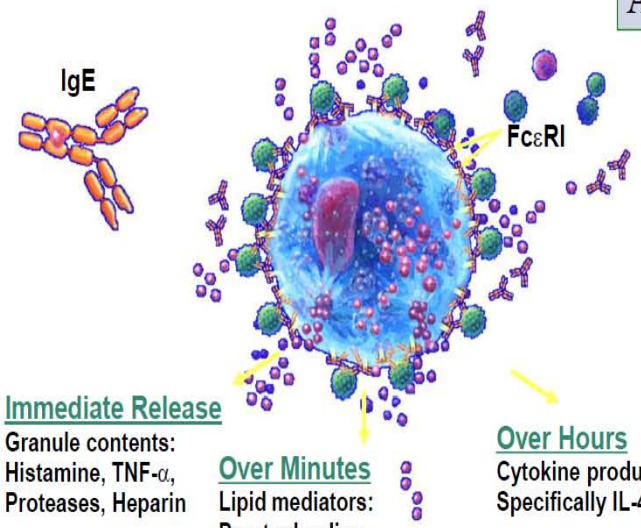
Anti-IGE mAb

Histamine Blockade
Tricyclic Agents

Leukotriene Blockade
Cyclooxygenase Inhibitors

Nutraceuticals
DAO supplement
Vitamin C
Quercetin
Stinging Nettle
Butterbur

Traditional Chinese (TCM) Herbal Medicine
Acupuncture

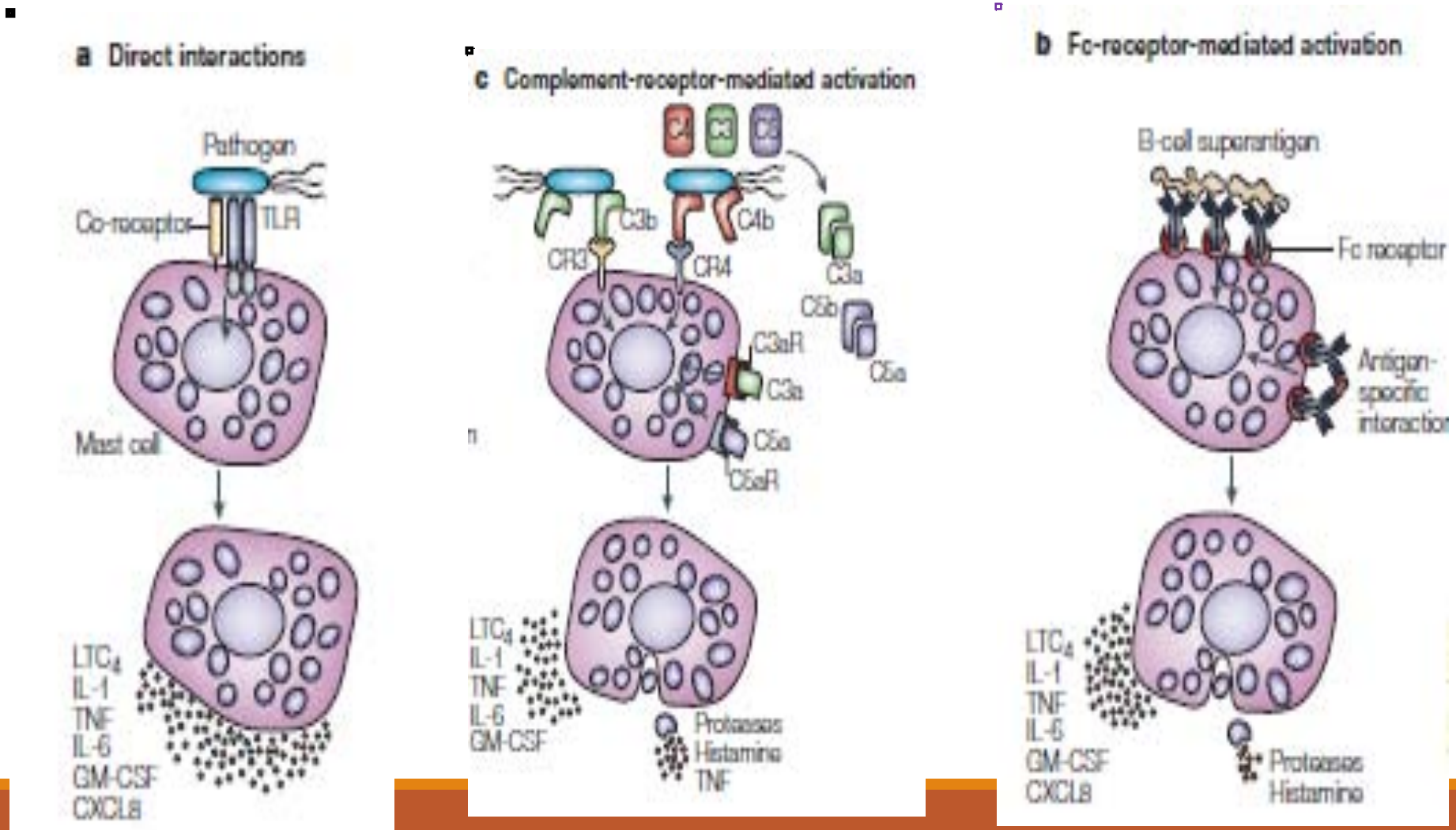


Theoharides et al, NEJM 2015; Engler et al, J Allergy Clin Immunol,2009;

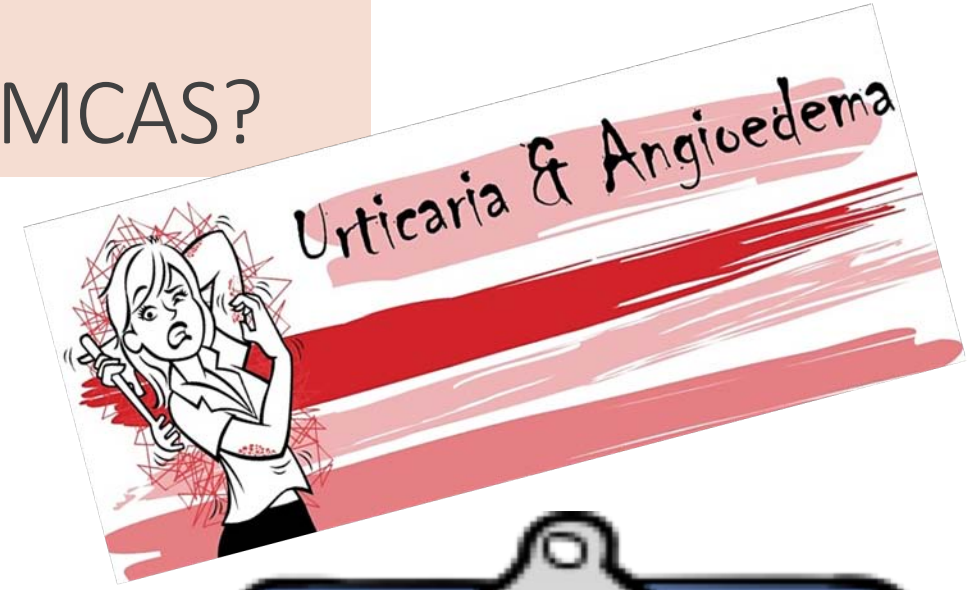
Roadblock #3:

Delay in diagnosis of MCAD

Not all Sensor triggered MC signaling is the same!



A CASE REPORT… Is it MCAS?

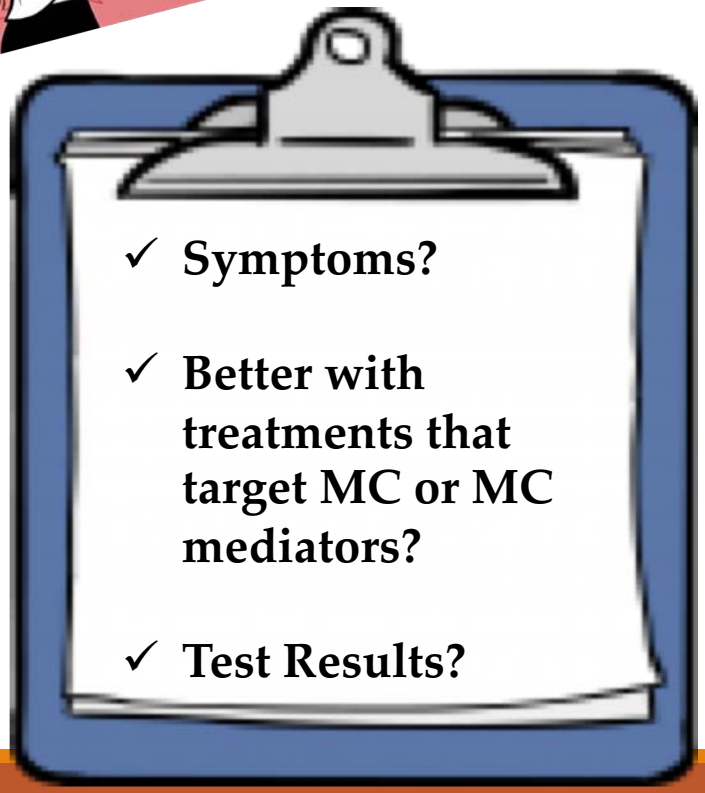


HER STORY…

Patient JK is a 41-year-old Caucasian Woman, now on disability.

JK has a history of chronic hives for over a year and comes for a second opinion on the cause of her hives, since the anti-histamines are no longer working to control her itchy rash.

She also has complained of episodes of bloating and has been treated for mood disorders and insomnia.



TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC With Differential/Platelet					
WBC	6.7		x10E3/uL	4.0 - 10.5	01
RBC	4.01		x10E6/uL	3.77 - 5.28	01
Hemoglobin	12.2		g/dL	11.1 - 15.9	01
Hematocrit	37.9		%	34.0 - 46.6	01
MCV	95		fL	79 - 97	01
MCH	30.4		pg	26.6 - 33.0	01
MCHC	32.2		g/dL	31.5 - 35.7	01
RDW	13.6		%	12.3 - 15.4	01
Platelets	293		x10E3/uL	140 - 415	01
Neutrophils	70		%	40 - 74	01
Lymphs	23		%	14 - 46	01
Monocytes	6		%	4 - 13	01
Eos	1		%	0 - 7	01
Basos	0		%	0 - 3	01
Neutrophils (Absolute)	4.7		x10E3/uL	1.8 - 7.8	01
Lymphs (Absolute)	1.5		x10E3/uL	0.7 - 4.5	01
Monocytes(Absolute)	0.4		x10E3/uL	0.1 - 1.0	01
Eos (Absolute)	0.0		x10E3/uL	0.0 - 0.4	01
Baso (Absolute)	0.0		x10E3/uL	0.0 - 0.2	01
Immature Granulocytes	0		%	0 - 2	01
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1	01

Low Total Serum IGE

Immunoglobulin E, Total	9		IU/mL	0 - 100	01
Complement, Total (CH50)	**63**	**High**	U/mL	22 - 60	01

Tissue Inflammation??

D001-IgE D pteronyssinus	**0.10**	**Abnormal**	kU/L
D002-IgE D farinae Mite	**0.09**	**Abnormal**	kU/L
E001-IgE Cat Hair/Dander	**2.23**	**Abnormal**	kU/L
E002-IgE Dog Epithelia	**0.15**	**Abnormal**	kU/L
G002-IgE Bermuda Grass	**0.13**	**Abnormal**	kU/L
G008-IgE Bluegrass, Kentucky	<0.08		kU/L
G017-IgE Bahia Grass	<0.08		kU/L
I100-IgE Cockroach,American	<0.08		kU/L
M001-IgE Penicillium notatum	**0.11**	**Abnormal**	kU/L
M002-IgE Cladosporium herbaru	<0.08		kU/L
M003-IgE Aspergillus fumigatu	**0.08**	**Abnormal**	kU/L
M004-IgE Mucor racemosus	<0.08		kU/L
M006-IgE Alternaria tenuis	<0.08		kU/L
M010-IgE Stemphylium botryosu	**0.08**	**Abnormal**	kU/L
T030-IgE Birch, White	<0.08		kU/L
T007-IgE Oak, White	**0.12**	**Abnormal**	kU/L
T008-IgE Elm, American (White			

Allergen-Specific IGE

	Absent	Very Mild	Mild	Moderate	Severe	Very Severe
Facial pain/pressure	0	1	2	3	4	5
Facial congestion/fullness	0	1	2	3	4	5
Nasal obstruction/blockage	0	1	2	3	4	5
Discolored or pus nasal discharge or post-nasal drip	0	1	2	3	4	5
Decreased sense of smell	0	1	2	3	4	5
Headache	0	1	2	3	4	5
Fever	0	1	2	3	4	5
Halitosis (bad breath)	0	1	2	3	4	5
Fatigue (tiredness)	0	1	2	3	4	5
Dental pain	0	1	2	3	4	5
Cough	0	1	2	3	4	5
Ear pain/pressure/fullness	0	1	2	3	4	5

