Pathos of Pathology:
Puzzles, Perplexities and Paradigms

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Ms. Reynolds receives financial reimbursement from Parkell for authoring a CE articles available at: www.parkell.dentalaegis.com and financial support to assist with presentation expenditures

Agenda:

- Introduction
- Phenomenal Review of Microbiology
- Eight 'Exceptional' Pathogens
- Bacterial Resistance
- Overview of Viruses and Cancer
- Headliners
- Wrap Up

WHY STUDY MICROBIOLOGY????
Microbes are the basis for virtually ANY disease and, besides, they are really cool critters…
At about 5 MILLION TRILLION TRILLION (that's not a double-word typo…), bacteria and archaea vastly outnumber ALL other life-forms on earth
A word or two about what a TRILLION represents: 1,000,000,000,000
Microbes have been recovered—ALIVE!—from the petrified gut of a 40 million year old bee!
An average adult inhales 14 pints of air and about 8 microbes every minute—approximately 10,000 critters daily!
Women harbor a greater variety of bacteria on their hands than men
In 2006, a probe at a South African gold mine turned up bacteria living nearly TWO MILES underground—living on the energy given off by radioactive rocks
Another species (Deinococcus radiodurans) can survive almost 10,000 times the dose of radiation lethal to humans—making it an ideal candidate for the cleanup of nuclear waste
Pseudomonas natriegens (an ocean-dwelling bacterium) can go from birth to reproduction in 10 minutes—in 5 hours a single cell could give rise to 1 BILLION+ offspring
Most bacteria have yet to be discovered—in 2003, one research team found more than a MILLION never-before-seen bacterial genes in ONE sea trolling excursion

Phenomenal Review of Microbiology

Different stains are the result of differences in the CELL WALLS
SUMMARY of Gram + Bacterial Cell Walls

- Thick
- Contains teichoic acid
- Vulnerable to penicillin and lysozyme
- 2 layers
- Low lipid content
- NO periplasmic space/porin channel
- NO endotoxin*

SUMMARY of Gram – Bacterial Cell Walls

- Thin
- Contains murein lipoprotein
- High lipid
- Periplasmic space
- Porin channel
- Endotoxin (LPS)- lipid A
- Resistant to lysozyme and penicillin attack

Most disease-causing microbes are gram - rods or gram - pleomorphic bacteria

Gram + cocci:

Non-mobile***
Do NOT form spores
Medically important:

- Streptococcus ("strips")
- Staphylococcus ("clusters")

Hyaluronidase is an enzyme most non-mobile bacteria need to make in order to invade tissue

Streptococcus

Usually arranged in chains or pairs
All streptococci are CATALASE NEGATIVE
Three groups:

- Beta-hemolytic (completely lyse RBC's)
- Alpha-hemolytic (partially lyse RBC's)
- Gamma-hemolytic (unable to lyse RBC's)

Beta-hemolytic streptococcus

- Produces **hemolysins*****
- Arranged into Lancefield groups (A-U)
- Group A streptococcus are important human pathogens
- Many strains are anti-phagocytic

Headliners: Germs in Tobacco Potential Source for infections Blamed on Smoking; John Pauly; lead researcher; immunologist; Roswell Park Cancer Institute (Buffalo, NY); study results appearing in Immunological Research; 9/2012; as reported in Science News; 3/13/2010; accessed on 2/25/13 at: https://www.sciencenews.org/article/germs-tobacco-are-potential-source-respiratory-infections-blamed-smoking

Researchers recently reported that live bacteria inhabit all types of tobacco products and that about 60% of cigarette filters contained tobacco particles
According to the researchers, these particles or 'flakes' not only hosted a variety of bacterial toxins but 'bacteria grew from greater than 90% of the randomly selected flakes'
When cultured with blood, the study team demonstrated that the 'tobacco-derived bacteria frequently destroyed the red blood cells'
Bacteria from tobacco, grown in the lab with blood, are surrounded by remnants of RBCs destroyed by bacterial toxins in a process called hemolysis
Scientists have long known that smokers and people exposed to secondhand smoke experience high rates of respiratory infections due to impaired lung function and/or immunity but, in light of this recent research, cigarettes themselves may be the source of those infections--Source: Amy Sapkota; lead researcher; University of Maryland (College Park); results appearing in Environmental Health Perspectives (online edition); 2010

Group A Streptococcus ('GAS') (Streptococcus pyrogenes)

'Microbial post-it notes'

Causative for:

- Streptoccal pharyngitis
- Pyogenic infections
- Tonsillitis
- Scarlet fever/ Rheumatic fever

GAS is **highly communicable** and primarily **spread through person-to-person contact**

As the body tries to fight off a strep infection, it can sometimes produce antibodies that attack both the strep bacteria and healthy cells

Streptococcus pyogenes is one of the most frequent pathogens of humans

It is estimated that between 5-15% of individuals harbor the bacterium, usually in the respiratory tract, without signs of disease

When the bacteria are introduced or transmitted to vulnerable tissues, a variety of types of suppurative infections can occur

Headliners: 'Flesh-eating bug ate my face!' one British tabloid screamed in the 1990's

The story took off like wildfire, with gruesome descriptions of limbs rotting in front of peoples eyes, faces melting away, and emergency amputations to save lives

Just another tabloid rumor, or something people should be losing sleep over?

There has been a recent increase in variety, severity and sequelae of Streptococcus pyogenes infections, and a resurgence of severe invasive infections, prompting descriptions of 'flesh eating bacteria' in the news media

The bacteria can invade the body with wrath—causing a very serious infection called necrotizing fasciitis

It is an extremely life-threatening illness, which requires extensive treatment

This can sometimes necessitate amputation or result in severe disfigurement

Headliners: Lose 70 Pounds in 15 Days with Flesh-Eating Bacteria!

According to the article, a 'new, mutated' strain of Streptococcus pyogenes cuts through fat 'like a buzz saw'—eliminating 'an incredible 3 inches of ugly, unsightly flab per hour'!

