Presentation 2 – William Meggs

Chemical Sensitivity

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Objectives

- Brief history of environmental medicine in the United States
- First descriptions of chemical sensitivity
- Epidemiology of chemical sensitivity
- Mechanisms of chemical sensitivity
- Research needs

What initiated my interest in Environmental Medicine?

- Personal witnessed 'miraculous cures'
- Polymyositis
  - Case of Wheat intolerance
- Rheumatoid arthritis
  - Case of milk intolerance
  - Challacombe & Brostof, eds, Food Allergy & Intolerance, 2ed
- Crohn's disease
  - Cigarette intolerance

Basic Approach of Environmental Medicine

- Some diseases are induced &/or exacerbated by environmental factors.
- Some diseases are optimally managed by environment eliminations.
- Individual susceptibility
- Environmental factors in diseases
  - Chemicals naturally occurring in foods
  - food additives
  - chemicals and biologicals in air & water
  - body flora & fauna.

Contrast

- **Mainstream Medicine**
  - If a person is sick, they need to have chemicals added to their bodies.
- **Environmental Medicine**
  - If a person is sick, they need to have chemicals removed from their bodies.

Complementarity: if a person is sick, there are specific indications for having chemicals added to their bodies, & specific indications for having chemicals removed from their bodies. The challenge is to find these indications.

Early Beginnings

- **Food intolerance**
- **Group of allergists in the Midwest, 1930's**
- **"Masked food allergy"**
  - Tolerance of food if ingested daily
  - Period of abstinence followed by re-exposure results in acute reaction
- **Cyclical vs. Fixed food allergy**
  - REF: *Food Allergy* by Rinkel HJ, Randolph TG, Zeller M. CC Thomas, Springfield IL, 1951. [out of print].

Diagnostic Approach

- Period of avoidance
- Re-exposure
- Monitor for symptoms
- Non-reaginic allergy [not IgE mediated]

Case Report: Dr. HJ Rinkel

- **Son of egg farmer**
- **Impecunious medical student with family**
- **Father sent gross of eggs each week**
- **Profuse rhinorrhea**
  - Multiple physician visits without help
- **Egg was suspected**
- **Egg avoidance for five days– rhinorrhea improved**
- **Ate birthday cake containing egg and had severe reaction**

Descriptions of Systemic Manifestations of 'Food Allergy'

- Fatigue
- Headache
- Brain-fag, depression, psychosis
- Myalgias
- Arthralgias, arthritis
- Cardiovascular manifestations
  - Fluid retention
  - Tachycardia

Methodology

- Setting: private practice
- Detailed history
- Trial & error
- Abstinence followed by re-exposure
- Carefully record signs & symptoms of illness -- emphasis on subjective symptoms
- Generalizations from individual cases
- No longitudinal data other than anecdotes

Fasting

- Introduced by Dr. Donald Mitchell, Montreal dermatologist & environmental physician
- Hospital practice
- Fast on spring water with sodium and potassium bicarbonate [2:1] until symptoms clear
- Re-expose to foods one by one

Rotation Diet

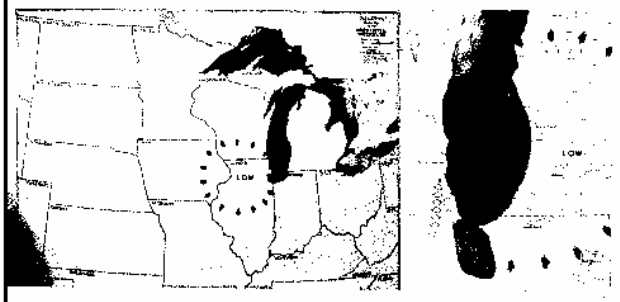
- One food per meal
- Repeat each food every 5 to 7 days
- Monitor for reactions
- Use organically grown, untreated, pure foods
- Eliminate any foods with untoward reactions

Pesticide Sensitivity

- Patient tested and found allergy to peaches
- Patient reported peaches from abandoned orchard gave no reaction
- Patient found to be intolerant of grocery store peaches but tolerant of peaches from abandoned orchard
- Sulfites, fungicides, insecticides