Please estimate your medication usage as indicated below based on your care for the last 12 months:

Nasal steroid sprays (Vancenase, Flonase, Nasonex, Rhinocort, Nasacort, etc)
I currently use these medications (Y) N
I used these medications for a total of few weeks weeks in the last 12 months

Anti-histamines (Allegra, Claritin, Zyrtec, etc)
I currently use these medications (Y) N
I used these medications for a total of everydays weeks in the last 12 months

Antibiotics
Number of courses in last 12 months 5-6
I spent a total of 5-6 weeks on antibiotics in the last 12 months
My longest course of antibiotics lasted 10 days

Please comment on how the nasal problem has affected your recent work and social status as listed below

In the last 12 months, I missed a total of 20 days of work/school due to nasal problems

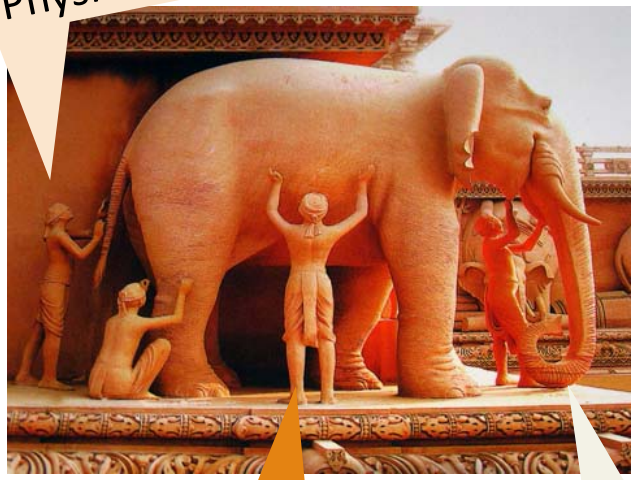
In the last 12 months, I did not leave home for weeks days due to my nasal problems

In the last 12 months, I visited a doctor or nurse 7 times for my nasal problems

In the last 12 months, I had 7 acute infections of my nose/sinuses

Delayed Diagnosis of her Primary Immune Deficiency (PID)?!#

Primary Care Physician



ENT

Pulmonologist

Many faces of Mast Cell Activation

Thyroid Panel With TSH			
TSH	1.360	uIU/mL	0.450 - 4.500
Thyroxine (T4)	6.1	ug/dL	4.5 - 12.0
T3 Uptake	30	%	24 - 39
Free Thyroxine Index	1.8		1.2 - 4.9
Thyroid Antibodies			
Thyroid Peroxidase (TPO) Ab	11	IU/mL	0 - 34
Antithyroglobulin Ab	<20	IU/mL	0 - 40
Siemens (DPC) ICMA Methodology			
Chronic Urticaria			
cu index	**>50.0 High**		<10.0
The CU Index(R) test is the second generation Functional Anti-FceR test.Patients with a CU Index(R) greater than or equal to 10 have basophil reactive factors in their serum which supports an autoimmune basis for disease. * This test was developed and its performance characteristics determined by Viracor-IBT Laboratories.It has not been cleared or approved by the FDA.			
Immunoglobulin E, Total	10	IU/mL	0 - 100
Tryptase	9.3	ug/L	2.2 - 13.2

IgE receptor auto-antibodies

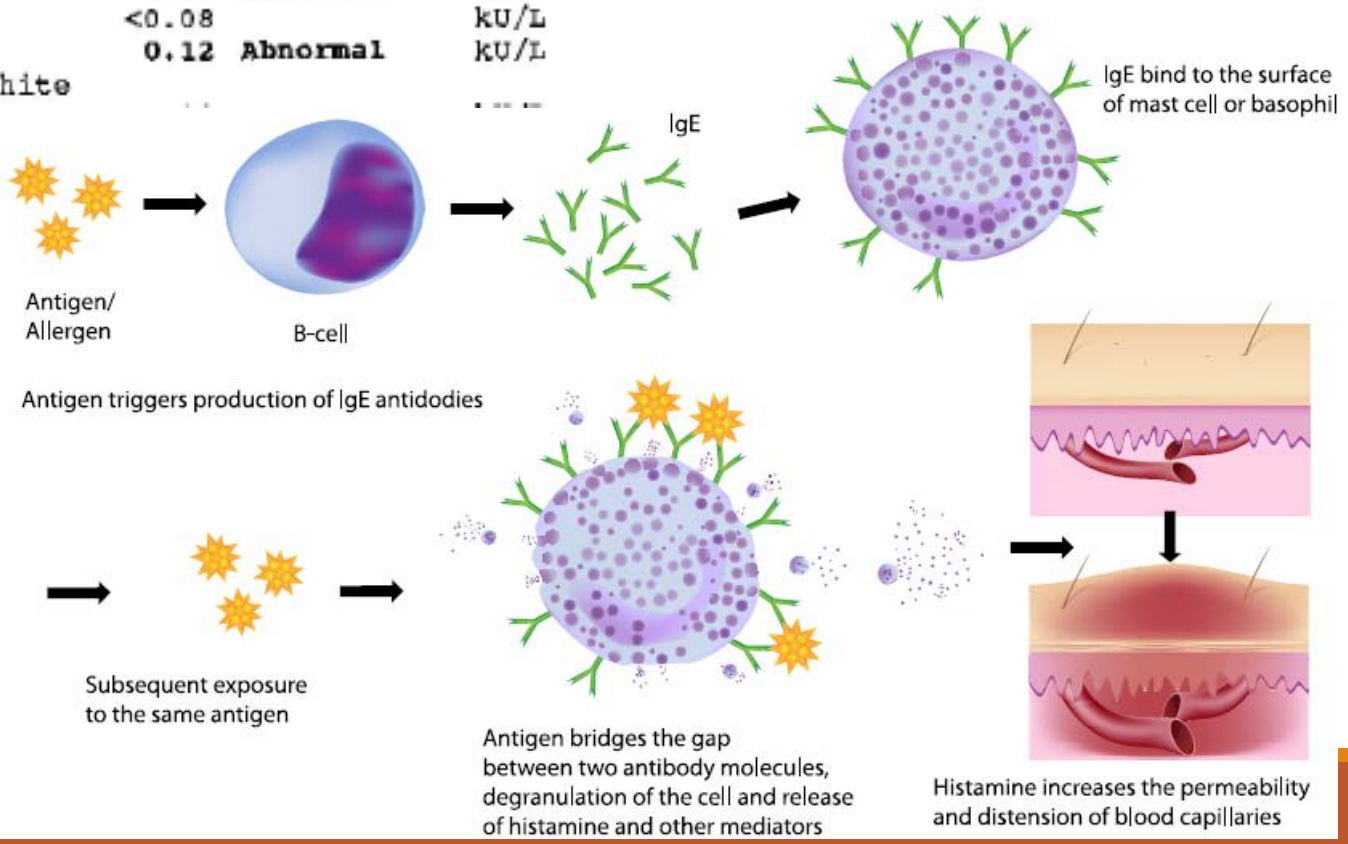
Trytpase >8 mcg/ml or higher, Hypertryptasemia?

