From Tragedy to Triumph to Trepidation
Antibiotics at Age 70

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Disclosures
I have no disclosures relevant to this presentation
From Tragedy to Triumph

Sir Alexander Fleming
Sir Alexander Fleming 1928

• The prepared mind, luck or both
  – Fleming was going through old plates that were left out while he was on vacation for 4-5 weeks
  – These had been placed in detergent but a few were not covered with detergent
  – He observed mold growing on one of the plates and commented that the colonies of Staphylococci were not growing near the mold
  – At this point there are many biological facts that do not add up, but the bottom line is that he launched an investigation into the inhibitory substance in the mold

The famous plate with *Penicillium* mold (preserved in the archives of St. Mary’s hospital)
Fleming and Penicillin

• Fleming pursued the substance in the mold, which he named penicillin
• Fleming was unable to concentrate the substance from the mold due to lack of “chemical assistance”
• Although he published a few papers, he gave up his pursuit in 1935
Penicillin 10 years Later
Florey, Chain and Heatley

• Howard Florey, Ernst Chain and Norman Heatley
  – first looked at lysozyme
  – renewed interest following the success of sulfonamides (1935)
  – decided to look at penicillin
• Learned to extract, concentrate and stabilize penicillin
• “miraculous” results obtained in a mouse model in 1940

The First Two Patients 1941

• First patient was Albert Alexander, a 43 yo constable who was septic and covered with pustules
  – Heatley: “He was oozing pus everywhere”
  – Treated, improved dramatically
  – Penicillin re-crystallized from his urine and used on another patient
• 15 yo septic patient Arthur Jones cured by using some of the re-crystallized penicillin from Alexander and the remaining supply of penicillin
  – However, Alexander relapsed and died because they ran out of penicillin
The War in England

The Mold in Dr. Florey’s Coat
The Story of the Penicillin Miracle
ERIC LAX

During the early part of the war, Florey and others purposely contaminated their lab coats with their special strain of Penicillium in case their lab was blown up by the Germans.

Florey and Heatley in US

- In 1941, Howard Florey and Norman Heatley came to America to try to convince our government to back large scale production of penicillin because the war in England prevented further development of penicillin.
- Meet with Dr. John Fulton at Yale who became a major supporter of penicillin
  - Fulton was a former Rhodes Scholar who had worked with Florey in England.
- Heatley stayed on to work with Merck to help develop penicillin in Rahway, NJ.
- December, 1941. US enters war and penicillin is not a top priority.
Anne Miller

- March 14, 1942, 33 yo Anne Miller was dying of septicemia in New Haven Hospital following a miscarriage
- Her doctor (John Bumstead) had met another doctor (John Fulton) who was a champion of Howard Florey’s research. Fulton called the Chair of the Committee on Chemotherapy in DC and he authorized a call to Merck
- Merck released 5.5 grams of penicillin (about a teaspoon which represented 50% of the total US supply)
- After a small first dose (no toxicity), she was injected every 4 hours for a few days
- She died, 57 years later, at age 90

Penicillin in the United States

- Due to success with penicillin and Anne Miller, US Government saw the potential of penicillin for treating wound infections
- However, with our entrance in to WW II, it was not a high priority
- A fire would soon change that
- But first, football
Boston College vs Holy Cross  
November 28, 1942

- BC was 8-0, ranked number 1 in the nation by AP  
  - Had given up only 19 points all season  
- Holy Cross was 4 and 4  
- BC was a 3 touchdown favorite  
- If they won this game, BC was going to be invited to the Sugar Bowl as the highest ranked team in college football  
- Game played before 41,000 fans at Fenway Park

“The Greatest Upset of the Time”

- Holy Cross changed up it’s defensive schemes and BC got “trapped”  
- Holy Cross easily won 55-12  
- BC had planned a huge victory celebration at the Cocoanut Grove nightclub in Boston’s South End  
  - The loss saved the lives of BC fans/players
The Cocoanut Grove