Sensitivity to 'Air Pollution'

- South Wind
- Industrial area
- Symptoms flare in some individuals when the winds are from the south



Gas Appliances

- Burn unvented natural gas in cook stoves, water heaters
- Patients turn off their gas for 5 to 7 days, use a hot plate, toaster oven, electric frying pan, etc., then turn it back on.
- "Shock Reactions" are diagnostic
- Homes with gas cook stoves have levels of sulfur dioxide and oxides of nitrogen above levels allowed in factories
  - Hollowell et al, LBL, early 1980's

Chemical Sensitivity

- **Individual susceptibility**
- **Products of combustion**
  - Tobacco smoke, vehicle exhaust, furnace fumes, gas appliances
- **Perfumes and fragrances**
- **Products for Cleaning**
- **Pesticides**
- **Chemicals in foods and food additives**
- **Paints and other solvents**
  - Outgassing of VOCs

•Randolph TG. Human ecology and susceptibility to the chemical environment. CC Thomas, Springfield,1962.

Micro-organism Intolerance

- Life on humans
- Susceptibility to toxins from micro-organisms colonizing our bodies

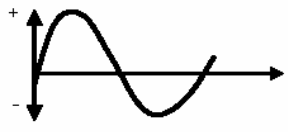
- Chronic candida vaginitis
  - IgE to candida
  - TH2 vs. TH1 helper lymphocytes
  - Host defense to candida is ablated
  - Small number of organisms produce huge symptoms
  - Treatment is desensitization to candida

'*Spreading*' Phenomenon

- With continued exposures, the numbers of substances a person is sensitive to increases.

Stimulatory & Withdrawal Symptoms

- Paired sets of symptoms
  - 0, 1+ & 1-, 2+ & 2-, 3+ & 3-, 4+ & 4-
- Exposure to the agent causes stimulatory symptoms
- Elimination of the agent causes an associated withdrawal symptom
- Examples:
  - Seizure/coma
  - Mania/depression



Environmental Control Unit

- Developed in 1950's, USA
- A hospital unit to isolate patients, de-adapt them from their environment, and reintroduce agents one-by-one
- Attention to air, water, food
- All Environmental Control Units in this country have been shut down, though there are operating units in Canada, England, Germany, and Japan

Examples of Diseases Evaluated in Environmental Control Units

Respiratory	Asthma, Rhinitis, Sinusitis, Pneumonitis
Musculoskeletal	Myositis, Arthritis, Collagen Vascular diseases
Gastrointestinal	Irritable Bowel Syndrome, Inflammatory Bowel Disease
Dermatological	Dermatitis, Rosacea, Cutaneous Vasculitis

Examples of Diseases Evaluated in Environmental Control Units

Cardiovascular	Unstable angina, hypertension, Arrhythmias, Vasculitis, Recurrent Anaphylaxis
Autoimmune Diseases	Multiple sclerosis, SLE, vasculitis, myositis
Neurological	Migraine, Seizures
Psychiatric	Bipolar disorder, Depression, Psychosis

Environmental Control Unit Protocol

- Highly Individualized
- Day One
  - Admitted to unit
  - History and physical examination with extensive environmental, dietary, and occupational history.
  - Routine laboratory testing was performed.
  - No inhalants on the unit

Environmental Control Unit Protocol

- Stage 1: Approximately 5 to 7 days
- Fasting stage
  - Patients fasted on distilled spring water
  - Monitored for withdrawal symptoms: headache, nausea, vomiting, myalgias, arthralgias, etc.
  - Alkaline salts: 2:1 $NaHCO_2$:$KHCO_2$
  - Monitored for electrolyte abnormalities, dehydration: Rehydrate with IV, glass bottles
  - Fast terminated when withdrawal symptoms end

Environmental Control Unit Protocol

- Stage 2: Approximately 10 to 20 days
- Food testing to establish a safe diet
- 'Suspected Safe' Foods eaten on rotation
- Each meal consisted of single organically grown pure food
- Monitor for adverse reactions