Immunoglobulins A/G/M, Qn, Ser			
Immunoglobulin G, Qn, Serum	532 Low	mg/dL	700 - 1600
Immunoglobulin A, Qn, Serum	85	mg/dL	70 - 400
Effective September 10, 2012, the reference interval for Immunoglobulin A, Qn, Serum will be changing to:			
	0 - 11 months		11 - 58
	1 - 2 years		20 - 101
	3 - 6 years		44 - 189
	7 - 12 years		62 - 236
	13 - 17 years		77 - 278
	18 years and older		91 - 414
Immunoglobulin M, Qn, Serum	221	mg/dL	40 - 230

Hypogammaglobulinemia

JK's CU: Many Triggers of MCA

D001-IgE D pteronyssinus	0.10	Abnormal	kU/L
D002-IgE D farinae Mite	0.09	Abnormal	kU/L
E001-IgE Cat Hair/Dander	2.23	Abnormal	kU/L
E002-IgE Dog Epithelia	0.15	Abnormal	kU/L
G002-IgE Bermuda Grass	0.13	Abnormal	kU/L
G008-IgE Bluegrass, Kentucky	<0.08		kU/L
G017-IgE Bahia Grass	<0.08		kU/L
I100-IgE Cockroach,American	<0.08		kU/L
M001-IgE Penicillium notatum	0.11	Abnormal	kU/L
M002-IgE Cladosporium herbaru	<0.08		kU/L
M003-IgE Aspergillus fumigatu	0.08	Abnormal	kU/L
M004-IgE Mucor racemosus	<0.08		kU/L
M006-IgE Alternaria tenuis	<0.08		kU/L
M010-IgE Stemphylium botryosu	0.08	Abnormal	kU/L
T030-IgE Birch, White	<0.08		kU/L
T007-IgE Oak, White	0.12	Abnormal	kU/L
T008-IgE Elm, American (White			



Does JK have MCAS? Yes.

- ✓ **Symptoms?**
- ✓ **Test Results?**
- ✓ **Better with treatments that target MC or MC mediators?**

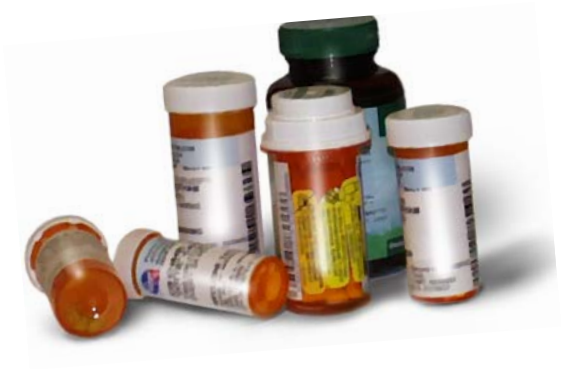
hives, GI/ bloating
neuro-psychiatric illness.

Elevated plasma histamine
Tryptase 8 ng/ml; 4.8 ng/ml
EGD- more than 40 MCs/HPF

Tried diphenhydramine, cetirizine, ranitidine, clemastine, cimetidine, loratadine
– “my life is H*** 24-7, 365 days of the year”

Lessons from Urticaria

Chronic Urticaria (CU) Care: Tailored Diagnostics and Therapeutics



- **IgE-mediated reactions from foods, drugs, or other allergens**

Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies

****

Chronic infections: viral infections- hepatitis B and C, EBV, herpes simplex virus; Helicobacter pylori infections; and helminthic parasitic infections

Complement component deficiencies

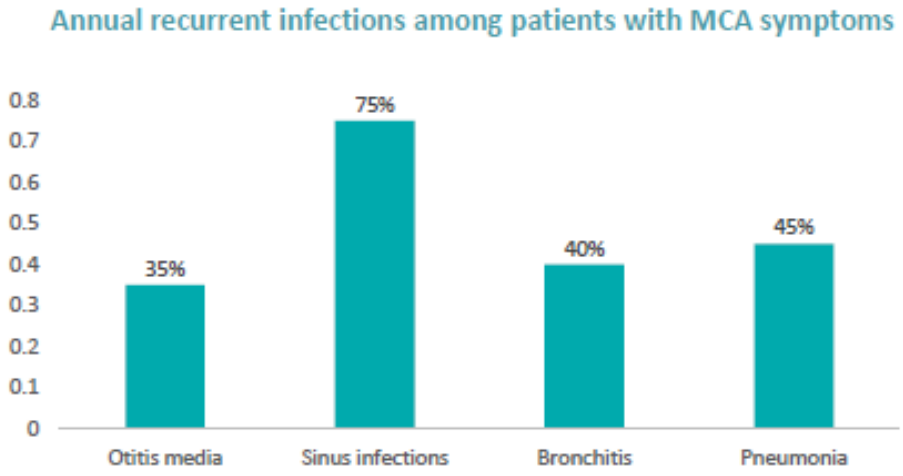
Serum sickness or other immune-complex mediated processes

Autoimmune/Connective tissue diseases, systemic lupus erythematosus and rheumatoid arthritis

thyroid disease (both hypothyroidism and hyperthyroidism)

neoplasms (particularly lymphoreticular malignancy and lymphoproliferative disorders)

Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies



A Mast Cell Activation Syndrome as a presenting sign of a Primary Immunodeficiency?

1. Eight or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or elsewhere on skin, after age 1.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections.
10. A family history of Primary Immunodeficiency.

