The Vitamin D Newsletter Nov 2005

Pascal's Wager and Pandemic Influenza

As we wait for this year's influenza epidemic to begin, keep in mind we are also waiting for the "big one"—the pandemic (*pan:* all, *demic:* people). A severe influenza A pandemic will kill many more Americans than died in the fall of the World Trade Center, the Iraq war, the Tsunami, and during Hurricane Katrina combined. Perhaps a million or two in the United States alone. Such a disaster would tear the fabric of our society. Our entire country would resemble New Orleans after Katrina.

It's only a question of when, not if, it will come. Pandemics come every 25 years or so, severe ones every hundred years or so. The last pandemic occurred in 1968. It was the Hong Kong flu and it killed 34,000 Americans. Prior to that, in 1918, the Spanish flu killed more than 500,000 Americans along with several million others around the globe. So many, in fact, that they couldn't bury the bodies. Stanford University. **The Influenza Pandemic of 1918.**

Young healthy adults that had been in the prime of their lives in the morning were drowning in their own inflammation by noon, grossly discolored by sunset, and dead by midnight. It was the body's overwhelming immune response to this influenza virus —macrophages releasing large amounts of inflammatory agents (called cytokines and chemokines) into the lung of the afflicted—that resulted in the millions of deaths. Kobasa D, Takada A, Shinya K, Hatta M, Halfmann P, Theriault S, Suzuki H, Nishimura H, Mitamura K, Sugaya N, Usui T, Murata T, Maeda Y, Watanabe S, Suresh M, Suzuki T, Suzuki Y, Feldmann H, Kawaoka Y. **Enhanced virulence of influenza A viruses with the haemagglutinin of the 1918 pandemic virus.** Nature. 2004 Oct 7;431(7009):703–7.

Keep in mind that the Germans recently discovered that vitamin D is intimately involved in reining in these macrophages, thereby holding their cytokine production back so they don't overshoot and kill their owner along with the invader. Helming L, Bose J, Ehrchen J, Schiebe S, Frahm T, Geffers R, Probst-Kepper M, Balling R, Lengeling A. **1alpha,25-Dihydroxy vitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation.** Blood. 2005 Dec 15;106(13):4351–8.

Antigenic Shift

Your annual flu shot won't help when the "big one" hits, because the virus will have gone through what they call an antigenic shift (abrupt change), making current vaccines ineffectual. A new vaccine that is specific to the new virus must be manufactured and this will take time. It would be prudent to obtain in advance some antiviral drugs from one's doctor. Because once the pandemic starts, whether it be this year or 10 years from now, the supply of antivirals will probably be insufficient and the lines will be long.

Conflicting Theories

You may find it surprising that influenza remains an enigma. Current theory holds that influenza infects in the same manner as the measles does: one person gets it then gives it to others who, in turn, give it to others in a chain of infectious events. This theory has some problems. For example, Dr. Carolyn Buxton Bridges of the CDC recently published a review paper on the transmission of influenza. She noted, "Our review found no human experimental studies published in the English language literature delineating person-to-person transmission of influenza." Bridges CB, Kuehnert MJ, Hall CB. **Transmission of influenza: implications for control in health care settings.** Clin Infect Dis. 2003 Oct 15;37(8):1094–101.

Most experts think that pandemic strains originate in birds or other animals. Doctors Ann Reid and Jeffery Taubenberger of the Armed Forces Institute of Pathology recently wrote, "it is important to recognize that the mechanisms by which pandemic strains originate have not been explained yet." Furthermore, there is a persistent theory that influenza lies dormant, not in birds or in swine, but in humans, where it mutates into a killer strain. Reid AH, Taubenberger JK. **The origin of the 1918 pandemic influenza virus: a continuing enigma.** J Gen Virol. 2003 Sep;84(Pt 9):2285–92. Hilleman MR. **Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control.** Vaccine. 2002 Aug 19;20(25–26):3068–87.

So, get this year's flu shot and stock up on some antivirals. In the meantime, let's see if we can uncover some ignored facts that might improve one's family's chances when the next pandemic arrives.

Influenza's Seasonal Nature and Dr. R. Edward Hope-Simpson

Last month we saw that aggressive treatment of vitamin D deficiency prevented children from getting infections. Although Dr. Rehman didn't differentiate between viral and bacterial infections, most of the illnesses vitamin D prevented were probably viral. Rehman PK. **Sub-clinical rickets and recurrent infection.** J Trop Pediatr. 1994 Feb;40(1):58.