Environmental Control Unit Protocol

- Stage 3: Approximately 7 days
- Food testing to test highly suspect foods, pesticides, additives
- Patients continue their safe diet on 5 to 7 day rotation
- Highly suspect foods and contaminated foods introduced as single feedings, one by one

Environmental Control Unit Protocol

- Stage 4: Approximately 7 days
- Chemical testing
- Highly individualized
- Challenge testing to natural gas, vehicle exhaust, items from home

Environmental Control Unit Protocol

- Stage 5: Discharge
- Patients have been taught to evaluate reactions and avoid those things that make them sick
- Patients instructed to continue rotation diet of safe foods
- Patients instructed to modify home and work environment, automobile, etc.

Interpretation of Results

Adaptation Syndrome(s)

Generalized Adaptation Syndrome

REF: Selye, H.

Stage I. Preadaptation (Nonadapted)	Shock Reaction (Acute reactivity to chemicals)
Stage II. Addicted (Adapted) IIa. Adapted IIb Maladapted	 Tolerance Chronic Illness
Stage III. Postadapted (Nonadapted)	Exhaustion

Specific Adaptation Syndrome

- Mal-adaptation to a single substance
- Substance is tolerated without acute reactions but there is chronic disease
- Elimination of one substance leads to withdrawal symptoms then resolution of chronic disease
- Re-exposure to that substance leads to acute reactions

Chemical Stress Syndrome.

Stage 0. Normalcy	Tolerance of chemical exposures, wellness without symptoms
Stage 1. –algia	Sensory Hyper-reactivity. Subjective symptoms associate with chemical exposures. (arthralgias, myalgias, irritable bowel syndrome, etc.)
Stage 2. –itis	Inflammatory reactions to chemicals (arthritis, myositis, inflammatory bowel disease,etc.)
Stage 3. –osis	Fibrosis. Necrosis. Tissue destruction (arthritic deformities, muscle atrophy and necrosis,etc.)

Chemical Stress Syndrome

- **Dynamic**
- **Patients move back and forth through the stages**
- **Exposures drive patients between the stages**
  - Eliminating inflammatory chemicals moves patients to lower stages
  - Exposure to inflammatory chemicals move patients to higher stages
- **Stage 3 – Fibrosis and scarring – is permanent**

Emphasis

- Exposures to the Chemical Environment induces and exacerbates known diagnosable valid medical conditions with findings on physical exam and laboratory testing.
- These diseases can go into remission with environmental control

Suppression of Environmental Medicine in the USA

- **Small group of physicians**
- **Close ties to commercial interests**
- **"There is no scientific evidence that environmental medicine is efficacious."**
- **Argumentum *ad hominem* – attack the person, not the argument.**
  - Led to name change from *Clinical Ecology* to *Environmental Medicine*
  - Distinct from the specialty of *Occupational & Environmental Medicine*

Suppression of Environmental Medicine in the USA

- **Position statements: pts are crazy & doctors are quacks**
  - AMA, AAAAI, California Medical Society
- **Industry funded conferences**
  - After National Research Council Conference recommended federal funding of research ECU
- **Insurance companies to deny payment**
- **Physicians lost their licenses**
- **Network TV shows roasting physicians & pts**

Treatments

- Avoidance
- Provocative/neutralization
  - **Dermal injections**
- Vitamins
- Sauna detoxification
- Anti-fungals

Controlled Studies of Treatment Efficacy

- Literature is sparse.
- Controlled studies of provocative/neutralization were negative.

Survey of Treatment Efficacy

- Self-reported
- 917 self-reported MCS patients
- 101 treatments
  - **Environmental medicine**
  - **Holistic therapies**
  - **Nutritional supplements**
  - **Detoxification techniques**
  - **Prescription drugs, …**

Gibson PR, Elms AN, Ruding LA. Perceived Treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. Environ Health Perspective 2003;111:1498-1504.