'I went from 210 pounds to 140 pounds in 15 days with the help of fat-eating bacteria. Now when my husband invites those young starlets in bikinis to hang out by the pool, I don't feel so insecure.'--Wife of a well-known producer

A word or two about trustworthy sources

Headliners: Degrading a Defense: Bacteria Use Enzyme to Escape Trap; ScienceNews; 2/25/06

Like a cloak of invisibility, an enzyme released by Strep A bacteria lets them slip away from the body's staunchest defenders

Neutrophils attack bacteria by eating them OR they can release 'neutrophil extracellular traps' ('NETs')—the fibrous NETs are made up of DNA and toxic compounds that can catch and kill pathogenic microbes

Disease-producing bacteria such as GAS produce an enzyme that degrades the traps—likely DNases

Researchers speculate that this discovery could guide a new approach to fighting disease—although finding ways to target only pathogenic DNase must come first

'Manipulating this one factor has a big effect on the disease-causing potential of bacteria. [Rather than killing the bacteria with resistance-promoting antibiotics,] we're basically allowing the immune system to do its job.'--Victor Nizet; University of California (San Diego); lead researcher

Headliners: Microscopic Revelations Point to New Blood Infection Therapies; Source: Department of Critical Care Medicine; Cumming School of Medicine; Tier II Canada Research Chair; Pulmonary Immunology, Inflammation and Host Defence, study results published in CELL Host & Microbe; study results posted 1 MAR 2018 by Andrea Kingwell (for the Office of the Vice-President of Research; accessed 4 MAR 2018 at: https://www.ucalgary.ca/utoday/issue/2018-03-01/microscopic-revelations-point-new-blood-infection-therapies

Researchers at the University of Calgary have for the first time been able to observe how the human body responds to often lethal fungal blood infections in the lung—and what they saw surprised them

As expected, neutrophils rushed to the scene of the infection—but then the cells swarmed, clustered and jammed up the blood vessels causing a dangerous stroke-like blockage

'For some reason the lung itself has a lot of the main type of immune cell, the neutrophil. We knew this, but the reasons why they are in the lung has remained mysterious. Our initial thought was that neutrophils would capture fungi the same as they capture bacteria. But they became so activated they started to clump and cluster together and actually block the bloodstream.'--Source: Dr. Bryan Yipp; lead researcher

It is worth noting that most research has been on bacterial sepsis but these researchers wanted to focus on **fungal sepsis** because it is less well understood and fungal infections are growing in number and severity

Candida albicans is a notorious human fungal pathogen that causes thrush and serious systemic infections

Opportunistic Candida albicans often lives inconspicuously as part of the human normal flora—but it can switch to become an aggressive pathogen (especially in people whose immune systems are already compromised by pre-existing diseases or those taking certain medications)

The threat posed by both free and biofilm-bound forms of this fungal pathogen is constantly growing—virulent C. albicans strains are becoming increasingly resistant to the few drugs that are available to treat them

Read more at: https://phys.org/news/2017-10-drug-resistance-fungi.html#jCp

VIRIDANS GROUP STREPTOCOCCI

- Big, heterogeneous group of strep bacteria
- No Lancefield group
- Not bile soluble
- 'Viridis' is Latin for GREEN; (produces greenish tint on blood agar)
- Most viridans strep are alpha-hemolytic
- Normal inhabitants of the nasopharynx and gingival crevices

The viridans streptococci cause 3 main types of infections:

- Dental infections*
- Endocarditis*
- Abcesses

Dental infections:

Some of the viridans streptococci (especially S. mutans) can bind to teeth by dextrans and ferment sugar, which produces acid and dental caries

Growth of oral bacteria requires adhesion to a surface because the constant flow of host secretions thwarts the ability of planktonic cells to grow before they are swallowed

Endocarditis:

Dental manipulations send viridans streptococci into the bloodstream where they can implant on the endocardial surface of the heart (most commonly on damaged valves) by producing an extracellular dextran

Most common VIRIDANS:

- **S. mutans (pit and fissure caries)**
- S. sobrinus (smooth surface caries)
- S. salivarius (septicemia)
- S. mitis (endocarditis)
- **S. sanguis (plaque colonization and endocarditis)******
- **Streptococcus gordonii******

Streptoccocus mutans

Long implicated as being a major player in caries formation, Streptococcus mutans is a microbe that continues to be studied intensively in the oral health field

Despite scientific advancements in cariology in the past 150 years, dental caries remains a serious issue worldwide—particularly in children where it is the primary source of tooth loss

In the United States, 42% of children of ages between 2 to 11 have had dental caries in their primary teeth and, in the adult population, dental caries and periodontal diseases affect 60–90% of individuals worldwide--Source: Rouabhia M and Chmielewski W: Diseases associated with oral polymicrobial biofilms. Open Mycol J 6: 27–32. (2012)

Understanding the mechanisms behind caries generation involving Streptococcus mutans is crucial in order to control, prevent and treat dental caries

An important virulence factor for any microbe is its ability to adhere to biological structure—understanding of how Streptococcus mutans 'sticks' to tooth surface is a key factor in caries control

The process of plaque biofilm formation begins the formation of salivary pellicle specifically adsorbed to the acquired enamel pellicle (AEP)—single S. mutans cells or their aggregates fuse with pellicles via two independent mechanisms: sucrose-dependent and sucrose-independent--Source: Krzyściak W et al: The virulence of Streptococcus mutans and the ability to form biofilms; European Journal of Clinical Microbiology & Infectious Diseases; April 2014, Volume 33, Issue 4, pp 499-515; posted online 10/24/13; accessed 3/10/16 at: http://link.springer.com/article/10.1007/s10096-013-1993-7/fulltext.html#CR30

The sucrose-dependent mechanism of plaque formation is based on **glucosyltransferases ('GTFs')** produced by S. mutans in combination with glucan-binding proteins (GBPs)—GTFs play critical roles in virulent dental plaque development and are responsible for glucans formation from sucrose

Investigations involving S. mutans cells proved that they exhibit a different expression of some proteins in comparison to planktonic cultures and were associated with a higher tolerance to low pH as compared to planktonic cultures—allowing them to thrive in an acidic biofilm necessary for caries development

Researchers from the UK and Japan were able to re-create the 3D structure of an enzyme that plays a key role in tooth decay caused by S. mutans--Source: Keisuke Ito et al: Crystal Structure Of Glucansucrase From The Dental Caries Pathogen Streptococcus mutans; appearing in the Journal of Molecular Biology; 408 (2):pp. 177-378. 4/29/11

The structural information provides critical insight into how the enzyme **'GTF-SI'**—a glucansucrase—catalyzes glucan development leading to plaque biofilm development

The synthesized glucans provide the possibility of both bacterial adhesion to the tooth enamel and microorganisms to each other—a mechanism that favors the formation of biofilm

