The Psychoneuroimmune Components of Immunity in Allergy and Asthma

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The University of Mississippi Medical Center
Jackson, MS
Disclosures

- Research Support
  - NIH
  - Sanofi
  - Stallergenes

- Annals of Allergy, Asthma and Immunology
  - Editor-in-chief
Objectives

1. Describe the mechanisms involving perception, hypophyseal, pituitary adrenal connections and their interactions with various immune components as a basis for the adverse immune effects of excess psychological stress.

2. Discuss the impact of excessive psychological stress on various clinical components of patients with allergic and asthmatic diseases and how stress may impact disease risk as well as ideas activity.
Health

- a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity (WHO)
- Cannot be attained or maintained solely by “pills or procedures”
- Involves the initiation and maintenance of homeostasis
- Influenced by multiple “nonphysical” components
  - outlook
  - provider-patient relationship (the entire health care team)
  - recognition of relationships between spirituality and health
Major Heath Challenges in Western Society

• Chronic Diseases increasingly prevalent
  – Hypertension/cardiovascular disease
  – Diabetes mellitus/metabolic syndrome
  – Cancer
  – Allergy/Asthma

• Most (?all) chronic diseases have an inflammatory/immune component

• Increasingly obese and sedentary society

• Increasing levels of societal stress
  – economic
  – environmental
  – philosophical

• Western Medicine is increasingly technology driven which has often minimized the whole person approach (body, mind, spirit)
But Doctor, I’m Not Stressed...

- Our society has become increasingly stressed
  - Pressures of life
    - Finances
    - relationships
  - Fear of dangers
    - natural
    - man-made
  - Loss of hope in the future

- Up to 75% of all office visits to physicians are stress related
How does the mind affect the immune system?
Clinical Definition of Stress Response

- Not just the event (stressor)
- The psychophysiological response to the event
  - Acute ("I’m under a lot of stress")
    - fight or flight
    - Combination of HPA and ANS with rapid resolution
    - Often healthful (exercise, emotional excitement)
  - Chronic (I’m stress out!)
    - anxiety, depression, worry
    - Endocrine/immune “exhaustion”
    - Typically maladaptive
- Major factors that impact the nature, magnitude, and duration of the response
  - Outlook - Optimism vs pessimism
  - Social support system – nuclear family, fraternal organization, community
  - Belief system - spirituality
Neuroimmune-Endocrine Interactions

Each point of influence in the stress-immune paradigm may be affected by certain variables, including:
- Polymorphisms of hormone and cytokine receptors and ligand promoters.
- Individual hormone and cytokine levels
- Hormone and cytokine receptor-specific cell populations and density of receptors

POINTS OF INFLUENCE FOR INDIVIDUAL STRESS EFFECTS ON IMMUNE RESPONSE

STRESSOR

STRESS PERCEPTION

Pituitary

ACTH

CNS

SNS

Ganglion

Post Ganglionic Nerve

Adrenal Gland

NOREPINEPHRINE

EPINEPHRINE

CORTISOL

IMMUNE CELLS

APC

Plasmocyte

T cell

CYTOKINES

CHEMOKINES

CELL ACTIVATION

ALTERED IMMUNITY

Th1/Th2

Treg

INFLAMMATORY DISEASE

RISK / ACTIVITY
Effect of Acute Stress Superimposed on Chronic Stress on Immunoregulatory Cytokine Production by Human PBMC

An in vitro model

Salicru and Marshall 2007
Effect of Acute Stress Superimposed on Chronic Stress on Immunoregulatory Cytokine Production by Human PBMC

An in vitro model

Salicru and Marshall 2007
Effect of Acute Stress Superimposed on Chronic Stress on Immunoregulatory Cytokine Production by Human PBMC
An in vitro model

Salicru and Marshall 2007
Pre Exam Daily Hassles Scale Predicts Degree of Stress-induced Cytokine Change

* pre vs. post exam : p = 0.03
** low vs. high Hassles : p = 0.02

Marshall et al. 1998
Relationship between PSS and $T_{REG}$ Levels in Normal Human Peripheral Blood

$CD4^+CD25^{high}FoxP3^+$

n = 78
r = -0.31,
p = 0.0017
Further Focusing Immune Effects of Stress: Genetic Biomarker Approach
Variability in laboratory immune parameters is associated with stress hormone receptor polymorphisms