Survey of Treatment Efficacy

- Treatments were expensive
  - Averaged spending 1/3 of income on Rx
- Three most highly rated therapies
  - Chemical avoidance rated beneficial by 95% of respondants
  - Creating a chemical-free living space rated beneficial by 95% of respondents
  - prayer
- Other therapies had mixed ratings

Gibson PR, Elms AN, Ruding LA. Perceived Treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. Environ Health Perspective 2003;111:1498-1504.

Recommendation of patient advocacy group

- Avoidance
  - Avoid physicians. They are expensive and will not make you better.
  - Avoid chemicals. Put all of your funds into creating a chemically free living space.

Contemporary Era

Chemical Sensitivity in General Populations

State	Prevalence	Seriously affected
NC*	30%	4%
CA**	15.9%	7%
NM**	15%	
GA**	12.6%	4%
Sweden	30%	

* Chemical sensitivity, ** multiple chemical sensitivity syndrome

References

- NC: Meggs WJ, Dunn KA, Bloch RM, Goodman PE, and Davidoff AL. Arch Environ Health 1996;51:275-282.
- CA: Kreutzer R, Neutra RR, Lashuay N. Amer J Epid 150:1-12 (1999).
- NM: Voorhees RM. Memorandum from New Mexico Deputy State Epidemiologist to Joe Thompson, Special Council, Office of the Governor. 13 March 1998.
- GA: Caress SM, Steinemann AC, Waddick C. Arch Environ Health (in press).
- Sweden: Millqvist E. Presentation, 19th International Symposium on Man and His Environment in Health and Disease. Dallas, TX. June, 2001.

Chemical sensitivity

- **Acquired Intolerance of airborne chemicals**
- **Products of combustion**
  - Tobacco smoke, vehicle exhaust, furnance fumes, gas appliances
- **Perfumes and fragrances**
- **Products for Cleaning**
- **Pesticides**
- **Paints and other solvents**
  - Outgassing of VOCs

Accepted & Associated syndromes

- **Accepted**
  - Irritant contact dermatitis
  - Airborne contact dermatitis
  - Irritant induced asthma & rhinitis
  - Solvent neurotoxicity
- **Associated**
  - MCS
  - RADS
  - RUDS
  - SBS

MCS

- Multiple chemical sensitivity syndrome
- Defined by occupational physician
  - Mark Cullen, MD, Yale University
- Onset with a chemical exposure
  - No longer considered necessary
- Sensitive to multiple chemicals of diverse classes
- More than one organ system involved
  - Respiratory system
  - Nervous system
  - Cullen M. Occup Med: State of Art Reviews. 1987:2;655-662

RADS

- Reactive airways dysfunction syndrome
- Defined by pulmonologist
- Asthma-like illness
  - Bronchial hyper-reactivity
- MCS with one organ system involvement
- Onset with a single acute chemical exposure
  - Brooks S et al. Chest 1985:88;376-384.

RUDS

- Reactive upper-airways dysfunction syndrome
- Upper airway analogue of RADS
- Rhinitis and sinusitis developing in association with an acute chemical exposure
- Subjects meet Cullen definition for MCS
  - Meggs WJ and Cleveland CH Jr. Rhinolaryngoscopy findings in patients with the multiple chemical sensitivity syndrome. *Arch of Environ Health* 1993;48:14-18.

SBS

- Sick building syndrome
- First described by WHO committee
- Widespread reports of illness among workers in tightly sealed buildings containing a host of indoor air pollutants
- Respiratory & neurological symptoms dominant
- Prevalence is 30% of inhabitants of sick buildings

Studies of MCS Patients

Highly Biased List

Olfaction in 'MCS'

- Controlled study
- Odor thresholds
- Nasal resistance
- Beck depression inventory
  - Doty RL et al. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. Arch Otolaryngol Head Neck Surg. 1988 Dec;114(12):1422-7.