A previously unidentified strain of streptococcus (called '**A12**') was found to neutralize acid by metabolizing **arginine**—additionally, A12 inhibited growth and intercellular signaling pathways of Streptococcus mutans

With hopes of developing an A12 oral supplement, the researchers stated that 'A12-like organisms may play crucial roles in promotion of stable, health-associated oral biofilm communities by moderating plaque pH and interfering with the growth and virulence of caries pathogens' --Source: Huangn X et al: Characterization of a highly arginolytic Streptococcus species that potently antagonizes Streptococcus mutans; Applied and Environmental Microbiology; accepted manuscript posted online 29 January 2016; accessed on 3/14/16 at: http://aem.asm.org/content/early/2016/01/25/AEM.03887-15

The research team recently received a five-year, $3 million grant from the U.S. National Institute of Dental and Craniofacial Research to study A12 and related bacteria in the mouth

The ability of bacteria of the S. mutans species to form biofilms is significant the context of caries etiology—**Streptococcus mutans are also implicated in the development of infective endocarditis (IE)**

In an intensive review exploring the virulence potential of Streptococcus mutans, researchers found that strains of S. mutans may cause the aggravation of ulcerative colitis—and may indeed be involved in the pathogenesis of ulcerative colitis--Source: Kojima A et al: Infection of specific strains of Streptococcus mutans, oral bacteria, confers a risk of ulcerative colitis; Nature Scientific Reports 2, Article number: 332 (2012); published online 26 March 2012

'We clearly showed that infection of specific strains of S. mutans is one of the risk factors in aggravating inflammation of ulcerative colitis ('UC'). This is the first report describing the involvement of oral bacteria in UC pathology.'--Statement from the study investigators

Streptococcus Sanguis

Features of S. Sanguis

- Production of glycans from sucrose
- Binding to extracellular matrix proteins, platelets, & salivary proteins
- Ability to specifically co-aggregate with other oral microflora
- Genetic competence

S. sanguis **directly binds to oral surfaces** and serves as a tether for the attachment of a variety of other oral microorganisms which colonize the tooth surface, form dental plaque, and contribute to the etiology of both caries and periodontal disease

S. sanguis has been long recognized as a leading cause of **bacterial endocarditis**, a disease of high morbidity which is fatal if untreated

Headliners: Penicillin resistance is being observed in this group of organisms

Such antibiotic resistance is both surprising and disquieting because the viridans streptococci (including S. sanguis) historically are classified as 'penicillin sensitive' and for many years were believed to be unable to become resistant to ß-lactam antibiotics

Headliners: Platelets as Mediators of the Vascular Response to Infection; Source: Dermot Cox; appearing in Vascular Responses to Pathogens; pp. 23–30; 2016; accessed on 14 MAR 2018 at: https://www.sciencedirect.com/science/article/pii/B9780128010785000030

As previously mentioned, bacteria that typically possess binding proteins are the streptococci species—most notable species (besides Streptococcus mutans) include **Streptococcus sanguinis*** ** and **Streptococcus gordonii*** **

These bacteria express a family of related, highly glycosylated proteins on their surface that bind directly to platelet glycoprotein (GP) Ib—the S. sanguinis protein that interacts with platelet GPIbα is a serine-rich glycoprotein called SrpA

On S. gordonii there are multiple adhesive proteins

Headliners: Blood Clots May Be Triggered By Dental Plaque Bacteria; Society for General Microbiology. (2012, March 26); Medical News Today; Howard Jenkinson; lead researcher; Professor of Oral Microbiology and Head of Research at the University of Bristol's School of Oral and Dental Sciences; and Dr. Steve Kerrigan; Royal College of Surgeons in Ireland (RCSI); results presented at the Society for General Microbiology's Spring Conference in Dublin; March 2012; accessed on 25 Feb 2015 at: http://www.bristol.ac.uk/news/2012/8364.html

Streptococcus gordonii is a normal inhabitant of the mouth and contributes to plaque that forms on the surface of teeth—if they are introduced into the blood stream, these microbes are able to masquerade as human proteins

Researchers discovered that S. gordonii is able to produce a molecule on its surface that lets it mimic the human protein fibrinogen (a blood-clotting factor) which in turn activates platelets causing them to clump inside blood vessels

These unwanted blood clots encase the bacteria, protecting them from the immune system and from antibiotics that might be used to treat infection

'In the development of infective endocarditis, a crucial step is the bacteria sticking to the heart valve and then activating platelets to form a clot. We are now looking at the mechanism behind this sequence of events in the hope that we can develop new drugs which are needed to prevent blood clots and also infective endocarditis. About 30% of people with infective endocarditis die and most will require surgery for replacement of the infected heart valve with a metal or animal valve. Our team has now identified the critical components of the S. gordonii molecule that mimics fibrinogen, so we are getting closer to being able to design new compounds to inhibit it. This would prevent the stimulation of unwanted blood clots.'--Researchers

The researchers are also looking more widely at other dental plaque bacteria that may have similar effects to S. gordonii

'We are also trying to determine how widespread this phenomenon is by studying other bacteria related to S. gordonii. What our work clearly shows is how important it is to keep your mouth healthy through regular brushing and flossing, to keep these bacteria in check.'--Study leaders

A word or two about platelets

The primary function of platelets is to patrol the vasculature and seal vessel breaches to limit blood loss—however, it is becoming increasingly clear that they also contribute to pathophysiological conditions like thrombosis, atherosclerosis, stroke and **infection*** **

Platelet surface receptors like GPIb, αIIbβ3, TLR2 and TLR4 are involved in direct platelet-bacteria interactions—plasma proteins like fibrinogen and vWF enable indirect interactions

Platelet granules contain numerous proteins that modulate the immune response as well as agents which can directly lyse bacteria

Headliners: New Targets Revealed for the Treatment of Inflammatory Conditions; Source: Wersäll A et al: Mouse Platelet Ral GTPases Control P-Selectin Surface Expression, Regulating Platelet–Leukocyte Interaction; appearing in Arteriosclerosis, Thrombosis, and Vascular Biology (2018); posted 15 FEB 2018 by the University of Bristol; accessed on 14 MAR 2018 at: https://medicalxpress.com/news/2018-02-revealed-treatment-inflammatory-conditions.html