The Cocoanut Grove
Quick History of The Cocoanut Grove

- Built in 1927 went from very popular to dormant during prohibition to the place to be seen in 1942
- Official capacity around 600
- One of the exits was a revolving door
- Other exits locked with chains so patrons could not sneak out

The Fire

- Over 1000 people packed in
- A busboy lit a match to make enough light to see a socket so he could replace a bulb
- Artificial palm tree caught fire
- Within 12 minutes, the club burned down
- Many patrons trapped by stuck revolving door and blocked exits
- 492 deaths and many burn victims
The Cocoanut Grove: Aftermath

Aftermath of the Fire
“The Fire That Made Penicillin Famous”*

- The Cocoanut Grove fire was used by local authorities as a “Rehearsal for Possible Blitz”
  - All emergency medical supplies and support staff were utilized
- 180 burn victims were shipped to Boston City Hospital and treated with conventional therapy for burns
  - Tannic acid and silver nitrate
  - Some were given a new sulfa drug as well
- 40 others were sent to MGH
  - MGH team led by Dr. Oliver Cope was studying burn treatments following Pearl Harbor and the new treatments were being tested at MGH
  - With approval from Washington, MGH received permission to contact Merck to obtain a new experimental drug

*Sheehan, J. and Ross, R.N. Yankee Magazine, pp. 125-203. 1982

The Fire That Made Penicillin Famous

- Merck staff worked 24 hour shifts to produce as much penicillin as possible
- 4 days after the fire, The Boston Globe reported “police escorts from 4 states accompanied a consignment of an as-yet unnamed drug rushed to the MGH early this morning from Merck for the treatment of fire victims..... A 32 liter supply of the drug will be used to prevent infections from burns.”

Sheehan, J. and Ross, R.N. Yankee Magazine, pp. 125-203. 1982
Email from Dr. Grant Rodkey
January, 2013

“Steve: I never knew of this Yankee Magazine article before. It is excellent and written with real authority by John Sheehan. However, I do remember those days vividly. Most active Attending Surgeons in the city were away in military service, so a heavy burden fell on residents and medical students in the care of these patients.

By April 1943 we were using penicillin in some ward patients. Every dose had to be administered by an intern/resident, and the patient’s urine had to be collected for re-cycling the penicillin. The dose was 10,000 units! Yes, Dr. Chester Keefer was the czar!”

The Fire That Made Penicillin Famous

• Preceding the fire, less than 100 Americans had been treated with penicillin
• After the fire, the media brought national attention to the “miracle drug”
• The pharmaceutical companies began large scale production of penicillin
• Penicillin became the second highest priority of the war effort in 1943
“...the Americans improved the methods of production so that on D Day there was enough penicillin for every wounded man who needed it.” Fleming, 1945

Credited with saving lives of 10-15% of all WWII casualties!
Other Medical Achievements

- Surface and Surgical Management
  - Gauze impregnated with boric petroleum replaced tannic acid
- Fluid management
  - Plasma transfusion had never been done “in mass”
  - 1200 units donated the day after the fire, 3800 units used
- Respiratory management
  - Many of the victims had evidence that they inhaled a toxic substance during the fire and new treatments were developed for respiratory management
Fire Safety Standards

- Revolving doors were outlawed and then allowed if the revolving door is placed between two outward-opening exit doors
- Exit doors had to be clearly marked and free from blockage
- Non-combustible decorations
- Emergency lighting and sprinklers

Triumph
Miracle Drugs
Golden Age
The Golden Years 1942-2000

- Scientists all over the world started working on discovering new antibiotics
- Soil samples taken from the tires of airplanes that had landed from exotic destinations and cultured for fungi
- Antibiotics were considered “Miracle Drugs”

Tuberculosis

BRITISH MEDICAL JOURNAL
LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis
First Combination Therapy