Olfaction in MCS

- results do not support the hypothesis that MCS is associated with greater olfactory threshold sensitivity
- MCS is associated with:
  - decreased nasal airway patency exacerbated by challenge
  - depression
  - increased respiration rate

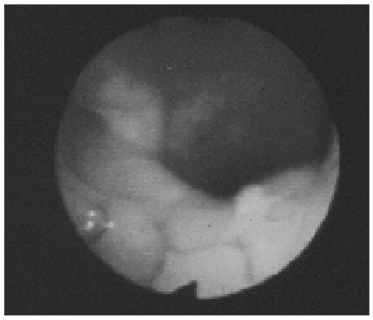
Challenge Tests

- Controlled study
  - Subjective sensitivity versus tolerant
- Exposure to side-stream tobacco smoke
- Significant increase in symptoms
  - nasal congestion, headache, chest discomfort or tightness, and cough
- Significant increase in nasal resistance
  - Bascom et al.

Physical Findings in MCS

- Edema and hypertrophy of the airways
- Abnormal mucous
  - Thick, white to yellow, crusty exudates
- Nodular hyperplasia
- Hemorrhage
- Injection
  - Posterior pharynx, uvula, soft pallet
- Discoloration
  - Pale yellow to white patches of mucosa with prominent blood vessels

Meggs WJ, Cleveland C. Rhinolaryngoscopic examination of patients with the multiple chemical sensitivity syndrome. Arch Environ Health. 1993 Jan-Feb;48(1):14-8.



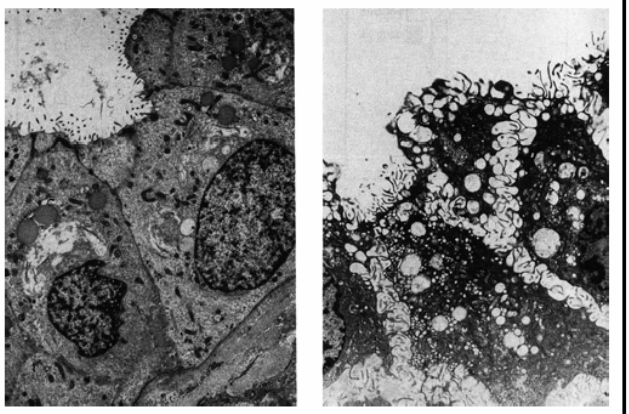
Nasal bx study of MCS pts

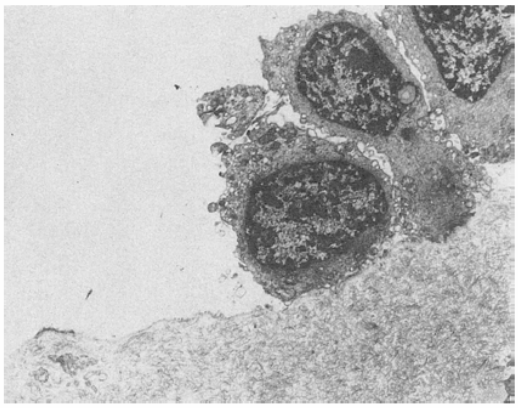
- Controlled study
- Patient group developed chemical sensitivity after chlorine dioxide exposure
- Meet case definitions for MCS
- Nasal biopsies
  - H&E
  - Light microscopy
  - Stains for nerve fibers & SP

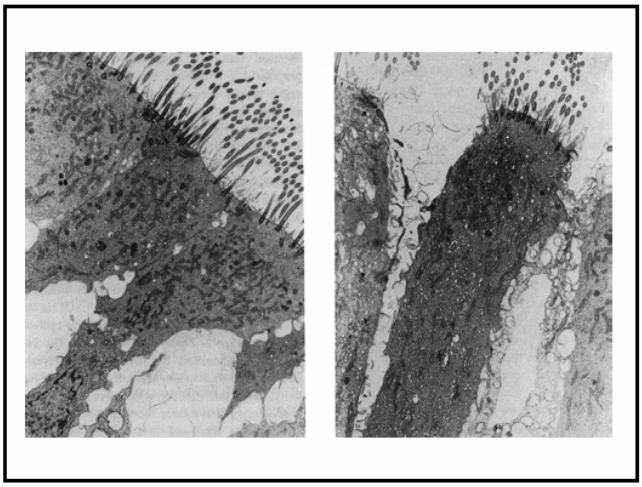
RE Toxicol Environ Health A. 1996;34(4):383-96.

