

How Epidemiology Got Under My Skin and Now I Work on the Worst Disease You've Never Heard Of

2008 BYU Honored Alumni Lecture
College of Physical and Mathematical Sciences
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Centers for Disease Control and Prevention

I am grateful to represent this year the many alumni from the College of Physical and Mathematical Sciences whose great achievements make us all proud to be BYU alumni. I have worked in the Herpes virus Branch at the CDC for over 10 years. You might think there is no greater conversation stopper than telling a new acquaintance that you work on herpes (actually, we say that we don't have herpes but we're working on it). But, my mathematics degree prepared me well for social rejection. I was used to being treated like a leper when someone would ask what I studied, and I would respond "Math". Today, you'll hear some about both subjects—math and herpes—and later you'll be able to watch your friends and family scatter when you try to tell them about today's lecture. I'll also tell you about the field of epidemiology. One goal of my lecture is that by the end you will be able to explain that epidemiology is not the study of skin. But my main goal is to explain what I do and how my degree from the College of Physical and Mathematical Sciences helped prepare me for my job. Now, I'm not worried about speaking for too long and going over my time limit. When I took combinatorics from Dr. Wayne Barrett, he had to go out of town and miss the lecture. He told us that he would need to give a makeup lecture because math classes had a fixed amount of content that needed to be covered. He told us that social sciences, on the other hand, could afford to eliminate any number of lectures, because their content could be compressed into even the smallest amount of time. So, insomuch as epidemiology has aspects of social science, if I'm running short on time I can simply skip slides and you won't miss any content.

Let me begin by giving you a pop quiz. Among the following conditions, which is the most frequent cause of death or permanent disability in the United States? Congenital, meaning present at birth:

- *Down syndrome
- *Sudden infant death syndrome
- *Fetal alcohol syndrome
- *Spina bifida
- *Anencephaly
- *Congenital cytomegalovirus (CMV)
- *Congenital toxoplasmosis

Now, hold onto your answer while I tell you the story of how this condition was discovered. In 1881, Ribbert observed large cells in the kidneys of a stillborn child, and later described them as protozoan-like cells. Unlike these pre-historic scientists, it was not obvious to Ribbert what caused the intranuclear inclusions nor did he know whether those cells were linked to any sort of disease. In 1925, two scientists noticed a similarity between these unusual cells and two herpes viruses that caused shingles and genital herpes.

Now we'll take a brief intermission to talk about herpes viruses. Despite the common misconception that herpes viruses refer exclusively to sexually transmitted infections, they are spread in many ways, and cause well-known diseases such as oral cold sores (usually HSV-1), chicken pox (VZV), mono (EBV and CMV), and roseola (HHV-6), whose fever and rash occur in most infants by the time they are one year-old. The link to herpes viruses suggested that the funny-looking cells might be caused by an infection that had the same properties as herpes viruses. Namely, that initial infection, termed "primary infection", is followed by a latent period where the virus does not replicate, but lies dormant inside the body. The virus can reactivate at some subsequent time, for reasons that remain obscure. This can be seen with cold sores, which reappear at unexpected, but aggravating, intervals, and with shingles, also known as herpes zoster, which is a reactivation of varicella-zoster virus, the virus that causes chicken pox. With many of the herpes viruses, it is also possible to be re-infected with a different strain of the same virus.

Now, back to our story. In 1932, Wyatt observed that these unusual intranuclear inclusions, the dot to the left of the arrow, were frequently associated with a rare, lethal congenital infection that was characterized by a splotchy, purple rash, jaundice, and swollen liver and spleen. He proposed the name "generalized cytomegalic inclusion disease" for this condition, and provided the most compelling evidence to date that the infection might be responsible for the lethal disease. Scientists in different laboratories were working feverishly to identify the virus that was responsible for these enlarged cells with intranuclear inclusions. Labs led by Smith, Rowe, and Weller, each independently isolated the virus. In a remarkable instance of scientific rigor taking precedent over

the pursuit of individual honors, the three labs exchanged their viruses in advance of publication in order to confirm one another's findings. Weller proposed the name "Cytomegalovirus", meaning, large cell virus.

However, identifying the virus was only the beginning. Many microorganisms have been found that don't necessarily have links to disease. They could cause as-of-yet unidentified diseases, or they could just be mere passengers. There were many unresolved questions, most important of which, was whether CMV actually caused the damage observed in the newborns. If CMV was responsible, other questions became relevant. How many people are infected? How frequent is congenital infection? Is congenital infection the only concern? What are the disease outcomes? How is CMV transmitted? Does it matter when a pregnant woman gets CMV? Is the fetus protected if a woman got CMV infection prior to pregnancy?