Platelets are often thought of as nothing more than cells which stop us bleeding when we cut ourselves. This couldn't be further from the truth and this study showcases the complexity of these small cells as well as a previously unknown signalling pathway within them. I'm hopeful that the findings will lead to further research into this area of platelet function and the development of new treatments for platelet-mediated inflammatory conditions.'--Source: Andreas Wersäll; lead author and Ph.D. student in the Poole Group (part of Bristol Platelet Group); commenting on the research

Competence stimulating peptide ('**CSP**') is produced by many streptococcal species and is instrumental in such activities as biofilm formation, antimicrobial resistance, and acid tolerance of dental plaque biofilm
Streptococcus mutans employs competence-stimulating peptide to stimulate mutacin production from bacteriocins
Bacteriocins are antibacterial proteins produced by bacteria that kill or inhibit the growth of closely related strains—their biogenesis is thought to modulate the growth of competitor organisms occupying the same microecological niche
Because Streptococcus mutans is in fierce competition with other bacteria for successful colonization and biofilm formation, the ability of this microbe to synthesize the small cationic peptides known as **mutacins**—derived from bacteriocin—greatly enhances strep's ability to survive and thrive in oral biofilms
Mutacin-mediated cell killing is also considered a source of nutrients during nutrient-limited conditions
The mutacins produced by Streptococcus mutans are divided into two groups**: lantibiotic mutacins** and unmodified mutacins
Lantibiotics are highly modified peptide antibiotics made by a small group of Gram positive bacterial species such as Streptococcus mutans—approximately 50 lantibiotics have been identified since 1927 when the first lantibiotic was discovered
MU 1140 is a lantibiotic that is generating much excitement in the research community—it was discovered while trying to understand the mechanism of action for Streptococcus mutans
Preclinical testing on MU 1140 has demonstrated the molecule's novel mechanism of action—this molecule has proven active against all Gram-positive bacteria against which it has been tested (including methicillin-resistant Staphylococcus aureus ['MRSA'], vancomycin-resistant Enterococcus faecalis ['VRE'] and Clostridium difficile ['C. diff'])
MU-1140 has been shown to be effective against drug resistant tuberculosis
Oragenics is pursuing the first-ever synthetic route to commercial-scale production of a lantibiotic using the process illustrated below:

- In February 2013, Oragenics announced that along with Intrexon they discovered a promising new purification process for MU-1140 which demonstrated significant progress towards commercial production of MU-1140

Why all the fuss about a 'new' antibiotic?

- The need for novel antibiotics is increasing as a result of the growing resistance of target pathogens—the CDC estimates that bacteria resistant to known antibiotics have resistance rates as high as 70% for many Gram-positive infections

Staphylococcus

- GENERALLY harmless inhabitant of the normal flora community
- Has POWERFUL arsenal of enzymatic and exotoxin weapons
- Important characteristics of Staphylococcus:
- Non-mobile
- Non-spore forming
- Gram + grapelike clusters

- Facultative aerobe
- Typical lesion = abscess

Staphylococcus aureus

- Produces coagulase and hyaluronidase
- Produces pigmented compounds called carotenoids
- MAJOR producer of leukocidins (destroy phagocytes)
- Destroyed phagocytes make up bulk of pus
- **Hyaluronidase** is an enzyme most non-mobile bacteria need to make in order to invade tissue

During the 1970s a strain of Staphylococcus aureus resistant to the antibiotic methicillin, was isolated and consequently vancomycin (the most powerful antibiotic in our arsenal) became the primary antibiotic used to combat staphylococcus infection

KEY: Patients can carry or be colonized by MRSA but have no signs of active disease (they can become infected later on)—for example, from one-quarter to one-third of patients colonized with MRSA become infected which can attack the skin and soft tissue, cause a form of pneumonia or invade the bloodstream

The oral cavity is an important site of S. aureus colonization and demonstrates that conditions modifying the oral environment—such as the presence of periodontitis and of fixed prosthetic restorations—may promote S. aureus carriage and may favor the spread of more pathogenic strains--C Passariello et al: Influence of oral conditions on colonization by highly toxigenic Staphylococcus aureus strains; appearing in Oral Diseases; 12/14/2011

In 1997 a strain of S. aureus resistant to vancomycin was isolated, and people are once again exposed to the threat of untreatable staphylococcus infection

In April of 2014, WHO released its first report on global antimicrobial resistance and revealed that this serious threat is no longer a prediction for the future—it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country

'Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill. Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine. Unless we take significant actions to improve efforts to prevent infections and also change how we produce, prescribe and use antibiotics, the world will lose more and more of these global public health goods and the implications will be devastating.'--Source: Dr Keiji Fukuda; Assistant Director-General for Health Security; World Health Organization

Headliners: Drug-resistant Infections Could Lead to 10 Million Extra Deaths a Year: A Report; Haroon Siddique; reporting for The Guardian; posted on 12/11/2014; accessed on 8/6/15 at: http://www.theguardian.com/society/2014/dec/11/drug-resistant-infections-deaths-soar-10m-by-2050-report

According to a report commissioned by UK Prime Minister David Cameron, failure to tackle drug-resistant infections will lead to at least 10 million extra deaths a year and cost the global economy up to $100 TRILLION by 2050

A 'low estimate' of the current number of annual global deaths is put at 700,000.

Annually, the costs of global mortality from antibiotic resistant infections stands at $70-$75 TRILLION

The stark figures were believed to be the first to quantify the potential impact of antimicrobial resistance (AMR) and are intended to be used to make the case to global leaders that urgent action is needed

No country is considered immune from the threat but for some regions and nations the outlook is particularly bleak—the world's most populous countries, India and China, face 2 million and 1 million deaths a year respectively by 2050

One in four deaths in Nigeria by 2050 is forecast to be attributable to AMR—the report warned that Africa as a continent 'will suffer greatly'

'We cannot allow these projections to materialize for any of us, especially our fellow citizens in the Bric (Brazil, Russia, India, China) and Mint (Mexico, Indonesia, Nigeria, Turkey) world, and our ambition is such that we will search for bold, clear and practical long term solutions.'--Jim O'Neill; former Goldman Sachs chief economist; chair of the investigative group authoring the report

A Primer on Bacterial Resistance

Key Problem: Depending on species, a new generation of microbes comes along every 20 minutes or so—on average, bacterial populations will double twice per hour (translation: one human generation is equal to half a million bacterial generations)