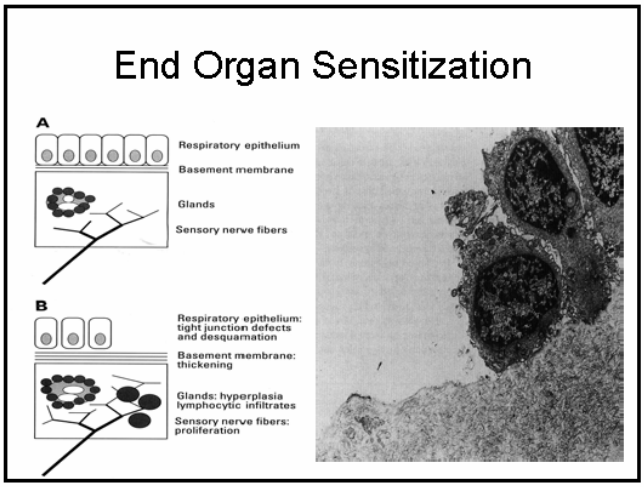
Pathological Features

- Chronic inflammation with lymphocytic infiltrates
- Glandular hyperplasia
- Basement membrane thickening
- Nerve fiber proliferation
- Desquamation of the respiratory epithelium
- Defects in tight junctions



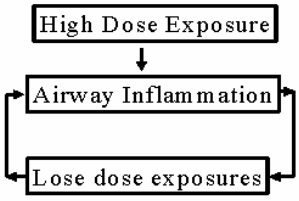


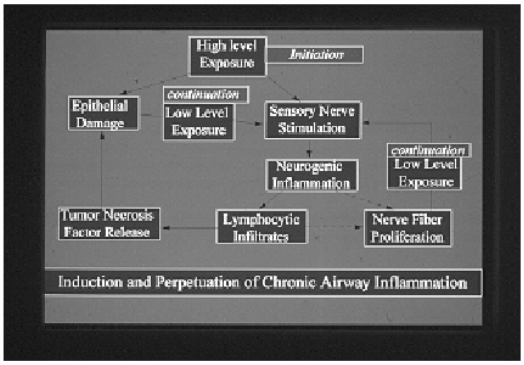



End Organ Sensitization
A
Respiratory epithelium
Basement membrane
Glands
Sensory nerve fibers
B
Respiratory epithelium: tight junction defects and desquamation
Basement membrane: thickening
Glands: hyperplasia lymphocytic infiltrates
Sensory nerve fibers: proliferation

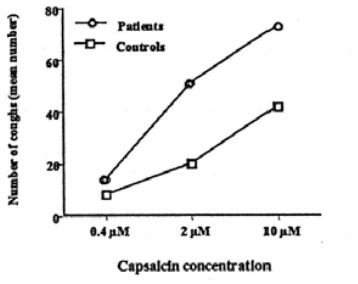
Induction Mechanism

- Positive feed back loop
- Induction exposure produces neurogenic inflammation





Millqvist Capsaicin inhalation cough test in patients with "Sensory Hyperreactivity"



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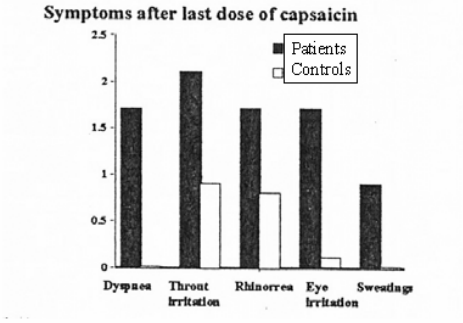
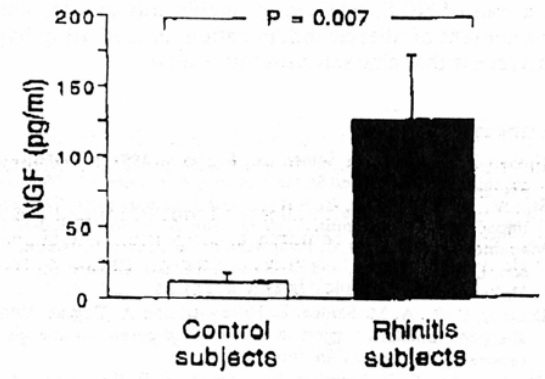


Millqvist E, et al. Provocations with perfume in the eyes induce airway symptoms in patients with sensory hyperreactivity.Allergy. 54(5):495-9, 1999 May.