By 1971, Weller was able to gather considerable evidence that CMV played a causal role in cytomegalic inclusion disease, the oft-times lethal disease affecting newborns. His main findings were that congenital CMV infection was the primary concern, rather than CMV infection in children or adults, that congenital CMV had diverse and serious symptoms, and that congenital CMV disease was more frequent than congenital rubella syndrome during epidemic years. Still, important questions remained.

Weller helped answer the basic questions, but his student, Charlie Alford, was the driving force behind answering key questions during the next 25 years. Alford was a pediatrician/virologist at the University of Alabama-Birmingham Medical School. In Birmingham, steel was still king, but the city was also becoming known for its strong biomedical research community. Out of the group Alford assembled, came a preponderance of the most important results of the next quarter century, contained in more than 100 scientific articles on congenital CMV. As I go on to tell you about what CMV does, much of the knowledge began with key findings out of UAB.

Returning to one of our important CMV questions, how many people are infected with CMV? Early findings from UAB have recently been confirmed with nation-wide data: CMV infection affects more than half of the general population, but prevalence is highest among minority populations.

Congenital infection, that is, CMV infection that is present at birth, occurs in approximately 1 in 150 newborns. CMV is the most common viral congenital infection, and will go on to disable 1 in 750 live-born children.

Remember this quiz? Which of these conditions is the most frequent cause of death or disability in the U.S.? Well, you guessed it. The answer is congenital CMV. It turns out that disability caused by congenital CMV is more prevalent than fetal alcohol syndrome, Down syndrome, neural tube defects, or pediatric AIDS. In a recent paper we stated that, "Perhaps no single cause of birth defects and developmental disabilities in the United States currently provides greater opportunity for improved outcomes in more children than congenital CMV." This is what I work on. Congenital CMV is one of the great, unrecognized health problems in our country. It is perhaps the worst disease you've never heard of.

To give you an idea of the numbers, each year in the U.S., nearly 30,000 children are born infected with CMV, more than 100 die, and more than 5,000 develop permanent disabilities. Congenital CMV is also thought to be responsible for spontaneous abortions and stillbirths, but the actual numbers are unknown.

Congenital CMV can cause transient symptoms, but is of most concern because of its permanent symptoms, which can include hearing loss, vision loss, and mental retardation. These disabilities can be present at birth but they can also develop later during childhood, and they often worsen over time. Children affected by congenital CMV can experience one or more symptoms, and symptoms can vary in severity.

UAB researchers and others have found that CMV is transmitted through close contact with infected bodily secretions. The most common transmission routes are child-to-adult through close contact, person-to-person via kissing or sexual contact, and mother-to-child via breast milk. It turns out, though, that young children are the most likely to be shedding CMV in their bodily fluids. They are sometimes known as the CMV super-spreaders. Thus, transmission from young children is of particular concern to pregnant women. The expectant mother may then infect her fetus with CMV.

With rubella, infection during the first trimester is of the most concern. With CMV, however, fetal infection can occur no matter what trimester maternal infection occurs. But, the most severe disabilities tend to be associated with first-trimester infection.

Is your baby protected if you had CMV before? In other words, is there such thing as prior immunity? For most infectious diseases, we know this is the case. However, those of you who have caught a cold more than once know that prior infection, even with the same species of virus, does not necessarily convey complete protection against future attacks. Unfortunately, this

is the case with CMV. The UAB group has estimated that prior CMV infection is 70% protective, but incomplete protection has discouraged vaccine manufacturers, who worry about the feasibility of a CMV vaccine.

Now that you have an idea of what happens with congenital CMV, you might wonder, "What can be done about congenital CMV?" Unfortunately, the news isn't so good. When we visited UAB recently, Bill Britt told us that one of the greatest disappointments he's had is that despite discovering much about congenital CMV, what is offered to expecting mothers is much the same as it was 30 years ago.

The ideal solution to the congenital CMV problem would be a safe, effective vaccine. In the early 1970s, Stanley Plotkin, the developer of the rubella and rotavirus vaccines, tried his hand at CMV. His vaccine proved ineffective, and subsequent efforts have not borne fruit. Unfortunately, technical challenges and lack of interest on the part of vaccine manufacturers has meant that, after over 30 years of trying, there is no promising CMV vaccine candidate on the near horizon.

What about medical treatments? Some have proposed and tested antiviral medications on infected newborns. The drug ganciclovir achieved modest success in reducing the progression of CMV-related hearing loss in severely affected infants. However, ganciclovir has high toxicity and so is only recommended for severely affected infants. Different treatments have been proposed for pregnant women, the most promising of which is CMV-specific hyper immune globulin—essentially, plasma transfused from donors with high levels of CMV antibodies. Whether this very expensive treatment is effective remains very controversial. To sum up, medical interventions are limited and their effectiveness controversial. So why does progress in disease prevention seem to be so slow?