• Quickly learned the *M. tuberculosis* became resistant to streptomycin during treatment
  – Cured patients relapsed
  – These patients had streptomycin resistant strains
• 1951, isoniazid introduced and used in combination with streptomycin
• 5 new TB drugs developed between 1952-1962
  – Remain mainstay of modern therapy

Surgeon General of the United States
William Stewart 1967

“The time has come to close the book on infectious diseases. We have basically wiped out infection in the United States.”
Highlights of 60 Years of Antibiotics

The 50’s: vancomycin, erythromycin, tetracycline, colistin
The 60’s: methicillin, metronidazole, ampicillin, gentamicin, nalidixic acid, clindamycin
The 70’s: cefazolin, amoxicillin, minocycline, fosfomycin, tobramycin, cefoxitin, ticarcillin, amikacin
The 80’s: piperacillin, amox/clav, ceftriaxone, ofloxacin, mupirocin, ciprofloxacin, azithromycin, moxifloxacin
The 90’s: clarithromycin, levofoxacin, cefepime, pip/tazo, quinopristin/dalfopristin
2000’s: linezolid, daptomycin, ertapenem, tigecycline, doripenem, televancin
2010: ceftaroline, fidaxomicin

Drug/Bug Combinations Without Detectable Resistance

Penicillin and Group A Beta-Strep
Trepidation

Trepidation
Antibiotic Resistance
There Is No Antibiotic Resistance

There Is No Antibiotic Resistance

The Bacterial Revolution

The Bugs Fight Back!
The Microbiologist’s Perspective

Evolution: The Short Course

- 3.85 billion years old: Bacteria
- 210 million years old: Real Mammals
- 60 million years old: Human-like Mammals
- 30 million years old: Monkeys
- 2.5 million years old: Direct Ancestors
- 0.2 million years old: Neanderthals
- 0.125 million years old: Homo Sapiens
- 70 years old: Antibiotics
Dominance of Bugs over Drugs

• Bacteria are the dominant species on the earth
  – rapid multiplication rate
  – natural mutation rate
  – ability to transfer or move genes via transformation, conjugation, transduction and transposition
• Collectively, these properties allow bacteria to survive, change and eventually flourish under intense selection pressure

Early Warning

• Fleming was working with mutants of *S. aureus* that could be grown in the presence of increasing concentrations of penicillin
• He was concerned that if patients did not take a full course of treatment, resistant strains would appear
• Another concern: an oral form of penicillin was produced and was available without prescription
A Dire Prediction

“The greatest possibility of evil in self medication is the use of too small doses so that instead of clearing up infection, the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save”


Why Do Bacteria Become Resistant to Antibiotics?

• We are trying to kill them
• They are trying to eat and reproduce
• What would you do if someone was trying to kill you while you were trying eat and/or reproduce?
How Bacteria Become Resistant to Antibiotics

• Make enzymes that break-down antibiotics
  – Beta-Lactamases break down the beta-lactam ring of penicillins and cephalosporins
  – There are around 1700 different ones
• Mutate to alter the target sites of antibiotics
• Mutate so antibiotics cannot interfere with DNA synthesis/replication

It’s an Accolade for the Bugs When We Use Initials
When They Become Really Nasty
They Get Initials or Numbers

Nasty Enough
- *Klebsiella pneumoniae*
- *Enterobacter cloacae*
- *S. aureus*
- *C. difficile*

Really Nasty
- ESBL, KPC, NDM, CRE
- ampC *E. cloacae*
- MRSA, VISA, VRSA
- *C. difficile* 027/NAP1/ B1

Resistance Patterns in
*Klebsiella pneumoniae*
It was on a short-cut through the Intensive Care Unit (ICU) that Albert was first approached by a member of the Antibiotic Resistance.
S. aureus Resisting Antibiotics Over the Years