- single-blindly in a placebo-controlled, randomized study
- 30-min exposure to perfume,
- increase in eye irritation, cough, and dyspnea, after both the airway and eye exposures



Sanico et al. Am J Respir Crit Care Med. 2000 May;161(5):1631-5.

Plasma Levels of substance P, VIP, NGF

- Controlled study
- Three groups
  - MCS
  - Atopic eczema/dermatitis
  - Normal control group
- Measurements at baseline and after chemical challenge
  - Oil based paint

REF: Kimata H. Effect of exposure to VOCs on plastma lefvels of neuropeptides, NGF & histamine in patients with self-reported chemical sensitivity. Int J Hyg Enviro Health 2004;207:159-163.

Results

- Baseline plasma levels of SP, VIP, NGF, but not histamine were elevated in MCS group but not other groups.
- VOC exposure increased plasma SP, VIP, NGF in MCS pts but not other two groups.
- Exposure to VOCs increased skin wheal response to histamine in MCS but not other two groups.

REF: Kimata H. Effect of exposure to VOCs on plastma lefvels of neuropeptides, NGF & histamine in patients with self-reported chemical sensitivity. Int J Hyg Enviro Health 2004;207:159-163.

Controlled Study of Male Painters with MCS

- Controlled challenge booth study, community recruitment
- no difference in sensations of smell
- No difference in CNS symptoms
- Difference in subjective rating of symptoms related to irritation (i.e., eyes, nose, throat, skin, and breathing difficulties)
- No differences in nasal cavity, eye redness and serum cortisol levels.
- Trend (P = 0.056) in decline of serum prolactin levels
  - Georgellis et al. Multiple chemical sensitivity in male painters; a controlled provocation study.International Journal of Hygiene & Environmental Health. 206(6):531-8, 2003 Oct.

Mechanisms

Older Concept

- Extrinsic Airway Inflammation
  - Allergic in origin
- Intrinsic Airway Inflammation
  - Allergy testing is negative
  - No extrinsic cause, intrinsic to the system
  - Non-allergic or Intrinsic asthma
  - Non-allergic rhinitis

Contemporary Concept

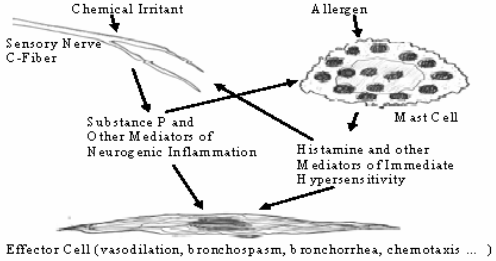
- Allergic Airway Inflammation
  - Inflammation initiated by airborne proteins on pollen grains, mold spores, dust mite feces, coach roach debri, airborne mammalian proteins
- Irritant Airway Inflammation
  - Inflammation initiated by non-protein, lower molecular weight chemicals such as solvents, fumes, products of combustion, VOCs

Mechanisms

- Allergic Inflammation
  - **Proteins** cross link IgE molecules on Mast Cell surfaces, leading to the release of histamine and other allergic mediators
- Neurogenic Inflammation
  - **Chemicals** bind to chemoreceptors on sensory nerve C-fibers, leading to the release of Substance P, Calcitonin Gene Related Peptide, and other neurogenic mediators

Crossover Network

- Nerve fibers have histamine receptors
- (some) Mast cells have substance P receptors



What about extra-airway manifestations of chemical sensitivity?