Living with Mast Cell Activation Syndrome

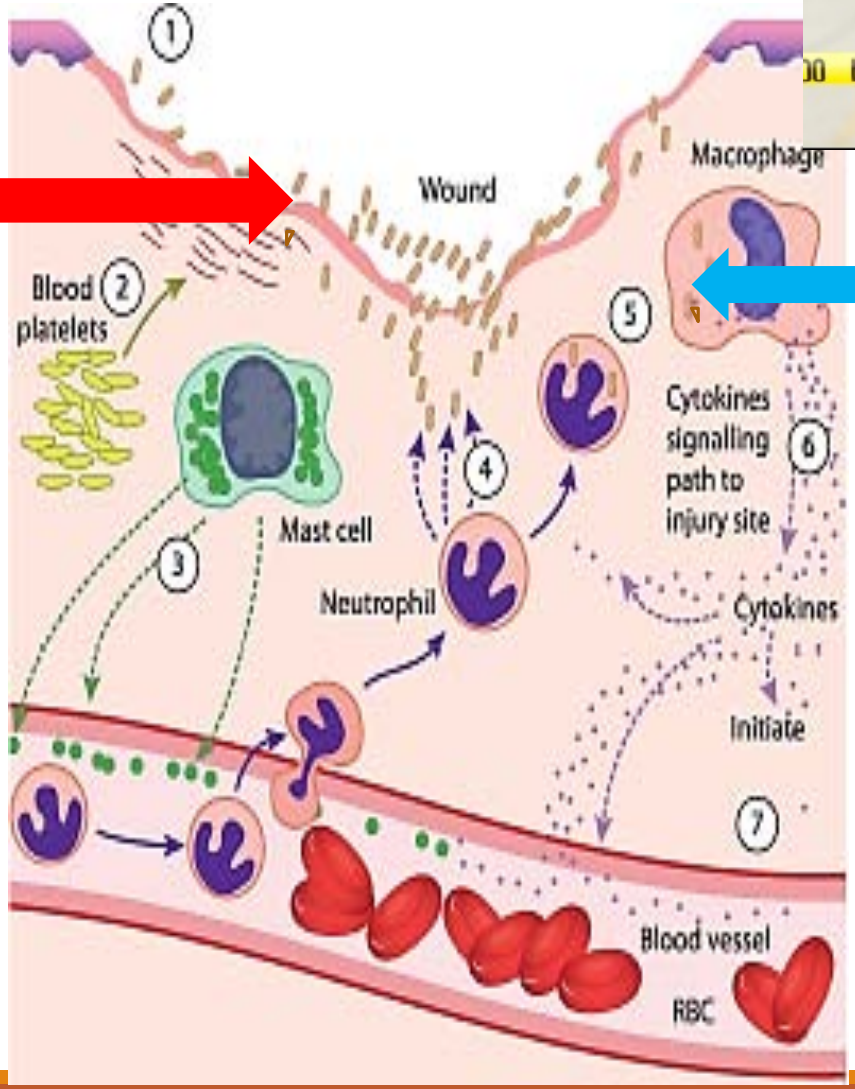
TEAM WORK!

Mast Cell Activation (MCA)

Danger Signals

(1)
Damage Alert:
<u>Endogenous, self alarm signals, indicating danger:</u>

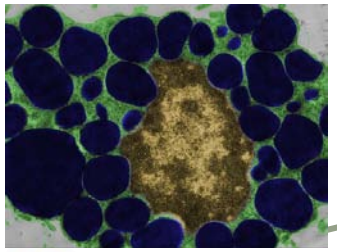
breakdown products of hyaluron (made when vessels are damaged). mammalian DNA, RNA, heat shock proteins (Hsps), interferon a, interleukin-1beta, CD40-L

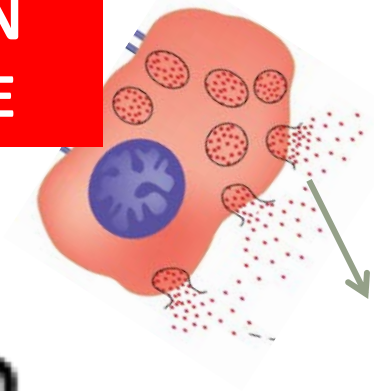


(2)
Threat recognition & Response

pattern recognition receptors (PRRs) membrane-bound Toll-like receptors (TLRs), Complement receptors, Immunoglobulin Receptors on MCs

MAST CELL ACTIVATION SYNDROME





Cytokines

Histamine
Heparin
Leukotrienes

Chemokines
Tumor
Necrosis factor

Serotonin
Nerve
Growth
Factor

Enzymes
Chymase
Tryptase

1) Symptoms?
2) Better with treatments that target MC or MC mediators?
3) Test Results?