That speeds up the 'evolutionary cycle' considerably--allowing for 'survival mutations'

Headliners: Hard Living Breeds Superbugs; Valerie Ross; reporting for Discover; 2/2010

Physicians have long known that an incomplete course of antibiotics can promote bacterial resistance—warnings are often included to 'finish all this medication'

Researchers have been studying how such resistance can develop—they found that when E. coli were treated with doses of ampicillin too low to kill all of the cells, some of the surviving microbes suffered DNA damage that was hastily (and often inaccurately) patched up

The sloppy repair job left behind mutations—some of which gave rise to not only ampicillin resistance but also to two other antibiotics the microbes had never encountered

"It's the bacterial equivalent of 'That which doesn't kill you makes you stronger'."--James Collins; study investigator; biomedical engineer; Boston University

40 or 50 bacterial generations will be generated in 24 hours (the equivalent to 1,400 human years)—and each generation will be stronger and have a greater survival rate

The trouble is, researchers are finding that most of the microbes that are killed with antibiotics, antibacterials, and other measures are the 'good guys'—leaving behind a less diverse, more pathogenic bacterial population

Another advantage that microbes have is that they are extremely promiscuous—even though they can reproduce asexually by splitting in two, they often link up with other microbes of the same species or even a different species

In doing so, microbes are capable of swapping bits of genetic material (their DNA) before reproducing

Bacterial versatility means bacteria can acquire useful traits without having to wait for mutations in the immediate family

The process is even faster with antibiotic resistance than it is for other traits because the drugs wipe out the resistant bacterium's competition

There are other ways bacteria can pick up genes—the DNA can come from viruses which have acquired it while infecting other microbes

Gram + rods:

- Bacillus
- Clostridium
- Corynebacterium
- Listeria Bacillus

Bacillus

Bacillus represents a genus of Gram+ bacteria which are commonly found in nature (soil, water, and airborne dust)

Some species are natural flora in the human intestines

A unique characteristic of this bacterium is its ability to produce endospores when environmental conditions are stressful

Although most species of Bacillus are harmless, two species are considered medically significant: B. anthracis and B. cereus

Bacillus anthracis

Causative for anthrax--an acute infectious disease most commonly occurring in wild and domestic lower vertebrates (cattle, sheep, goats, camels, antelopes, and other herbivores)

But it can also occur in humans when they are exposed to infected animals or tissue from infected animals

When swallowed, anthrax spores may cause lesions from the oral cavity to the cecum

The **oropharyngeal variant**, in particular, is unfamiliar to most physicians

The clinical features of oropharyngeal anthrax include:

- Fever and toxemia
- Inflammatory lesion(s) in the oral cavity or oropharynx
- Enlargement of cervical lymph nodes associated with edema of the soft tissue of the cervical area
- High case-fatality rate

Clostridium

One member of the Clostridium family—Clostridiuim difficile—is becoming a microbe to watch!

Clostridium difficile infection (CDI) is considered the most common healthcare associated infection in the United States

CDI differs from most other infections as it usually occurs after treatment with antimicrobial therapy—the most commonly associated agents that CDI is associated with include clindamycin, ampicillin, cephalosporins, and fluoroquinolones

It is estimated that CDI costs the United States healthcare system $5 billion every year—and that the incidence for CDI has increased over the past 2 decades

KEY: Severe C. diff infection of the colon most often occurs after a patient has taken a course of broad-spectrum antibiotics—any CDF not killed by the antibiotics can multiply without competition from other microbes and become overgrown

Although Clostridium are a gram positive, anaerobic type of bacteria killed by exposure to oxygen, they can also form resistant structures called endospores when stressed— endospores can remain dormant for decades, germinating into living bacteria under optimal conditions for their growth and success

This allows people infected with C. diff to become CARRIERS

Not surprisingly, antibiotic resistance is also becoming more common with this bug

During the past decade, mutations in the bacterium have transformed C. diff from a rare nosocomial infection to one that can spread rapidly in hospitals and has spilled out into the community

Now, infection of healthy individuals with few or no risk factors is not uncommon and increasing recurrence rates have been reported

'We're in the midst of an epidemic of C. difficile that's caused by a newer strain. There are certain mutations in the genes that allow this strain to produce much more toxin than the older strain of C. difficile.'--Neil Fishman, M.D.; Director of the Department of Healthcare Epidemiology and Infection Control; Director of the Antimicrobial Management Program for the University of Pennsylvania Health System

Because of the more than 400% increase in C. diff infections since 2000, physicians have been scrambling to find a cure for the ever-stronger strains of this this pathogen

Headliners: University of Texas Health Researcher Awarded $1.9 million NIH Grant to Study Clostridium difficile Infections; University of Texas Health Science Center (Houston); Public release report; 7/9/15; Accessed on 8/6/15 at: http://www.eurekalert.org/pub_releases/2015-07/uoth-ura070915.php

Charles Darkoh, Ph.D., a researcher at The University of Texas Health Science Center at Houston, was recently awarded a five-year, $1.9 million R01 grant by the National Institutes of Health (NIH) to develop a non-antibiotic treatment for Clostridium difficile infections

Because C. diff has found multiple ways to survive several antibiotics, Darkoh plans to concentrate his work on finding ways to prevent C. diff from releasing toxins and making the existing toxins inactive—in doing so, the treatment would give good bacteria time to repopulate the gut and allow the immune system to naturally clear the infection

Already, Darkoh's laboratory has identified potent novel compounds that prevent production and inactivate the C. diff toxins—during the pre-clinical study, the team plans to identify the target and mechanism of inhibition of the compounds, evaluate the compounds on different strains of C. diff and examine the efficacy of a cocktail of these compounds that would work as a combination therapy to prevent illness from C. diff

Headliners: Did the Hospital Give You Diarrhea?; The You Docs; appearing in the Idaho Statesman; 7/28/12

Bacteriotherapy may be the answer!