Organ system involvement in chemical sensitivity

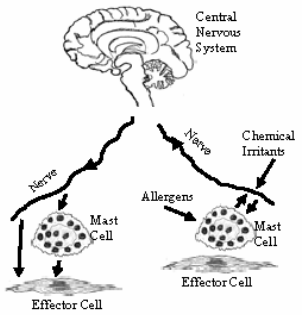
Respiratory	Asthma, Rhinitis, Sinusitis, Pneumonitis
Musculoskeletal	Myositis, Arthritis, Collagen Vascular diseases
Gastrointestinal	Irritable Bowel Syndrome, Inflammatory Bowel Disease
Dermatological	Dermatitis, Rosacea, Cutaneous Vasculitis

Organ system involvement in chemical sensitivity

Cardiovascular	hypertension, Arrhythmias, Vasculitis, Recurrent Anaphylaxis
Neurological	Migraine, Fatigue, Cognitive dysfunction, Seizures, Coma
Psychiatric	Bipolar disorder, Depression, Psychosis

Neurogenic Switching

- The site of inflammation can be switched from the site of stimulation
- Occurs in both allergic and irritant airway inflammation
- May play a role in many disease processes



Examples of Neurogenic Switching

- Gustatory rhinitis
- Food allergy leading to asthma & rhinitis
- Millqvist perfume challenges
- Airbourne contact dermatitis
- Systemic anaphylaxis
  - Animal models with ablation of neural pathways

MCS & Gulf War Illnesses

Bell IR, Warg-Damiani L, Baldwin CM, Walsh ME, Schwartz GE. Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings. Mil Med. 1998 Nov;163(11):725-32.

- "Among PGW veterans, the subset with worse health associated with marked increases in chemical odor intolerance since their military service had a significantly higher odds ratio for exposure to multiple chemicals, notably wartime pesticides and insect repellent, than did comparison groups."

MCS & Gulf War Related Illnesses

- **British cohort study**
- **"Operational Criteria"**
- **Gulf cohort: MCS & pesticide exposure, {adjusted OR = 12.3, 95% CI [5.1, 30.0]}**
  - Reid S et al. Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans. American Journal of Epidemiology. 153(6):604-9, 2001 Mar 15

	MCS	CFS
Gulf	1.3%	2.1%
Bosnia	0.3%	0.7%
Era	0.2%	1.8%

Proctor SP. Chemical sensitivity and gulf war veterans' illnesses. [Review]. Occup Med. 15(3):587-99, 2000 Jul-Sep.

- "In several studies of GW veterans, using differing criteria and varying assessment measures for CS and MCS, the prevalence rates for CS are reported to be 36-86% in Department of Veterans' Affairs patient populations and 0.8-20% in general cohorts of GW veterans. The rates of MCS are 2-6%."

Kipen et al. Prevalence of chronic fatigue and chemical sensitivities in Gulf Registry Veterans. Archives of Environmental Health. 54(5):313-8, 1999 Sep-Oct.

- VA's Gulf War Registry
- Questionnaire responses
- "CFS & MCS may constitute an appreciable portion …"

CFS	15.7%
MCS	13.1%
Both	3.3%

Animal Model of MCS

- Flinders Sensitive Line (FSL) rats
- selective breeding for increased responses anticholinesterase agent
- increased sensitive both to a variety of drugs
- Increased broncheal hyper-responsiveness
  - Overstreet DH. Djuric V. A genetic rat model of cholinergic hypersensitivity: implications for chemical intolerance, chronic fatigue, and asthma. [Review] [56 refs] *Annals of the New York Academy of Sciences. 933:92-102, 2001 Mar.*

Research Needs: Study of Specific Diseases in Environmental Control Units

- Controlled studies
  - Blinded whenever possible
  - Consider sleep challenges to odorous chemicals
- Diseases with definite parameters that can be followed
  - Subjective symptoms, physical findings, laboratory parameters
- Longitudinal studies
- Long term follow-up

Summary

- Environmental medicine grew out of and extended the scope of allergy
  - Extended diseases with environmental factor
  - Extended substances that induce disease in humans
- Research needs to be done to define the extent of and indications for specific diseases being induced and/or exacerbated by environmental exposures

References to Early Works

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