RHINITIS

Headaches
BRAIN
FOG

ASTHMA

ANAPHYLAXIS

FOOD
Sensitivities
IBS

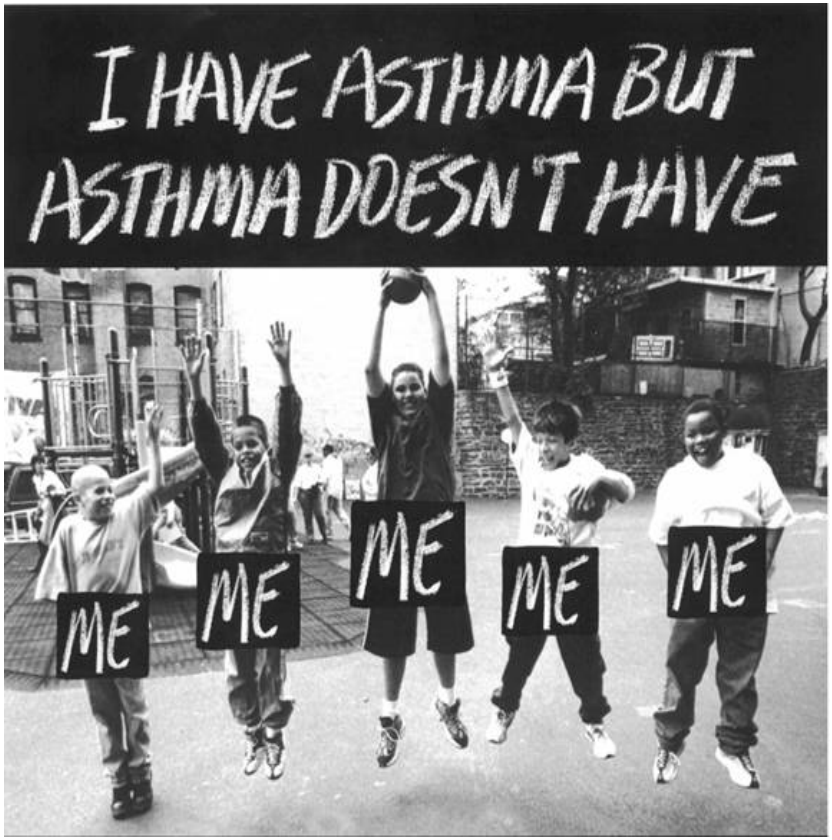
Pain
syndromes

Interstitial
Cystitis

Urticaria
Flushing
Angioedema

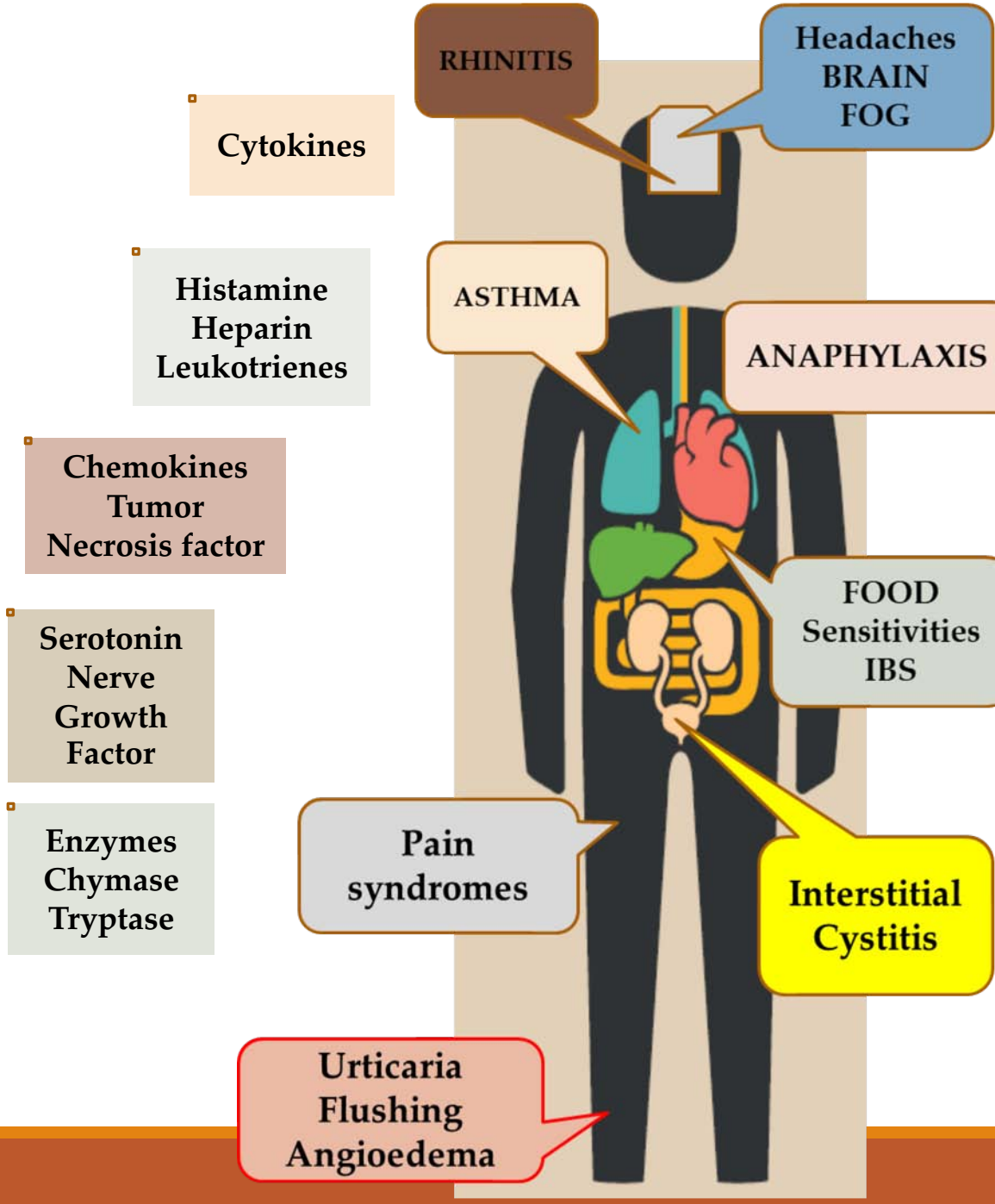
To Feel and Live Better – S.T.E.P. Up to Your Next Check Up!

- ✓**S**creen
  - Symptoms?
  - Risk Factors?
  - Previous treatments?
- ✓**T**ests -
  - MCAD
  - MCAD co-morbid illnesses
- ✓**E**ducate yourself
  - Triggers
  - Recognition of MCAS symptoms
- ✓**P**lan



MCAS DIAGNOSIS AND TREATMENT

Targeting the co-morbid disorders, Which are driving MC Activation



Allergen testing
Celiac Panel
EGD/ Colonoscopy

Some food (wheat/gluten, peanuts, eggs, nuts and shellfish, milk*, egg*, soy*)