One important reason for the lack of progress is a lack of awareness about congenital CMV among the general public, healthcare providers, and policy makers. In a survey of women of childbearing age, of all these conditions, awareness was lowest about congenital CMV. By a show of hands, how many of you had heard of congenital CMV before this lecture? This is the problem as we see it. At CDC we are trying to change this.

There are logical reasons for the lack of awareness. Most mothers do not know when they are infected because CMV often causes no symptoms in adults, or if symptoms are present, they are non-specific, usually a mild, flu-like illness. Many infected babies are asymptomatic at birth, so parents have no idea that problems may develop. When babies have symptoms, they are often non-specific as well, such as jaundice, small head size, or small-for-gestational age. Finally, congenital CMV usually cannot be diagnosed retrospectively. Unless a specimen such as blood, saliva, or urine, is collected within the first 2-3 weeks of life, there is no way of knowing whether a CMV-positive test was the result of congenital CMV. Post-natal transmission could have occurred, and in that case, the child is not at risk for CMV-related disabilities.

To deal with the problem of congenital CMV in the absence of effective medical interventions, we have advocated for prevention through basic public health measures. CMV is not transmitted by casual contact and is not easily transmissible. The message for women is to reduce exposure to urine and saliva while pregnant, especially through careful hand washing after contact with young children.

One thing we have done is to prepare brochures, web information, and podcasts. Let's listen to one of them (click on speaker). If you have family or friends who are pregnant or planning a pregnancy, I would encourage them to visit the CDC website for more information. The goal is to raise awareness about prevention and in so doing, increase the impetus for the development of medical interventions, especially vaccines.

So that is what I do. What I'd like to explain, is some of the influences that got me into epidemiology, and how my degree from the College of Physical and Mathematical Sciences prepared me for what I do. Humorist Patrick McManus told of how he fell out of a bus when he was a 5 year-old, hitting his head multiple times. His friend started laughing hysterically. McManus protested, "That's not funny." "No," his friend said, "but it explains so much." When I was 5, I slipped on an icy Logan road and got my lip caught in the door of our station wagon. You may think its funny, and maybe it explains a lot. My mom thinks it explains why I was always mouthing off.

Most kids do not say, "When I grow up I want to be an epidemiologist." I was no exception. I wanted to be a football player. With deepest apologies to all you Cougars, I was an Aggie fan, since we spent my kindergarten year in Logan. I wore this shirt every day until it wore out. Then we moved back to Wisconsin and I wanted to be a baseball player, the next Robin Yount for the Milwaukee Brewers.

Needless to say, professional sports didn't pan out for me and I decided to make my way to college. By the time I graduated I had toured much of the College of Physical and Mathematical Sciences. Before my senior year in high school I took Dr. Burton's Introduction to Computer Programming, and loved the problem solving. After my mission I took a statistics class from Dr. Fellingham. He urged us to pay the price to get our degrees, to focus, to make that commitment and get it done. That philosophy helped me, especially during graduate school. But my favorite classes at BYU were math and physics. It was hard to decide which to major in, but as I pondered relativity theory in 4th-semester physics, with joggers running at the 3/4th the speed of light away from trains traveling at 9/10th the speed of light, I decided, at almost the speed of light, that maybe I'd better major in math. My dad *has* said-the only people who want to go into math are the children of mathematicians. And when I managed a "B" in Don Robinson's challenging abstract algebra class, I briefly had visions of Fields' medals dancing in my head. But, deep down I realized that theoretical mathematics wasn't the right fit for me. After majoring in math, I wasn't sure what to do next. I felt like the ugly duckling.

I was 24 and wondering, "What am I going to be when I grow up?" David Wright suggested that there were other options for math undergrads besides becoming a math professor. So, my grad school applications went all over the place, to just about any program that used math.

Fortunately, I ended up at the University of Washington, where I met my favorite professor of all time. His name was Garry Odell. He had a long ponytail, often slept in his office on a cot (to make it easier to work), had a permanent twinkle in his eye, full of uncontainable and ever-present enthusiasm, the smartest professor in a group that included a member of the National Academy of Sciences and a McArthur fellow. A biography on the internet got it right when it said, "Anyone who meets Garry is struck by his easy smile, palpable enthusiasm, and overt brilliance." Garry said, "What I do scientifically to try to connect math/computer models ever more tightly to experimentally discovered and characterized molecular details has always been so much fun that I would do it with all my energy even if I had to pay, rather than be paid, to do it."

In Garry's mathematical biology class we used differential equations to model biological processes. For my class project I decided to use partial differential equations to model the geographic spread of infectious diseases. (Click on the red dot). I loved it!

One day I was talking on the phone with my older sister Adria about my class project of modeling the geographic spread of infectious diseases. She told me she had just read a fascinating book called *The Coming Plague*. This Pulitzer Prize-winning book introduced me to the term epidemiologist. I wasn't completely sure what an epidemiologist was but I thought that I might want to become one.

