What my Illness Taught Me About Health
(The Role of the Immunoglobulins)

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Charles Janeway, M.D.
Father of Clinical immunology

- Pediatrician-in-chief at Boston Children’s Hospital for 30 years

- Described “A gamma globulin emia” in children susceptible to infections
Patient: ARD

• Aug, 1997 - First symptoms: chin numbness
• Jan, 1998 - Rib tenderness
• March, 1998 - diagnosis: Multiple Myeloma
• March - June: 3 rounds of low-dose chemo
• July-Sept: Bone Marrow Transplant
Differential Diagnosis of Chin numbness/pain

- Multiple sclerosis
- Brain tumor
- Trigeminal neuralgia
- Herpes zoster
- Infection - neuritis
- Infection - systemic
- Cancer
- Functional
- Zebras
The law of parsimony

Par’si-mo’ny - Unusual or excessive frugality.
Adoption of the simplest assumption in the interpretation of data


**Investigative Findings**

Serum immunofixation revealed an IgA-kappa monoclonal gammopathy.

Bone x-rays revealed radiolucent lesions within the skull, ribs, clavicles, right ischium, and right mid-humerus. The left 5th rib was fractured.

A bone marrow biopsy showed a slight increase in overall cellularity (70%)

A fine needle aspirate of the left 7th rib revealed infiltration with atypical plasma cells.
Acquired immunodeficiencies

Bone marrow of a patient with multiple myeloma is replaced with malignant plasma cells, some of which are binucleate & multinucleate. Normally, the malignancy involves a single plasma cell clone.

The malignant plasma cell clone produces a single immunoglobulin isotype with identical antigen receptors. Hence, in multiple myeloma, the ability to produce a diverse group of antibodies is impaired, & the patients become unusually susceptible to infection with extracellular organisms.
Genetics

Cancer is a genetic illness:
It is not necessarily a hereditary illness.
### Laboratory Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Mild normochromic, normocytic anemia (H/H 11, 34)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>Markedly elevated (107 mm/hr)</td>
</tr>
<tr>
<td>Serum biochemistries</td>
<td>Mildly elevated calcium (10.3 mg/dL)</td>
</tr>
<tr>
<td>Serum protein electrophoresis/SPEP</td>
<td>Mild polyclonal elevation in gamma globulin (2.3 grm/dL)</td>
</tr>
<tr>
<td>Quantitative immunoglobulins</td>
<td>IgA hypergammaglobulinemia (1,880 mg/dL)</td>
</tr>
<tr>
<td>Immunofixation</td>
<td>Monoclonal IgA-kappa paraprotein</td>
</tr>
</tbody>
</table>
### Lab results (cont.)

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum interleukin -6</td>
<td>Absent</td>
</tr>
<tr>
<td>Urine protein electrophoresis (UPEP)</td>
<td>No protein in urine! 😊</td>
</tr>
</tbody>
</table>
# Myeloma Staging System

<table>
<thead>
<tr>
<th>Creatinine Level</th>
<th>STAGE</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;2mg/dL</td>
<td>IA</td>
<td>61 months</td>
</tr>
<tr>
<td>B&gt;2mg/dL</td>
<td>IIA,B</td>
<td>55 months</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>15 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β-2 microglobulin</th>
<th>Stage</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.004gm/L</td>
<td>I</td>
<td>43 months</td>
</tr>
<tr>
<td>&gt;0.004gm/L</td>
<td>II</td>
<td>12 months</td>
</tr>
</tbody>
</table>
Myelomatosis involving the skull
Pathologic Fracture and Lytic Lesions in Multiple Myeloma
Formation of Osteolytic Lesions in Multiple Myeloma

Myeloma cells secrete at least two molecules that modulate the bone microenvironment in a manner favorable to tumor growth. Receptor activator of nuclear factor κ-B ligand (RANKL) acts to stimulate osteoclast formation and activity leading to bone erosion, whereas dickkopf1 (DKK1) appears to inhibit osteoblasts, thus preventing repair of the lesions.