Rehm et al., 2012

### Table 2: Relationships Between β2AR and GR Polymorphisms and Immune Variables

<table>
<thead>
<tr>
<th></th>
<th>Effector</th>
<th>Regulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TH2</td>
<td>TH1</td>
</tr>
<tr>
<td>Gly16Arg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g/l/g/l</td>
<td>1.89</td>
<td>-18.70</td>
</tr>
<tr>
<td>g/l/g/y</td>
<td>2.17</td>
<td>-0.45 p=0.002</td>
</tr>
<tr>
<td></td>
<td>-0.02, 0.63</td>
<td>(2.75, 1.85)</td>
</tr>
<tr>
<td>arg/arg</td>
<td>2.58</td>
<td>-0.04 p=0.003</td>
</tr>
<tr>
<td></td>
<td>(0.23, 1.14)</td>
<td>(4.30, 2.21)</td>
</tr>
<tr>
<td>g/l/g/l</td>
<td>2.25</td>
<td>-17.21</td>
</tr>
<tr>
<td>g/l/g/l</td>
<td>2.05</td>
<td>-14 p=0.406</td>
</tr>
<tr>
<td></td>
<td>-0.49, 0.20</td>
<td>(2.24, 4.93)</td>
</tr>
<tr>
<td>g/l/g/l</td>
<td>2.17</td>
<td>-14.05 p=0.054</td>
</tr>
<tr>
<td></td>
<td>-0.45, 0.48</td>
<td>(0.01, 6.38)</td>
</tr>
<tr>
<td>Bcl1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c/l/c</td>
<td>2.20</td>
<td>-17.06</td>
</tr>
<tr>
<td>c/l/g</td>
<td>2.08</td>
<td>-0.05 p=0.736</td>
</tr>
<tr>
<td></td>
<td>-0.35, 0.25</td>
<td>(-0.38, 3.90)</td>
</tr>
<tr>
<td>g/l/g</td>
<td>2.10</td>
<td>-0.13 p=0.559</td>
</tr>
<tr>
<td></td>
<td>-0.57, 0.31</td>
<td>(-3.45, 2.80)</td>
</tr>
<tr>
<td>Ttll3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c/l/g</td>
<td>2.12</td>
<td>-17.75</td>
</tr>
<tr>
<td>c/l/g</td>
<td>2.14</td>
<td>0.06 p=0.523</td>
</tr>
<tr>
<td></td>
<td>-0.19, 0.38</td>
<td>(1.11, 2.99)</td>
</tr>
</tbody>
</table>

Values are reported as Difference/Relative Change, p value (confidence interval)

- Median is reported for skewed variables
- adj diff: adjusted difference
- adj rel chg: adjusted relative change
- Med: unadjusted median
- Avg: unadjusted average
- Light shading - 0.05 < p < 0.10
- Dark shading - p < 0.05
- Bold - significant interaction effects

N=207

Rehm et al., 2012
Interaction between age and Gly16Arg predicts Th2

Rehm et al., 2012
Interaction between BMI and Gly16Arg predicts Th1/Th2 ratio

Rehm et al., 2012
Interactions between allergic status and both Gly16Arg and Gln27glu predict Treg (n=87)

Rehm et al., 2012
Haplotype Analysis in Small Populations

- By combining SNP profiles, can further subdivide
- Theoretical possibilities include
  - Difference in receptor affinities
  - Differences in ligand production
- Currently examining SNPs of
  - Glucocorticoid receptor
  - β2 adrenergic receptor
  - IFNγ receptor
  - IL-4 receptor
  - IL-10 receptor
  - TGFβ receptor
Th1/Th2 Ratio Categorization by β2AR and GCR Haplotype

Xiang et al. 2015
IL10 (Tr1) Categorization by β2AR and GCR Haplotype

Xiang et al. 2015
Immune Effects of Acute and Chronic Stress on Immediate and Late Phase Skin Test Responses
Stress and anxiety effects on positive skin test responses in young adults with allergic rhinitis Heffner K et al. Ann Allergy Asthma Immunol (2014) 113:13-18
Stress and anxiety effects on positive skin test responses in young adults with allergic rhinitis Heffner K et al. Ann Allergy Asthma Immunol (2014) 113:13-18
Can Stress Worsen Existing Asthma?
Psychological distress and maladaptive coping styles in patients with severe vs moderate asthma. Lavoie KL et al. Chest 2010. 137:1324-31