So, I signed up for Epidemiology 101 at the University of Washington. There I had the privilege of learning from two of the best teachers of epidemiologic methods in the world. Noel Weiss taught us about making judgments about causation based on information on associations. As a cautionary tale, he told how miners in California during the gold rush would bury themselves up to their necks in dirt to ward off scurvy. They mistakenly concluded that since being on a ship in the ocean, with all that water, puts you at risk for scurvy, then having lots of earth around you would protect you. Tom Koepsell inspired us about how epidemiology can make a difference, as he told the detective story of how epidemiologists discovered that providing too much oxygen to preemies was causing retrolental fibroplasias, a form of blindness. This class got me excited about epidemiology, and I decided to go to Emory for my Ph.D. in epidemiology, because of its close proximity to the CDC.

As a Ph.D. student in epidemiology at Emory University, I began working on my dissertation with CDC virologist Phil Pellett. We worked on the epidemiology of human herpesvirus-8, and how HHV-8 affected people living with HIV. Phil was a wonderful mentor. He was a purveyor of fine puns who thoughtfully picked out Christmas presents for everyone in his lab. One year I received a north Georgia hiking book, another year a high quality tape measure to help with some remodeling we were doing. Phil introduced me to CDC movers and shakers (center and division directors), found financial support for me, directed peer review manuscripts to me, let me give talks in his place, and invited me to write reviews with him, in short, he made sure I had the experiences I needed. Despite being the son of a Methodist minister, he came to the Mormon Church with me. He was the kind of mentor and person I aspire to be.

Finally I received my diploma and was a full-fledged epidemiologist. But what, exactly, is an epidemiologist, and what do they do? Epidemiologists study factors affecting the health and illness of human populations. To study these factors, epidemiologists draw from the fields of statistics, mathematics, biology, and behavioral science. Epidemiologic methods have demonstrated the link between smoking and lung cancer, the role of folic acid in the prevention of birth defects, and the role of viruses in causing

cancer, including the link between human papilloma virus and cervical cancer. We epidemiologists like to think we're doing important work.

However, some critics cite the limitations of epidemiology, especially in efforts to link diet to chronic diseases such as colon cancer or heart disease...as you can see from this cartoon advertising Today's Random Medical News from the New England Journal of Panic-inducing Gobbledygook.

These are some of the epidemiology problems that I have worked on. Is human herpes virus 8 (HHV-8) transmitted through blood transfusions? Should the blood supply be screened for HHV-8? Why do some people with HHV-8 infection get Kaposi's sarcoma, a soft-tissue cancer, while others don't? What groups of women are at highest risk for CMV infection, and how frequently does it occur? By what route is CMV most commonly transmitted? Why do some mothers transmit the infection to their fetuses while others don't? What proportion of childhood hearing loss is due to CMV? What are effective ways to communicate to women of reproductive age about congenital CMV prevention?

Currently, I am working on something that is not very epidemiologic, but is exciting nonetheless. Next month the CDC is hosting the 2nd International Congenital CMV Conference.

In my current job as an epidemiologist, I don't do as much mathematics as I thought I might when I was majoring in math. And, surprisingly to me, some of the most important lessons I learned while studying math were not math lessons per se. For example, doing proofs in Lawrence Fearnley's real analysis class taught me rigor and logic in writing that I use regularly as I write scientific articles. Don Robinson's high expectations got me in the habit of asking myself whether I had thought about an issue hard enough to where I could really know what was going on. And finally, long before Donald Rumsfeld spoke about "known unknowns" and "unknown unknowns", my dad regularly pointed out the importance of making sure you knew which things you knew, and which things you didn't know. This has helped me as I read and evaluate the claims of epidemiologic studies.

I have arrived at a point where I love my work and feel that it is a useful contribution. But the more I do, the more I realize that my part, while potentially important, is still small, and that is OK. While growing up I dreamed of doing great things, but I've slowly come to see what my friend LeGrand Baker told me while we were reading the Book of Mormon together. "Mostly we have a big effect on a small number of people." For most of us, that is how the Book of Mormon scripture is fulfilled, "Thus God has provided a means that man, through faith, might work mighty miracles; therefore he becometh a great benefit to his fellow beings."

As I look back on those who have influenced my life, I realize that they came from all over and were very different one from another. Some spent years helping me, but most did small things that made important differences. Their influences cause me to believe in the importance of the small, ordinary interactions of everyday life. I believe that we need each other; we need each other to care, even just a little. We need to believe that small things are meaningful to others, and we need to do the small things. Some people will do things that are recognized by many as great. Most of us will do small things persistently that are great for a small number of people near to us. And I guess I would say that it was because of those good people, doing small things persistently, that I got epidemiology under my skin and ended up trying to prevent the worst disease you've never heard of.

Thank you.