When looking for ignored facts one should always start with epidemiology, the detective branch of medicine. Epidemiologists look for clues which will lead to theories. These theories can then be tested and, if true, could result in saving lives. One of the world's pioneering epidemiologists, R. Edward Hope-Simpson, used a meticulous, solitary approach to his work. It was he who discovered that the chickenpox virus was reactivated in adults, causing shingles. Dr. Hope-Simpson became famous. Hope-Simpson RE. **The Nature of Herpes Zoster: A Long-term Study and a New Hypothesis.** Proc R Soc Med. 1965 Jan;58:9–20.

In 1979, he turned his attention to influenza A. He studied two remote populations, one in Wales and the other in England. He found that most affected households had only one case of influenza. Furthermore, no serial time intervals could be identified in cumulative household outbreaks—that is, different families did not get sick one after another, but

around the same time. He discovered other facts that also did not fit with the theory that influenza A is primarily spread by person-to-person transmission. Hope-Simpson RE. **Epidemic mechanisms of type A influenza.** J Hyg (Lond). 1979 Aug;83(1):11–26.

The rest of his life was spent trying to make known a basic fact of influenza: it is distinctly seasonal. All theories about its transmission must take into account its seasonality. Hope-Simpson reminded us what Davenport said, "Epidemiological hypotheses must provide satisfactory explanations for all the known findings, not just for a convenient subset of them."

Epidemics' Timing Determined by Latitude

Going back to 1945, Hope-Simpson discovered that influenza epidemics above 30 degrees latitude in both hemispheres occurred during the six months of least solar radiation and that outbreaks in the tropics almost always occured during the rainy season. He thus concluded, "Latitude alone broadly determines the timing of the epidemics in the annual cycle, a relationship that suggests a rather direct effect of some component of solar radiation acting positively or negatively upon the virus, the human host, or their interaction." That is, something may be regularly reducing our immunity every fall and winter. Hope-Simpson RE. **The role of season in the epidemiology of influenza.** J Hyg (Lond). 1981 Feb;86(1):35–47.

In 2003 researchers confirmed that influenza epidemics in the tropics occur, with few exceptions, during the rainy season, when vitamin D levels should be falling. Shek LP, Lee BW. **Epidemiology and seasonality of respiratory tract virus infections in the tropics.** Paediatr Respir Rev. 2003 Jun;4(2):105–11.

In his 1981 paper, Hope-Simpson wondered how the same virus could cause influenza outbreaks at exactly the same time (middle of winter) over a six-year period (1969–1974) in two widely separated areas (Prague, Czechoslovakia and Cirencester, England). Surely, during the middle of the Cold War, infected people did not arrive at two locations hundreds of miles apart, in the middle of winter and for five years in a row to infect the well people! But there is something Prague and Cirencester have in common: they are both located at 50 degrees latitude.

In 1990 researchers confirmed a relative lack of country-to-country transmission, by looking at two countries with heavy tourist traffic between them. Heinz F, Tumova B, Scharfenoorth H. **Do influenza epidemics spread to neighbouring countries?** J Hyg Epidemiol Microbiol Immunol. 1990;34(3):283–8.

Decreasing Sunlight Activates Latent Virus

Hope-Simpson rejected the theory that each year's virus is only transmitted from actively infected persons to well persons, concluding instead that the facts were more consistent with transmission by symptomless carriers. Carriers who become contagious when the sun is either in the other hemisphere, or obscured by the rainy season. He theorized that the annual movement of the sun caused a "seasonal stimulus that reactivates latent virus in the innumerable carriers who are everywhere present, so creating the opportunity for

epidemics to occur in the wake of its passage." And thus the celebrated Dr. Hope-Simpson committed heresy.

Everyone knows influenza transmission is direct: the ill infect those who are well. The accepted theory of pandemics is that the virus first spreads in birds, perhaps jumps to a mammal (pigs in 1918), then jumps to humans already infected with a common influenza strain. There it combines and mutates (reassortment) to a hybrid virus in the index case. That person then spreads it to others who spread it to others, etc. "No," said Hope-Simpson, "the epidemiology just does not fit that theory." "Heresy," said the experts.