- Penicillin (1941)
  - Moments to get first resistant strain
  - 2012: 92-97% of isolates are resistant to penicillin
- Methicillin (1959)
  - 2 years to get first resistant strain (1961)
  - Now 30-70% resistant
  - CA-MRSA
- Vancomycin (1950’s)
  - 1995: VISA and hVISA
  - 2002: first VRSA, Now 13
- Linezolid (2000)
  - Resistance reported in 2001
  - CLSI designated “R” Breakpoint 2010
- Daptomycin (2003)
  - Resistance reported in 2005 but still very rare
- Ceftaroline (2010)
Screening Anterior Nares for MRSA
The Queen’s Method

Trended Oxacillin-Resistance for *Staphylococcus aureus* Blood Isolates 1996-2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Total N</th>
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<tbody>
<tr>
<td>1996</td>
<td>4,777</td>
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<td>1997</td>
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<td>2010</td>
<td>9,133</td>
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<tr>
<td>2011</td>
<td>8,596</td>
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<td>2012</td>
<td>8,323</td>
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TSN® Database – USA, Eurofins., Chantilly, VA
Trended Oxacillin-Resistance for *Staphylococcus aureus* by Patient Status 1996-2012

Trepidation Money
Trepidation
Antibiotics
Don’t Make
Big
Money

Design The Ideal Drug

• Use in healthy people
• Oral
• Start early in life
• Take daily for rest of your life
• Examples
  – Lipitor
  – Viagra (qid)
Why Antibiotics Do Not Fit The Mold

• Give primarily to sick patients
• Short course therapy
  – 3 days to 2 weeks
• Newer agents rarely used for initial treatment
  – Saved for more serious infections
  – Expensive

Can an Antibiotic be Too Good?

• Ciprofloxacin and Levofloxacin
• Oral with great bioavailability
• Broad spectrum coverage
  – UTI, respiratory, STDs, GI, SST
• Short course
Levofloxacin Resistance in Common Gram Negatives
2012 data only

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total #</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
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<tbody>
<tr>
<td>E. cloacae</td>
<td>7,292</td>
<td>91.7</td>
<td>2.6</td>
<td>5.7</td>
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<tr>
<td>E. coli</td>
<td>218,918</td>
<td>76.2</td>
<td>0.8</td>
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<tr>
<td>K. pneumoniae</td>
<td>46,143</td>
<td>89.4</td>
<td>1.5</td>
<td>9.1</td>
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<tr>
<td>P. mirabilis</td>
<td>25,842</td>
<td>70.4</td>
<td>5.8</td>
<td>23.8</td>
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<td>P. aeruginosa</td>
<td>35,669</td>
<td>66.4</td>
<td>8.5</td>
<td>25.1</td>
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<td>A. baumannii</td>
<td>3,586</td>
<td>56.3</td>
<td>3.6</td>
<td>40.1</td>
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</tbody>
</table>

TSN® Database – USA, Eurofins, Chantilly, VA

Quinolone Resistance

- *Pseudomonas aeruginosa*
- *E. coli*
- *Neisseria gonorrhoeae*
- *Does the future hold another Darth Vader?*
- *Quinolones are important antibiotics: “choose wisely”*
The Z Pak

- 6 expensive pills in a small bottle was not working
- Created a marketing marvel, the Z pak
- Sales took off and this antibiotic became one of the most overused antibiotics of all time
- Better anti-inflammatory than antibiotic
Reasons For Trepidation
Getting A New Drug to Market

- 10 years, 1.0 to 1.7 billion dollars
- Changing rules for clinical trials makes it difficult to enroll patients
- Body site specific approval, not whole body
- Slow growth of antibiotics
  - Reserve, expensive, fear of resistance
- Pharmaceutical companies abandoning the market
  - 19 to 4
- GAIN Act (2011)
  - Extends patent, alters regulatory pathways