- Assessed levels of psychological distress and a range of disease-relevant emotional and behavioral coping styles in patients with severe vs moderate asthma.
- Eighty-four patients (50% women, mean [M] age 46 years) with severe (n = 42) and moderate (n = 42) asthma were recruited.
- Asthma severity defined according to American Thoracic Society criteria.
- Demographics and medical history interviews and pulmonary function and allergy testing.
- Completed questionnaires measuring asthma symptoms and the Millon Behavioral Medicine Diagnostic Inventory, which assesses psychologic distress and emotional/behavioral coping factors that influence disease progression and treatment.
Psychologic distress and maladaptive coping styles in patients with severe vs moderate asthma. Lavoie KL et al. Chest 2010. 137:1324-31

<table>
<thead>
<tr>
<th>MBMDI Subscale Category</th>
<th>Severe Asthma (n = 42)</th>
<th>Moderate Asthma (n = 42)</th>
<th>F</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Psychologic distress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anxiety-tension</td>
<td>54.7 (25.4)</td>
<td>38.3 (26.2)</td>
<td>4.02</td>
<td>.05</td>
</tr>
<tr>
<td>Depression</td>
<td>43.5 (28.7)</td>
<td>37.1 (31.1)</td>
<td>0.45</td>
<td>.51</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>36.2 (28.8)</td>
<td>21.8 (19.5)</td>
<td>6.72</td>
<td>.01</td>
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<tr>
<td>Emotional lability</td>
<td>47.3 (20.7)</td>
<td>40.7 (20.2)</td>
<td>1.09</td>
<td>.30</td>
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<tr>
<td>Guardedness</td>
<td>52.1 (18.1)</td>
<td>50.0 (15.1)</td>
<td>0.00</td>
<td>.96</td>
</tr>
<tr>
<td><strong>Emotional-attitudinal coping styles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness apprehension</td>
<td>59.6 (23.7)</td>
<td>41.3 (22.1)</td>
<td>9.57</td>
<td>.01</td>
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<tr>
<td>Pain sensitivity</td>
<td>61.5 (25.0)</td>
<td>38.7 (22.4)</td>
<td>10.65</td>
<td>.02</td>
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<tr>
<td>Future pessimism</td>
<td>56.3 (17.8)</td>
<td>35.5 (23.2)</td>
<td>8.53</td>
<td>.01</td>
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<tr>
<td>Spiritual absence</td>
<td>53.3 (30.4)</td>
<td>68.5 (34.2)</td>
<td>3.85</td>
<td>.05</td>
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<tr>
<td>Interventional fragility</td>
<td>48.2 (19.7)</td>
<td>31.2 (20.4)</td>
<td>7.18</td>
<td>.01</td>
</tr>
<tr>
<td>Information discomfort</td>
<td>53.7 (34.1)</td>
<td>53.0 (32.7)</td>
<td>0.00</td>
<td>.97</td>
</tr>
<tr>
<td><strong>Behavioral coping styles</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional deficits</td>
<td>50.0 (21.4)</td>
<td>39.2 (21.7)</td>
<td>5.48</td>
<td>.02</td>
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<tr>
<td>Social isolation</td>
<td>54.9 (27.2)</td>
<td>56.0 (19.5)</td>
<td>0.01</td>
<td>.93</td>
</tr>
<tr>
<td>Medication abuse</td>
<td>40.6 (23.8)</td>
<td>36.2 (23.3)</td>
<td>0.79</td>
<td>.38</td>
</tr>
<tr>
<td>Health service use excess</td>
<td>58.3 (25.1)</td>
<td>52.0 (22.6)</td>
<td>1.56</td>
<td>.22</td>
</tr>
<tr>
<td>Problematic compliance</td>
<td>53.4 (27.3)</td>
<td>73.9 (22.1)</td>
<td>4.32</td>
<td>.04</td>
</tr>
</tbody>
</table>
Rhinitis as an associated factor for Anxiety and Depression amongst adults Bella-Barahas M et al Braz J Oto 2016