Medications

Airbone Allergens

Insect stings or bites

Autoimmune Disorders

Infections

Physical stimuli, such as pressure, cold, heat, exercise or sun exposure

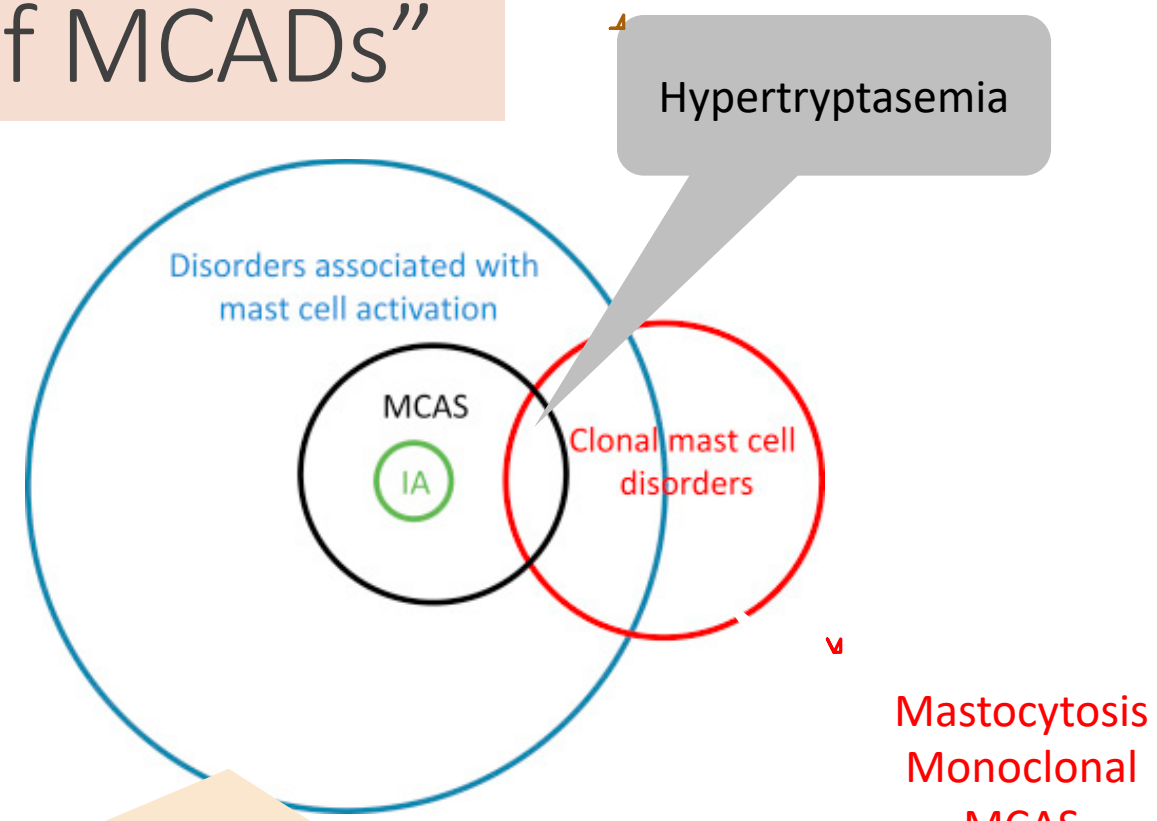
Allergen testing

<u>Rheumatology Panel</u>
ANA, RF, ANCA,
Thyroid Abs
Neuonal Abs
PIDD evaluation

PIDD evaluation
Primary
Immune
Deficiency
Disorder

EDS Screen?
Neuropathy?

MCAD Endotypes "flavors of MCADs"



Mastocytosis
Monoclonal
MCAS

- Allergic (IGE mediated) Disorders
- MC activation associated with chronic inflammatory/neoplastic disorders
- Physical Urticarias
- Chronic Autoimmune Urticaria

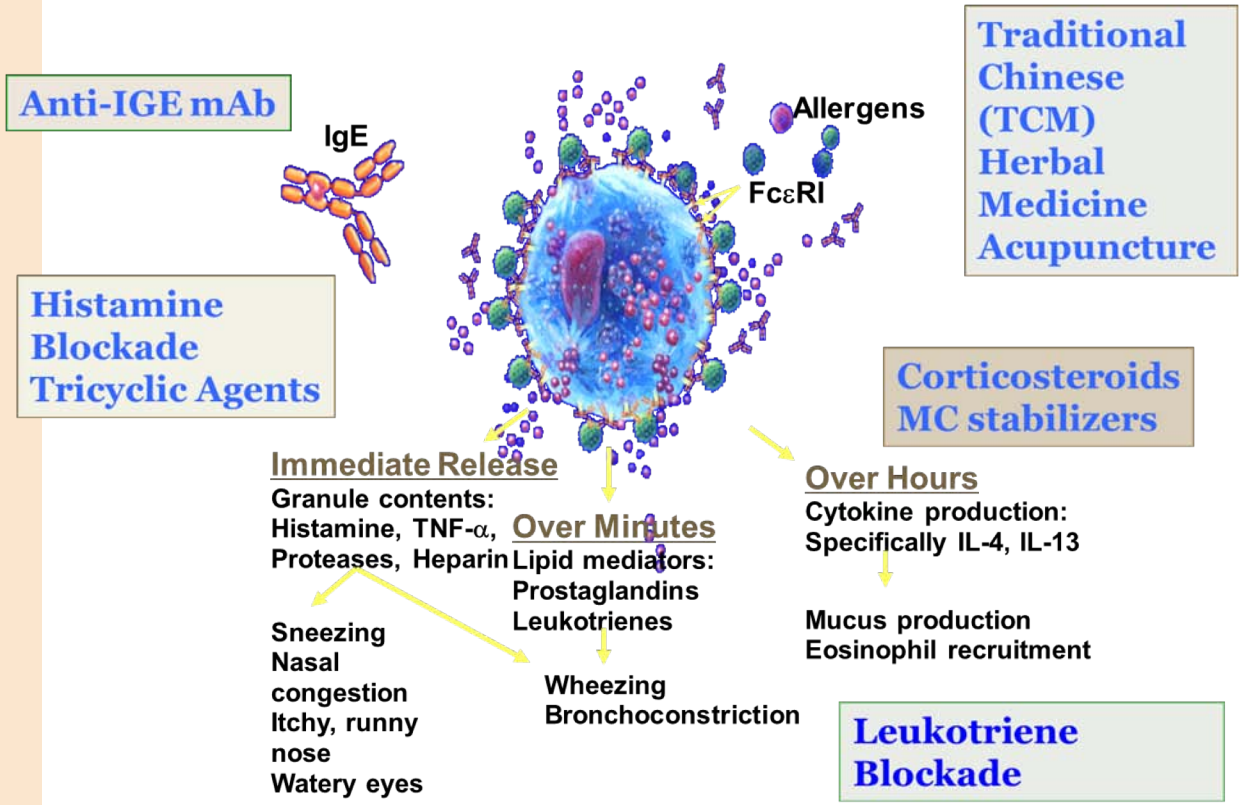
Allergens

- Avoidance measures (Diet, Environment)
- Medications: histamine blockade
- Desensitization (Immunotherapy)
- Traditional Chinese Herbal Therapy
- Omalizumab
- Anti-interleukin mAb