# Pathogenesis and Clinical Manifestations

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Underlying Cause</th>
<th>Pathogenic Mech</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia, Fractures, pain</td>
<td>Skeletal destruction</td>
<td>Osteoclast Activating Factors</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Light chain proteinuria</td>
<td>Tumor products: OAF, DNA</td>
</tr>
<tr>
<td>Anemia</td>
<td>↓production ↑destruction</td>
<td>Inhibitory factors Autoantibodies</td>
</tr>
<tr>
<td>Infection</td>
<td>Hypogamma-globulinemia</td>
<td>↓production ↑IgG catabolism</td>
</tr>
<tr>
<td>Neurologic Sx</td>
<td>Cord compression</td>
<td>M globulins</td>
</tr>
<tr>
<td>Bleeding</td>
<td>↓clotting factors</td>
<td>Tumor products</td>
</tr>
</tbody>
</table>
ANTICOAGULATION IN DEEP VEIN THROMBUS

Risk of Clot/thrombus vs. Risk of Bleed

Rule vs. Therapeutic principle

Complicating factors
- Cancer
- Steroids
- Impending surgery
- ? Underlying coagulation disorder
Playing the odds

Informed consent: 1998
1-3 % change of death from treatment
(down from 10-15 %)
30% chance of complete cure

---

n = 85
40 % still living
3 doing well
Stem cells harvested

Stem cells frozen

Patient given high doses of chemotherapy

Stem cells thawed

Stem cells infused back into the patient
Charles ("Charlie") Janeway, Jr. 1943-2003
“Father of Innate Immunity”
“How the Body Recognizes Foreign Invaders”
Factors involved in Healing

1. Education - accurate information
2. Positive attitude
3. Reducing stress
   - Relaxation
   - Exercise
   - Diet
4. Eliminating Negative Beliefs and Emotion
   - Eliminate Anger, Rage, Fear, Guilt
   - Forgiveness
   - Problem Solving
   - Goal setting - creating positive future goals
5. Positive visual imagery - commands and instructions to the body
Lance Armstrong

1996 - age 25 -
diagnosed with Testicular cancer
(metastases to stomach, lungs, brain)

2005 - age 34 -
wins 7th Tour de France

Allen Dyer

1998 - age 52
diagnosed with MM

2005 - age 60
2nd Tour de France
Ascention of Mt. Ventoux
Possible explanatory factors

- CHEMOTHERAPY
- Attitude
- Spirituality
- Prayer - Meditation
- Mind over matter
- Environment
- EXERCISE
- Diet
- Community
- Love/Family support
- Mountain climbing
- Hanging out with Buddhists
- FUN
- Genes
- Laughter
Explanatory factors (cont.)

Luck

Good Fortune  Blessing

Randomness
Indeterminacy
Exercise and Cancer

• Exercise improves immune function, lymph flow, and detoxification
• Helps regulate blood sugar levels
• Relieves both depression and anxiety
• Physical activity has also been shown to improve tolerance to chemotherapy.
• Fitness level prior to treatment helps endure the rigors of treatment.
Healthy behaviors (less smoking, drinking)

Social support (faith, communities, marriage)

Positive emotions hope/optimism (less stress, anxiety)

Health (less immune suppression, stress hormones, and suicide)

Religious involvement
BOWLING ALONE

THE COLLAPSE AND REVIVAL OF AMERICAN COMMUNITY

Robert D. Putnam
Figure 17: Frequency of Selected Formal and Informal Social Activities, 1975–1998
Figure 26: The Rise and Decline of League Bowling
Figure 11: Club Meeting Attendance Dwindles, 1975–1999
Figure 32: Trends in Protestant, Catholic, and United Way Giving, 1920s–1990s
Figure 27: The Growth of Spectator Sports, 1960–1997

Total live attendance (standardized for total U.S. population) at all NCAA football and basketball games, all Major League baseball, football, basketball, and hockey games, and NASCAR auto races.
Figure 75: From Generation to Generation, Patriotism Wanes, Materialism Waxes
### Table 4: Measuring Social Capital in the American States