Trepidation

Collateral Damage
Collateral damage

- Antibiotic resistance
- Altered normal flora
- Side effects

Dominance of Bacteria in Humans

The human body has $10^{13}$ human cells and $10^{14}$ bacterial cells
“Germs Are Us”

- Wonderful article by Michael Specter in The New Yorker (10/22/2012)
- Most of our normal bacteria are beneficial
- Very few bacteria cause disease
- Must be careful on how we use antibiotics

Normal Flora (Microbiome)

- Born sterile and quickly colonized by specific bacteria at specific sites
- $10^{14}-10^{15}$ total bacteria/human
  - Weighs about 3 pounds (same as a human brain)
  - I consider our normal flora an organ system
- 10,000 different species of bacteria
- Human genome has 23,000 genes
- Bacterial genome provides 4-8 million additional genes
Role of Microbiome

- Digest food
- Make vitamins that are absorbed
- Protect against colonization by other organisms
  - Yeast infections
  - Clostridium difficile
  - S. aureus
- Is part of our immune response an effort to protect our microbiome from pathogens??

The Fat Mouse Experiment

<table>
<thead>
<tr>
<th>Group 1 Mice</th>
<th>Group 2 Mice</th>
</tr>
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<tbody>
<tr>
<td>Fed antibiotics</td>
<td>Fed placebo</td>
</tr>
<tr>
<td>Normal Diet</td>
<td>Normal diet</td>
</tr>
<tr>
<td>Excess weight gain</td>
<td>Normal weight gain</td>
</tr>
</tbody>
</table>
The Fat Mouse

The Fat Mouse Theory

• Fecal bacteria in mice help metabolize diet
• Some of these bacteria are eliminated by antibiotics
• More calories are absorbed from the same amount of food
• May explain why sub-therapeutic amounts of antibiotics in animal feed promote growth in food animals
**H. pylori and Obesity**

- *H. pylori* may alter metabolism by controlling 2 stomach hormones
  - Ghrelin: associated with over-eating
  - Leptin: suppresses appetite
- In people with HP, ghrelin levels are lower than those without HP
  - HP may control ghrelin levels

**Intestinal Microbiota and Increased Risk of Adverse Cardiac Events**

- Production of trimethylamine-N-oxide (TMAO) from dietary phosphatidylcholine (lecithin) was found to be dependent on metabolism by the intestinal organisms
- Increased TMAO levels were associated with an increased risk of incident major adverse cardiac events

The Home Hygiene Health Hypothesis

- Infants and children raised in “sterile” homes may have under-developed immune system functioning
  - Babies born by natural vaginal birth have less allergies and less asthma than those delivered by caesarian section

- My view
  - A little dirt is good, a lot of dirt is not so good”

But we have too many illusions that we can, by writ, govern the remaining vital kingdoms, the microbes, that remain our competitors of the last resort for dominion of the planet. The bacteria and viruses know nothing of national sovereignties. In that natural evolutionary competition, there is no guarantee that we will find ourselves the survivor

The Future of Antibiotics and Resistance

From the World Economic Forum 2013

“Arguably the greatest risk….to human health comes in the form of antibiotic – resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall”

“Creatures”

- 1700 We have creatures on us
- 1890 Creatures cause disease
- 1970 Not all creatures cause disease
- 2000 Some creatures are beneficial
- 2013 Creatures cure disease (NEJM)

“Inestinal Repoopulation: The only time you should take crap from a spouse”

The History of Medicine

2000 BC – Here, eat this root
1000 AD – That root is heathen. Here, say this prayer.
1850 AD – That prayer is superstition. Here, drink this potion.
1920 AD – That potion is snake oil. Here, swallow this pill.
1945 AD – That pill is ineffective. Here, take this penicillin.
1955 AD – Oops...bugs mutated. Here, take this tetracycline.
2012 AD – 39 more "oops", try Gorillacillin
2013 AD – The bugs have won! Here, eat this root.

Anonymous via Don Smith, Modified by S. Brecher