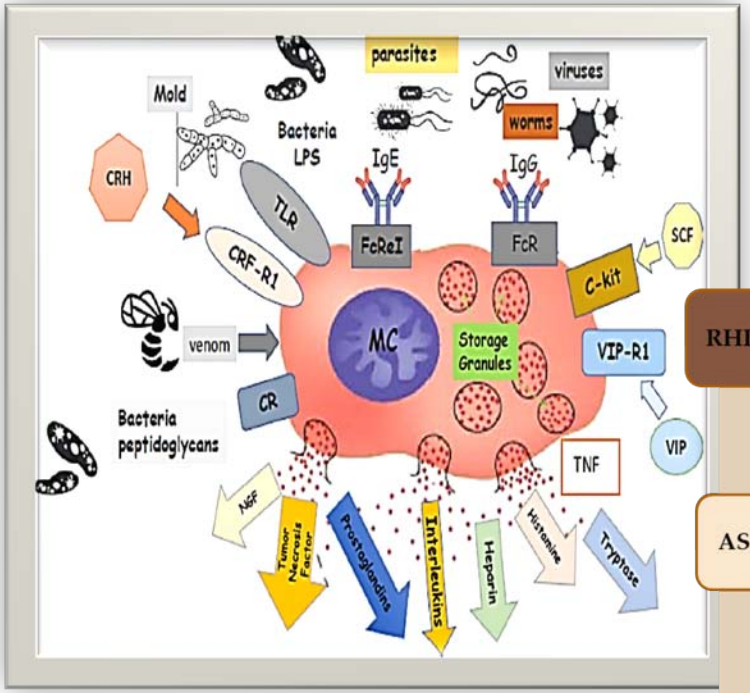
Autoimmune Disorders

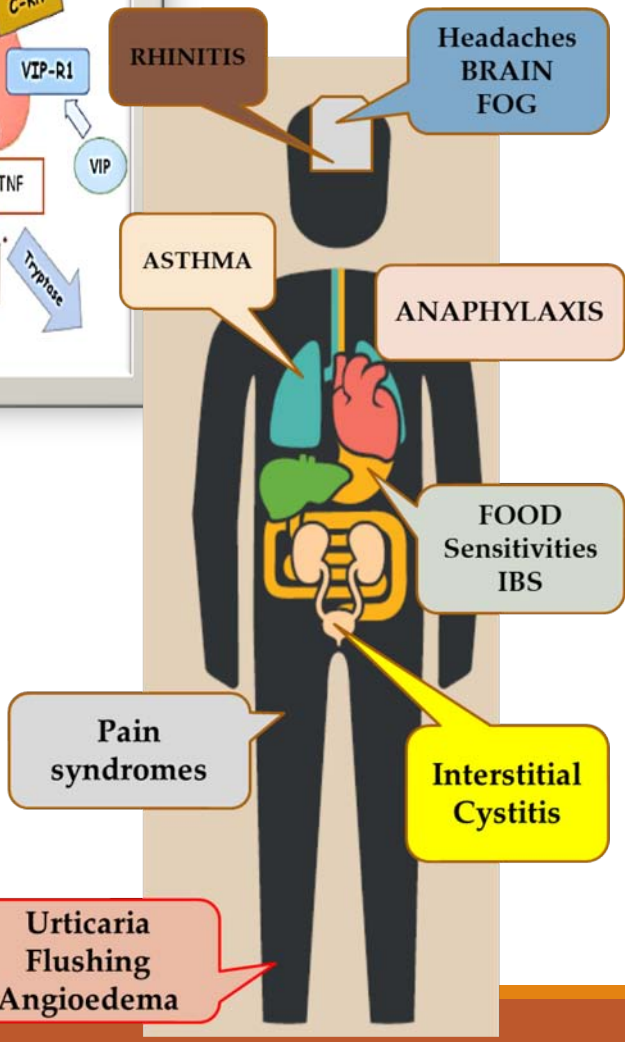
- Anti-inflammatory Agents
- Immune Globulin Supplement
- Traditional Chinese Herbal Therapy

Connective Tissue Disorders



MCA =“canary in the mine”



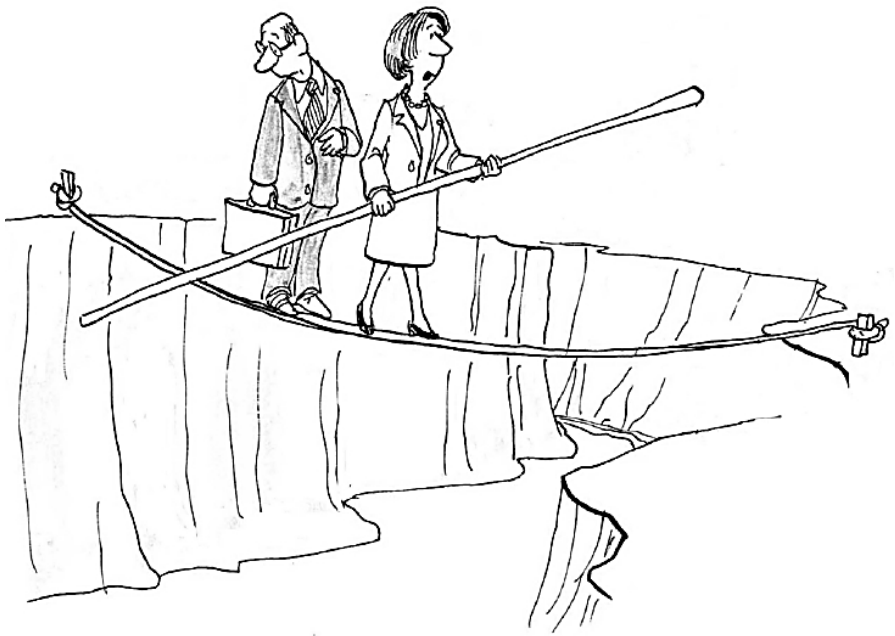


Primary Immune Deficiency

- Prophylactic Antibiotics
- Immune Globulin Supplement

Autoimmune Disorders

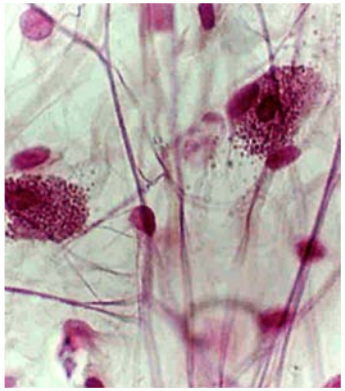
- Anti-inflammatory Agents
- Immune Globulin Supplement
- Traditional Chinese Herbal Therapy



"We want someone who's willing to take risks."

Gratitude!

Thank you!



It takes a village!

Patients and their families

Chiari Syringomyelia Foundation

Ehlers Danlos Society

The Mastocytosis Society

Contact Information

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AsktheAllergist
DrAnneMaitland