<table>
<thead>
<tr>
<th>Components of Comprehensive Social Capital Index</th>
<th>Correlation with Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures of community organizational life</td>
<td></td>
</tr>
<tr>
<td>Served on committee of local organization in last year (percent)</td>
<td>0.88</td>
</tr>
<tr>
<td>Served as officer of some club or organization in last year (percent)</td>
<td>0.83</td>
</tr>
<tr>
<td>Civic and social organizations per 1,000 population</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean number of club meetings attended in last year</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean number of group memberships</td>
<td>0.74</td>
</tr>
<tr>
<td>Measures of engagement in public affairs</td>
<td></td>
</tr>
<tr>
<td>Turnout in presidential elections, 1988 and 1992</td>
<td>0.84</td>
</tr>
<tr>
<td>Attended public meeting on town or school affairs in last year (percent)</td>
<td>0.77</td>
</tr>
<tr>
<td>Measures of community volunteerism</td>
<td></td>
</tr>
<tr>
<td>Number of nonprofit (501[c]3) organizations per 1,000 population</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean number of times worked on community project in last year</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean number of times did volunteer work in last year</td>
<td>0.66</td>
</tr>
<tr>
<td>Measures of informal sociability</td>
<td></td>
</tr>
<tr>
<td>Agree that “I spend a lot of time visiting friends”</td>
<td>0.73</td>
</tr>
<tr>
<td>Mean number of times entertained at home in last year</td>
<td>0.67</td>
</tr>
<tr>
<td>Measures of social trust</td>
<td></td>
</tr>
<tr>
<td>Agree that “Most people can be trusted”</td>
<td>0.92</td>
</tr>
<tr>
<td>Agree that “Most people are honest”</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Mortality is lower in high-social-capital states

Figure 86: Health Is Better in High-Social-Capital States
Figure 81: Kids Are Better Off in High-Social-Capital States
So What?

- Social capital operates through psychological and biological processes to improve individuals’ lives.

- People whose lives are rich in social capital cope better with traumas and fight illness more effectively.
Psycho Neuro Immunology
PNI

- The study of the link between psychological states and the functioning of the nervous system.

- The study of the interactions among the mind, immune system, and the neurological system that modulate susceptibility to disease or its progression.
In the Wake of the Tsunami

• PsychoSocial Care of Disaster Victims

Tsunami Survivors
P. Sabarinathan, 9 years, IV standard at
Government Middle School, Akkaraipettai

‘I am very scared to sleep. I get nightmares.
I want to play with friends all the time so that I feel better.’
TOWARDS RECONCILIATION
EVERYONE CAN MAKE A DIFFERENCE
Relaxation
Listening
Ventilation
Empathy
Social Support
Spirituality
Externalisation
Factors involved in healing

- CHEMOTHERAPY
- Attitude  Community
- Spirituality  Love/Family support
- Prayer - Meditation

- Mind over matter  Mountain climbing
- Environment  Hanging out with Buddhists
- EXERCISE  FUN
- Diet  Genes  Laughter
**Stressor Events**

**Cataclysmic Disaster**
- Effecting multiple people at the same time
  - Earthquake, war, terrorism

**Post-traumatic**
- Re-experience of stress event as a dream or flashback
  - War experience
  - Childhood abuse

**Personal**
- Major life event that have immediate effect but fade with time

**Background**
- Daily irritating events

**Uplifting**
- Positive events that make one feel good
<table>
<thead>
<tr>
<th>Conditions with mind-body connections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Allergic skin reactions</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Herpes</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Ulcers</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
</tbody>
</table>
The Stress of Adjusting to Change

- Death of Spouse: 100
- Divorce: 73
- Marital separation: 65
- Jail term: 63
- Death of close family member: 63
- Personal injury or illness: 53
- Marriage: 50
- Fired at Work: 47
- Marital reconciliation: 45
- Retirement: 45
- Change in health of family member: 44
- Pregnancy: 40
- Sex difficulties: 39
- Gain of new family member: 39
- Business readjustment: 39
- Change in financial state: 38
The Stress of Adjusting to Change