Bacteria are extracted from donor stools and are introduced into the intestines of someone infected with C. diff after the 'sample' has been processed

More and more clinics are popping up that have pre-screened fecal bacteria in donor banks—the gold standard is to deliver the donor sample via colonoscopy so the whole colon can be recolonized

The success rate of curing C. diff infections via bacteriotherapy is more than 90%--with virtually 'no negative side effects'

Corynebacterium

Diptheria is a contagious disease of man in which corynebacterium diphtheriae colonizes the mucous membranes of the fauces and pharynx and sometimes the larynx and trachea
The disease normally breaks out 2 to 5 days after infection
Untreated patients are infectious for 2 to 3 weeks
The disease proceeds when the bacteria's exotoxin blocks protein synthesis and ultimately kills systemic cells
The accumulation of dead cells, mucus, fibrous tissue and white blood cells forms the leathery pseudomembrane which can cause respiratory blockage and death, especially in children
Between 5% and 10% of diphtheria patients die--even if properly treated
Untreated, the disease claims even more lives
In the United States, diphtheria currently occurs sporadically, mostly among the Native American population, homeless people, lower socioeconomic groups, alcoholics and immigrants and travelers from regions with ongoing epidemics
Diphtheria usually affects the tonsils, pharynx, larynx and occasionally the skin
Symptoms range from a moderately sore throat to toxic life-threatening diphtheria of the larynx or of the lower and upper respiratory tracts
Many antibiotics are currently effective (including penicillin, erythromycin, clindamycin, rifampin, and tetracycline)—erythromycin or penicillin is the treatment of choice and is usually given for 14 days

Listeria

Listeriosis, a serious infection caused by eating food contaminated with the bacterium Listeria monocytogenes, has recently been recognized as an important public health problem in the United States
Outbreaks of foodborne listeriosis in the 1980s caused by Listeria monocytogenes demonstrated the severe nature of the illness and an exceptionally high mortality rate--particularly in vulnerable groups within the community
The pathogenesis of Listeria monocytogenes infection depends upon the ability of the bacterium to invade and replicate inside various cell types--including macrophages and epithelial cells
A person with listeriosis has fever, muscle aches, and sometimes gastrointestinal symptoms such as nausea or diarrhea
If infection spreads to the nervous system, symptoms such as headache, stiff neck, confusion, loss of balance, or convulsions can occur
The disease affects primarily pregnant women, newborns, and adults with weakened immune systems
Infected pregnant women may experience only a mild, flu-like illness; however, infections during pregnancy can lead to miscarriage or stillbirth, premature delivery, or infection of the newborn
Listeria monocytogenes is found in soil and water
Vegetables can become contaminated from the soil or from manure used as fertilizer
Headliners: Dole Salad Listeria Outbreak in the U.S. Ends with 19 Sick, 1 Dead; As reported by Carla Gillespie for Food Poisoning Bulletin; posted on 4/1/2016; accessed on 4/19/2016 at: https://foodpoisoningbulletin.com/2016/dole-salad-listeria-outbreak-in-the-u-s-ends-with-19-sick-1-dead
A Listeria outbreak linked to salads produced at Dole's plant in Springfield, Ohio ended with 19 people sickened and 1 death in the United States—additionally, in Canada, likely 14 people were sickened and three died--Centers for Disease Control and Prevention
Health officials used whole genome sequencing (WGS) to determine that the isolates of case patients in both countries were closely related genetically—genetic, epidemiologic and laboratory evidence indicated a link between packaged salad products produced at Dole's Springfield plant and the outbreak of listeriosis
In the US, onset of illness was reported from July 5, 2015 to January 31, 2016—the case patients ranged in age from 3 years to 83 (with a median age of 64)
74% of those sickened were female
Animals can carry the bacterium without appearing ill and can contaminate foods of animal origin such as meats and dairy products
The bacterium has been found in a variety of raw foods, such as uncooked meats and vegetables, as well as in processed foods, such as soft cheeses and cold cuts at the deli counter

Listeria is killed by pasteurization and cooking; however, in certain ready-to-eat foods such as hot dogs and deli meats, contamination may occur after cooking but before packaging!

Headliners: Scientists May Have New Weapon to Fight Listeria; As reported by Food Safety News; News Desk; posted 14 MAR 2018; accessed on 14 MAR 2018 at: http://www.foodsafetynews.com/2018/03/researchers-may-have-found-new-way-to-fight-drug-resistant-bacteria/#.WqliKkkwu-o

Researchers from North Carolina State University have pinpointed new compounds that may be effective in containing the virulence of Listeria—news of the discovery came during an ongoing listeriosis outbreak in South Africa that has sickened 1,000 and killed 180

The World Health Organization reported it was the largest outbreak ever documented in the world—it has been traced to processed meat products made with chicken paste and referred to as 'polony'

Investigators knew that inhibiting a particular enzyme of Listeria—known as glucose-1-phosphate uridylyltransferase (GalU)—led to dramatic modifications of the bacterial cell surface

These chemical modifications in turn rendered Listeria much less virulent and less able to cause illness

The researchers worked to identify potential compounds that could inhibit the function of GalU

'While our ultimate objective is to get away from antibiotics altogether, in the near term the antibiotic susceptibility opens up the possibility of combinatorial therapies that could include a GalU inhibitor and a known antibiotic such as cefotaxime. Ultimately, we believe if the GalU inhibitor is effective enough, the host—human or animal—should be able to eliminate the listerial population without antibiotics. For farmers working toward antibiotic-free farms, this could be a wonderful solution. This proof-of-concept study shows that small molecules can actually be developed to shut down the activity of one specific bacterial enzyme, leading to the suppression of virulence. This is clearly a new avenue for fighting drug-resistant bacteria.'--Statement from study authors Denis Fourches, Melaine Kuenemann, and Paul Orndorff

Neisseria

Neisseria gonorrhoeae

Each year, ~78 million people worldwide are infected with gonorrhea—in the United States, the Centers for Disease Control and Prevention estimates there are 820,000 new gonorrhea infections each year

Approximately 75% of all reported cases of gonorrhea are found in people who are 15 to 29 years of age

Gonococci attach to the host mucosal cell and, within 24-48 hours, penetrate through and between cells into the subepithelial space

Oral Gonorrhea

Usually oral gonorrhea presents with very few symptoms—pharyngitis in the majority of cases is asymptomatic but sometimes patients feel an unpleasant sensation in the throat and complain of profuse salivation; there may also be difficulty swallowing

While gonorrhea has traditionally been curable with antibiotics, resistance to treatment is on the rise—over the last 30 years, strains of gonorrhea have become less susceptible to certain treatments

Neisseria gonorrhoeae has developed resistance to almost every class of antibiotics used for gonorrhea treatment: sulfonilamides, penicillin, tetracycline, and fluoroquinolones (such as ciprofloxacin)

There are concerns that the disease is becoming untreatable

Headliners: Drug-Resistant Gonorrhea on the Rise, CDC claims; As reported by Ryan Jaslow; CBS News; 2/14/13; accessed on 4/8/13 at: http://www.cbsnews.com/8301-204_162-57569445/drug-resistant-gonorrhea-on-the-rise-cdc-claims/

According to research published 2/14/13 in the Morbidity and Mortality Weekly report, the CDC suggested the number of treatment-resistant infections to gonorrhea were still on the rise

'The development and spread of cephalosporin resistance in N. gonorrhoeae, particularly ceftriaxone resistance, would greatly complicate treatment of gonorrhea.'