<table>
<thead>
<tr>
<th></th>
<th>Allergic rhinitis (n = 111)</th>
<th>Non-allergic rhinitis (n = 34)</th>
<th>Controls (n = 96)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>51 (45.9)</td>
<td>18 (52.9)</td>
<td>10 (10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Severity scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>15 (13.5)</td>
<td>11 (32.4)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>25 (22.5)</td>
<td>3 (8.8)</td>
<td>2 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>11 (9.9)</td>
<td>4 (11.8)</td>
<td>7 (7.3)</td>
<td></td>
</tr>
<tr>
<td>No anxiety</td>
<td>60 (54.1)</td>
<td>16 (47.0)</td>
<td>86 (89.6)</td>
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</tr>
<tr>
<td><strong>Depression, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43 (38.7)</td>
<td>16 (47.1)</td>
<td>16 (16.6)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Severity scale</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>7 (6.3)</td>
<td>6 (17.6)</td>
<td>3 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>19 (17.1)</td>
<td>7 (20.6)</td>
<td>2 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>17 (15.3)</td>
<td>3 (8.8)</td>
<td>11 (11.5)</td>
<td></td>
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<tr>
<td>Not depressed</td>
<td>68 (61.3)</td>
<td>18 (53.0)</td>
<td>80 (83.3)</td>
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</tr>
</tbody>
</table>

n, subjects with characteristics of interest. Total number of subjects with symptoms of anxiety or depression was compared to groups with allergic rhinitis and non-allergic rhinitis and the controls using the Chi Squared test.
Rhinitis as an associated factor for Anxiety and Depression amongst adults  Bella-Barahas M et al  Braz J Oto 2016

### Table 3
Frequency of anxiety and depression based on the classification of allergic rhinitis symptoms.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Anxiety</th>
<th></th>
<th>Depression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>p</td>
<td>n</td>
</tr>
<tr>
<td><strong>Allergic rhinitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, n = 22</td>
<td>7</td>
<td>31.8</td>
<td>0.138</td>
<td>7</td>
</tr>
<tr>
<td>Moderate-severe, n = 89</td>
<td>44</td>
<td>49.4</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Symptom frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent, n = 28</td>
<td>13</td>
<td>46.4</td>
<td>0.953</td>
<td>9</td>
</tr>
<tr>
<td>Persistent, n = 83</td>
<td>38</td>
<td>45.8</td>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>

n, subjects with characteristics of interest.
p-value was obtained through the Chi Squared test.

### Table 4
Risk of anxiety and depression in subjects with rhinitis adjusted by sex.

<table>
<thead>
<tr>
<th></th>
<th>Anxiety</th>
<th></th>
<th>Depression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Allergic rhinitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>7.3</td>
<td>3.44-15.53</td>
<td>&lt;0.001</td>
<td>2.9</td>
</tr>
<tr>
<td>Men</td>
<td>3.4</td>
<td>0.98-12.0</td>
<td>0.06</td>
<td>2.1</td>
</tr>
<tr>
<td>Women</td>
<td>7.4</td>
<td>2.62-20.92</td>
<td>&lt;0.001</td>
<td>2.7</td>
</tr>
<tr>
<td>Adjusted by sex</td>
<td>5.7</td>
<td>5.58-12.44</td>
<td>&lt;0.001</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Non-allergic rhinitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>9.7</td>
<td>3.78-24.75</td>
<td>&lt;0.001</td>
<td>4.1</td>
</tr>
<tr>
<td>Men</td>
<td>5.4</td>
<td>0.78-37.16</td>
<td>0.12</td>
<td>1.11</td>
</tr>
<tr>
<td>Women</td>
<td>8.5</td>
<td>2.56-28.43</td>
<td>0.0002</td>
<td>4.2</td>
</tr>
<tr>
<td>Adjusted by sex</td>
<td>7.8</td>
<td>2.79-21.52</td>
<td>&lt;0.001</td>
<td>3.3</td>
</tr>
</tbody>
</table>

OR, odds ratio; 95% CI, confidence intervals at 95%; OR adjusted by Mantel and Haenszel.
p-value obtained by using Chi Squared or Fisher’s Exact Test.
* Compared vs. control group.
Can Stress *Cause* Asthma?
A birth cohort of 560 children with at least 1 parent with allergy or asthma from Baltimore, Boston, New York, and St Louis.