Death of Close Friend 37
Change to a different line of work 36
Change in number of arguments with spouse 35
Mortgage over $10,000 31
Foreclosure of mortgage or loan 30
Change in responsibilities at work 29
Son or daughter leaving home 29
Trouble with in-laws 29
Outstanding personal achievement 28
Wife begins or stops work 26
Begin or end school 26
Change in living conditions 25
Trouble with boss 23
Change in residence, school 20
Vacation, Christmas 12
Minor violation of the law 11
<table>
<thead>
<tr>
<th>Hassles</th>
<th>Uplifts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misplacing or losing things</td>
<td>Getting enough sleep</td>
</tr>
<tr>
<td>Troublesome neighbors</td>
<td>The weather</td>
</tr>
<tr>
<td>Concerns about owing money</td>
<td>Not working (e.g. on vacation)</td>
</tr>
<tr>
<td>Too many responsibilities</td>
<td>Getting into good physical shape</td>
</tr>
<tr>
<td>Planning meals</td>
<td>Quitting smoking</td>
</tr>
<tr>
<td>Having to wait</td>
<td>Sex</td>
</tr>
<tr>
<td>Being lonely</td>
<td>Spending time with family</td>
</tr>
<tr>
<td>Too many things to do</td>
<td>Shopping</td>
</tr>
<tr>
<td>Too many meetings</td>
<td>Making a friend</td>
</tr>
<tr>
<td>Gossip</td>
<td>Looking forward to retirement</td>
</tr>
<tr>
<td>The weather</td>
<td>Being complimented</td>
</tr>
<tr>
<td>Difficulties with friends</td>
<td>Going someplace that’s different</td>
</tr>
<tr>
<td>Difficulties with getting pregnant</td>
<td>Giving love</td>
</tr>
<tr>
<td>Auto maintenance</td>
<td>Being “one” with the world</td>
</tr>
<tr>
<td>Filling out forms</td>
<td>Flirting</td>
</tr>
<tr>
<td>Unchallenging work</td>
<td>Having good ideas at work</td>
</tr>
<tr>
<td>Problems with your lover</td>
<td>Socializing</td>
</tr>
</tbody>
</table>
Parasympathetic

- Stimulates flow of saliva
- Slows heartbeat
- Constricts bronchi
- Stimulates peristalsis and secretion
- Stimulates release of bile
- Contracts bladder

Sympathetic

- Dilates pupil
- Inhibits flow of saliva
- Accelerates heartbeat
- Dilates bronchi
- Constricts peristalsis and secretion
- Inhibits release of glycogen to glucose
- Conversion of adrenaline to noradrenaline
- Inhibits bladder contraction

Medulla oblongata

Yagus nerve

Chain of sympathetic ganglia

Solar plexus
FIGHT or FLIGHT

**Noticeable Effects**
- Pupils dilate
- Mouth goes dry
- Neck + shoulder muscles tense
- Heart pumps faster
- Chest pains
- Palpitations
- Sweating
- Muscles tense for action
- Breathing fast + shallow
- Hyperventilation
- Oxygen needed for muscles

**Hidden Effects**
- Brain gets body ready for action
- Adrenaline released for fight/flight
- Blood pressure rises
- Liver releases glucose to provide energy for muscles
- Digestion slows — or ceases
- Sphincters close — then relax
- Cortisol released (depresses the immune system)

F. Hedges
YOU BECOME STRESSED

Breathing Becomes Even More Rapid

Anxiety Increases

Shortness of Breath Increases

Breathing Muscles Tire

Anxiety Starts

Breathing Becomes Faster

Breathing Muscles Tire

Shortness of Breath Begins
Non-pharmacologic approach to anxiety

- Deep breathing
- Progressive muscle relaxation
- Guided imagery
The Relaxation Response

- Distracting thought
  - "one"
- Distracting thought
  - "one"
“Milt, I’m beginning to think that your illness is a disharmony of life energy”