CDC researchers (who added the previously recommended treatments cannot be routinely prescribed either)

Headliners: 'Super Gonorrhea' May Go Global, Become Untreatable; As reported by Elizabeth Armstrong Moore; News Staff; posted 4/19/2016; accessed 4/19/2016 at: http://www.newser.com/story/223779/super-gonorrhea-may-go-global-become-untreatable.html

In 2015, so-called 'super gonorrhea' emerged in the UK—and with continued spread, doctors are worried that the often azithromycin-resistant microbe may quickly become resistant to ceftriaxone as well--British Broadcasting Company

'The spread of high level azithromycin-resistant gonorrhea is a huge concern and it is essential that every effort is made to contain further spread.'--Dr. Elizabeth Carlin; president; British Association for Sexual Health and HIV

Headliners: This STD is Becoming 'Smarter' and Harder to Treat; As reported by Nicole Chavez for CNN; 7/8/2017; accessed 7/7/2017 at: http://www.cnn.com/2017/07/07/health/resistant-gonorrhea-antibiotics/

According to the WHO, gonorrhea is becoming harder—and, in some cases, impossible—to treat with antibiotics

'The bacteria that cause gonorrhea are particularly smart. Every time we use a new class of antibiotics to treat the infection, the bacteria evolve to resist them.'--Source: Teodora Wi; a human reproduction specialist; WHO

'It's important to understand that ever since antibiotics appeared on the scene, Neisseria gonorrhoeae has been fairly quick in developing resistance to all the classes of antibiotics that have been thrown at it.'--Source: Manica Balasegaram; director; Global Antibiotic Research and Development Partnership

From 2009-2014 the WHO says that several countries discovered a widespread resistance to drugs used to treat gonorrhea like ciprofloxacin, azithromycin and even last resort treatments such as extended-spectrum cephalosporins (ESCs)

According to the CDC, gonorrhea has developed resistance to nearly every class of antibiotics used to treat it such as penicillin, tetracycline and fluoroquinolones

In 2016, the WHO began advising doctors to switch to a two-drug combination: ceftriaxone and azithromycin after more than 50 countries reported that ESCs were no longer effective in some cases

In a 2017 report, data from 77 countries collected by WHO showed there is a widespread resistance to older, cheaper antibiotics and in some countries, the infection has become 'untreatable by all known antibiotics'

'In 2017, gonorrhea was named among 11 types of bacteria that health experts believe pose the greatest threats to human health because they are in urgent need of new antibiotics.'--Source: Marc Sprenger, WHO's director of antimicrobial resistance

Headliners: Scientists Develop New Antibiotic for Gonorrhea; Source: University of York's Departments of Biology and Chemistry; appearing in ScienceDaily; posted 1/4/2017; accessed on 1/6/2017 at: https://www.sciencedaily.com/releases/2017/01/170104103527.htm

Scientists at the University of York have harnessed the therapeutic effects of carbon monoxide-releasing molecules to develop a new antibiotic which could be used to treat the sexually transmitted infection gonorrhea

'The carbon monoxide molecule targets the engine room, stopping the bacteria from respiring. Gonorrhoea only has one enzyme that needs inhibiting and then it can't respire oxygen and it dies. People will be well aware that CO is a toxic molecule but that is at high concentrations. Here we are using very low concentrations which we know the bacteria are sensitive to. We are looking at a molecule that can be released in a safe and controlled way to where it is needed.'--Ian Fairlamb; professor; University of York; Department of Chemistry

Headliners: Listerine Mouthwash Inhibits Oral Gonorrhea Bacteria; Eric P. F. Chow, PhD et al; Melbourne Sexual Health Centre (Australia); study results published online 12/20/2016; Sexually Transmitted Infections; as reported by Laird Harrison for MedScape Medical News; posted 12/20/2016; accessed 1/10/2017 at: http://www.medscape.com/viewarticle/873506

In a randomized trial, 52% of the pharyngeal surfaces of men who rinsed and gargled with the Listerine (Johnson & Johnson Consumer, Inc.) mouthwash for one minute tested positive for Neisseria gonorrhoeae compared with 84% of the pharyngeal surfaces of men who rinsed and gargled with a saline solution

'With daily use, it may increase gonococcal clearance and have important implications for prevention strategies.'--Source: Eric P. F. Chow, PhD; lead researcher

The researchers acknowledge that the follow-up time in the study was short and caution that the effects of the mouthwash might be short-lived—they also stated that it is not clear if the oral mouthwash can reduce gonorrhea infections of the anus, vagina and urethra

Spirochetes

Although spirochetes are not a large group—there are only six genera—they have had tremendous impact on our lives

Both syphilis and Lyme disease are caused by these bacteria

Spirochetes are distinguished by their spiral shapes and their ability to corkscrew their way through gel-like tissues, causing a number of different diseases

Syphilis is caused by the spirochete Treponema pallidum and is spread primarily through sexual contact

According to the CDC, the rate of new cases of syphilis had plummeted in the 1990's and in the year 2000 it reached an all-time low since reporting began in 1941—however, new cases of syphilis doubled between 2005 and 2013 from 8,724 to 16,663

Untreated primary syphilis progresses to secondary syphilis six to eight weeks after the primary infection

Currently, syphilis can be cured in its early stages—a single intramuscular injection of long-acting Benzathine penicillin G (2.4 million units administered intramuscularly) is the regimen of choice (three doses at weekly intervals is recommended for individuals with latent syphilis)

While not as immediately threatening as antibiotic-resistant gonorrhea, syphilis has been quietly evolving resistance to some of the antibiotics that are used in place of penicillin

Notably, a class of antibiotics called macrolides (including erythromycin and azithromycin), are less effective against Treponema pallidum

Even though macrolides are not a top treatment choice for treating syphilis, there are many reasons health care providers choose them over penicillins—especially in cases of penicillin allergy

Headliners: Can oral infection be a risk factor for Alzheimer's disease?; Source: Olsen I and Singhrao SK; results published in Journal of Oral Microbiology; 9/2015; accessed on 4 Apr 2016 at: http://www.journaloforalmicrobiology.net/index.php/jom/article/view/29143

According to investigators, systemic inflammation may predict the onset of dementia—organisms such as **spirochetes*****, P. gingivalis, Herpes simplex type I virus, and Candida are among the prime candidate pathogens in Alzheimer's diseased brains

According to the researchers:

- 'The most convincing evidence for a causal relationship between oral bacteria and AD is noted for spirochetes which are both neurotropic and motile.'