- Wheezing was assessed every 3 months,
- Allergen-specific IgE yearly, and mononuclear cell cytokine responses at birth and yearly
- Environmental assessments include dust allergen and endotoxin, maternal stress, and indoor nicotine and nitrogen dioxide levels.

• Examined the association between prenatal and postnatal maternal stress and wheeze
• 417 children enrolled in a prospective birth cohort in Mexico City.
• Maternal negative life event (NLE) scores were ascertained in the second or third trimester of pregnancy and at the 48-month postnatal visit.
• Children's respiratory outcomes, caregiver report of ever wheeze, and wheeze in the past 12 months were obtained from the International Study of Asthma and Allergies in Childhood (ISSAC) survey administered at 48 months.
• Associations between prenatal and postnatal NLE scores and wheeze were analyzed using a modified Poisson regression approach adjusting for covariates.
Prenatal and postnatal stress and wheeze in Mexican children:

Sex-specific differences  
Prenatal and postnatal stress and wheeze in Mexican children:

Work-related stress, inability to relax after work and risk of adult asthma: a population-based cohort study Loerbraks A et al. Allergy 65: 1298-1305, 2010

- population-based cohort study
  - 5114 at baseline in 1992-1995

- Asthma was measured by self-reports.

- Two scales (‘work stress’ and ‘inability to relax after work’) that assessed psychologically adverse work conditions were extracted from a list of work-condition items by factor analysis

- Associations with asthma were estimated by prevalence ratios (PRs) and risk ratios (RRs) using Poisson regression with a log-link function adjusting for demographics,

- health-related lifestyles, body mass index and family history of asthma were also assessed.
Work-related stress, inability to relax after work and risk of adult asthma: a population-based cohort study Loerbraks A et al. Allergy 65: 1298-1305, 2010

<table>
<thead>
<tr>
<th></th>
<th>Age-and-sex adjusted*</th>
<th>Multivariable†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (% with prevalent asthma)</td>
<td>PR</td>
</tr>
<tr>
<td>Work stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1082 (4.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Medium</td>
<td>1037 (4.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>High</td>
<td>918 (7.0)</td>
<td>1.45</td>
</tr>
<tr>
<td>Z-score</td>
<td>–</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to relax after work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1256 (4.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Medium</td>
<td>1185 (5.9)</td>
<td>1.46</td>
</tr>
<tr>
<td>High</td>
<td>727 (7.3)</td>
<td>1.84</td>
</tr>
<tr>
<td>Z-score</td>
<td>–</td>
<td>1.52</td>
</tr>
</tbody>
</table>
Self-Reported Stressful Life Events During Adolescence and Subsequent Asthma: A Longitudinal Study
Oren E et.al *JACI: In Practice* DOI: (10.1016/j.jaip.2016.09.019)
Self-Reported Stressful Life Events During Adolescence and Subsequent Asthma: A Longitudinal Study Oren E et.al JACI: In Practice DOI: (10.1016/j.jaip.2016.09.019

[Diagram showing comparison of RR for Asthma at 16ry between Low and High Life Events Score for All, Males, and Females with corresponding p-values: All p=0.144, Males p=0.006, Females p=0.339.]

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Defining Stress as a Therapeutic Target

Essential Considerations

- Common vs individual definition of clinical stressors
- Common manifestations (clinical, laboratory) as biomarkers
- Identify stress response modifiers
  - Gender, race/ethnicity, culture
  - Lifestyle
    - Social class
    - Personal choices
    - Healthcare access
  - Support structures
  - Co-morbidities (underlying disease processes)
- Demystifying the psychological and spiritual components of health
Therapeutic Stress Management for Allergy and Asthma

Is it Worthwhile?

- It is the approach to clinical care that involves the *entire* patient
  - Body
  - Mind
  - Spirit
- It is (or at least should be) practiced in an evidence-based fashion
  - How many times have we tried a therapy based on a case report?
- It is commonly and increasingly utilized by many of our patients
- It requires a wide level of *current* knowledge about what modalities have and have not been shown to be effective
A happy heart is good medicine
and a cheerful mind works healing,
but a broken spirit dries up the bones.
Prov 17.22

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