Treponema Denticola

- Causative organism for necrotizing ulcerative oral diseases

The frequency of spirochetes is significantly higher in the brains of Alzheimer's disease patients compared to controls

The researchers stressed that '…it is important to recognize that infection can occur decades before the manifestation of dementia'

'If anaerobes of periodontitis play a major role in AD, dental hygiene and treatment will provide the AD prophylaxis from an early age as periodontitis is modifiable. However, improving oral hygiene and treating periodontal disease in the AD patient can be challenging since patients are often uncooperative. There is also need for training caregivers to assist with oral care in such patients.'--Researchers conclusion

VIRUSES

Unique characteristics:

- Energy-less
- Must have HOST CELL
- Composed of protein core (CAPSID) surrounding genetic material
- Outer lipid bilayer (ENVELOPE) or "naked"
- Complete virus is called virion
- "Small" (0.02-0.3 microns)
- Various host ranges
- Specificity is determined by viral attachment capabilities
- Helical or icosahedral in shape

Host cell outcomes:

- Death
- Transformation
- Latent infection
- Chronic slow infections

Human Papilloma Virus ('HPV')

The human papilloma virus (HPV) is one of the most common virus groups in the world to affect the skin and mucosal areas of the body

An estimated 14 million new HPV infections occur every year in the United States alone—with approximately half of these infections occurring among men and women ages 15 to 24

There are over 100 types—some types can cause verrucae (warts) and a few strains have been shown to increase the risk of certain cancers (cervix, penis, vagina, anus and oropharyngeal area***)

The Centers for Disease Control estimates that more than 10,000 new cases of HPV-associated oropharyngeal cancers are diagnosed in the United States each year

Researchers from UB and Roswell Park Cancer Institute published the first study showing an association between long-standing periodontitis and risk of tongue cancer in 2007—the UB researchers also demonstrated that periodontitis and HPV-infection appear to work in tandem to boost the chances of developing tongue cancer

'Evidence of periodontitis-HPV synergy has important practical implications because there is a safe treatment for periodontitis, but no treatment for HPV infection. If these results are confirmed by other studies, this has a tremendous relevance in predicting and intervening in the initiation and prognosis of HPV-related diseases, including head and neck cancers.'--Mine Tezal, D.D.S., Ph.D., assistant professor in the Department of Oral Diagnostic Sciences, UB dental school, and research scientist at Roswell Park Cancer Institute

Oral Cancer

- More than 34,000 Americans will be diagnosed with oral or pharyngeal cancer this year—it will cause over 8,000 deaths, killing roughly 1 person per hour, 24 hours per day
- Of those 34,000 newly diagnosed individuals, only half will be alive in 5 years—this is a number which has not significantly improved in decades
- The death rate for oral cancer is higher than that of cancers which we hear about routinely such as cervical cancer, Hodgkin's lymphoma, laryngeal cancer, cancer of the testes, endocrine system cancers such as thyroid, or skin cancer (malignant melanoma)
- The death rate associated with oral cancer is particularly high not because it is hard to discover or diagnose, but due to the cancer being routinely discovered late in its development

In order to discover pathology, you must first look for it

Manual palpation in combination with intraoral camera use is the ticket!

Often it is only discovered when the cancer has metastasized to another location—most likely the lymph nodes of the neck

Oral cancer is particularly dangerous because in its early stages it may not be noticed by the patient, as it can frequently prosper without producing pain or symptoms they might readily recognize

There are several types of oral cancers, but around 90% are squamous cell carcinomas

It has now been confirmed that younger age groups, including those who have never used tobacco products, have oral cancer which is HPV viral based

Headliners: HPV, Not Tobacco, is Major Cause of Oral Cancers; American Council on Science and Health; posted 4/6/2016; accessed 4/19/2016 at: http://acsh.org/news/2016/04/06/hpv-not-smoking-is-major-cause-for-oral-cancers/

While tobacco use and alcohol consumption continue to be recognized as major risk factors for head, neck and throat cancers, researchers are now identifying the primary cause head and neck malignancy is the human papillomavirus (HPV)

High-risk HPV strains cause cancer by using special proteins to disrupt healthy cells—it makes cells unable to repair themselves and unable to control how they are duplicated

The majority of oral cancers are cancers of epithelial cells, primarily squamous cell carcinomas—not unlike the cancers that affect the cervix

The human papilloma virus, particularly version 16, has been shown to be sexually transmitted between partners—and is conclusively implicated in the increasing incidence of young non-smoking oral cancer patients
The virus is transmitted by direct contact—HPV is transmitted only in the location it attaches to and never travels through the bloodstream—how it is infecting the mouth reflects a disturbing trend
'There is absolutely a link between oral sex and oral cancer.'--Dr. Ellen Rome, Cleveland Clinic
From a gender perspective, for decades this has been a cancer which affected 6 men for every woman—that ratio has now become 2 men to each woman

In the words of Michael Douglas:

"I knew something was wrong. My tooth was really sore, and I thought I had an infection. I had two rounds of appointments with ear-nose-throat doctors and periodontists. They each gave me antibiotics. And then more antibiotics, but I still had pain. I went to Spain with the family for the summer, and when I got back, a friend suggested I go to his doctor in Montreal. That doctor told me to open my mouth, took a tongue depressor, and then he looked at me. I will always remember the look on his face. He said, 'We need a biopsy.' There was a walnut-size tumor at the base of my tongue that no other doctor had seen. Two days later, after the biopsy, the doctor called and said I had to come in. He told me it was stage-four cancer."

One more HPV Tidbit:

According to recent studies, HPV infection can also raise cardiovascular disease risk

THANK YOU!