Hope-Simpson practiced medicine in the small village of Cirencester in southwest England. He went back and looked at 16 years of his medical records and found evidence of 20 influenza outbreaks spaced over those 16 years. In every outbreak, he found young children were the most frequently affected. Yet, not one of those outbreaks indicated the children as being the major disseminators of the virus. Furthermore, all ages seemed to get sick around the same time. He concluded, "Such age-patterns are not those caused by a highly infectious immunizing virus surviving by means of direct transmissions from the sick, whose prompt development of the disease continues endless chains of transmissions." Hope-Simpson RE. **Age and secular distributions of virus-proven influenza patients in successive epidemics 1961–1976 in Cirencester: epidemiological significance discussed.** J Hyg (Lond). 1984 Jun;92(3):303–36.

No one listened. Everyone knew, as they still do today: influenza only occurs when the sick infect the well. "I don't think so," said Hope-Simpson. In search of more evidence, he went to all the parishes in Gloucestershire, which are separated by many miles. He looked at burial records for the last 500 years and found evidence of repeated influenza epidemics. He concluded, "In each century, influenzal excess mortalities in Gloucestershire parishes coincided with the date of the relevant influenza epidemic as recorded from widely different parts of Britain." That is, long before modern rapid transit, everyone in Britain got the flu around the same time! How could it spread by one person infecting another when everyone all over Britain got sick at the same time—long before planes, trains, and automobiles? Hope-Simpson RE. **Recognition of historic influenza epidemics from parish burial records: a test of prediction from a new hypothesis of influenzal epidemiology.** J Hyg (Lond). 1983 Oct;91(2):293–308.

In fact, after studying influenza epidemics in schools, two scientists named Hoyle and Wickramasinghe also decided that direct spread by infected children could not explain what was happening. They theorized that influenza viral precursors were reaching earth on comets from outer space! Hoyle F, Wickramasinghe NC. **Influenza viruses and comets.** Nature. 1987 Jun 25–Jul 1;327(6124):664.

Content to stay on earth, Hope-Simpson published a detailed theory of influenza's infectivity in 1987, based on the facts he observed. Right or wrong, Hope-Simpson's paper is wonderful reading for anyone interested in influenza. Here is a great mind at work. He noted that any valid theory of influenza must explain a number of facts: Hope-Simpson RE, Golubev DB. **A new concept of the epidemic process of influenza A virus.** Epidemiol Infect. 1987 Aug;99(1):5–54.

- Vast explosions of disease, which may attack 15% or more of a large community

within six weeks, and then cease.
- Successive outbreaks of type A influenza in small, relatively remote communities often coincide closely, season after season, with those of the country as a whole and, although the virus changes, the identical strains of virus appear contemporaneously in the two situations.
- Cessation of epidemics despite abundant available non-immune subjects.
- Household outbreaks occur all at once, not one after another.
- Low secondary attack rates within households.
- Epidemic patterns of influenza have not changed in four centuries and do not appear to have altered with the increasing speed and complexity of human communications.

Solar Radiation As Stimulus

Hope Simpson proposed that symptomless carriers became infective in response to a seasonal stimulus and then infect others, causing simultaneous explosions of disease in widely different areas. Furthermore, he concluded that those who got sick were not particularly contagious. He proposed that the stimulus for infection "is dependent on variations in solar radiation, an extraterrestrial influence unaffected by the rapidity of human travel. The rapidity of influenza spread was as rapid in previous centuries as it is at present because it does not depend on case-to-case transfer." He added, "The primary agency mediating seasonal control remains unidentified." That is, if something is weakening our immune system every year, as regularly as the changing of the leaves and declining vitamin D levels, he didn't know what it was. Hope-Simpson's 1987 paper was his last and, in 1992, he compiled all his work on influenza into a book entitled *The Transmission of Epidemic Influenza (The Language of Science)*. He died in 2003, at the age of 95.

I wish Hope-Simpson could have lived a while longer, enabling him to read the work of Dr. Colleen Hayes and her colleagues from the University of Wisconsin-Madison. She is one of the brightest vitamin D researchers out there. In 2003, she reviewed the profound effect vitamin D has on the immune system, including the role vitamin D plays in fighting infections. Hayes CE, Nashold FE, Spach KM, Pedersen LB. **The immunological functions of the vitamin D endocrine system.** Cell Mol Biol (Noisy-le-grand). 2003 Mar;49(2):277–300.

Vitamin D As Possible Prevention

Yes, as regularly as the flu season, vitamin D levels plummet in the fall and winter, vitamin D has profound effects on the immune system, and vitamin D may be involved in influenza. But is there any direct evidence?

Two animal studies have shown vitamin D does indeed prevent the flu, yet a third study indicated it did not. Nothing after 1956. If you obtain and read the first citation referenced at the end of this paragraph, you will see that the very first animal paper indicating vitamin D protected rats from influenza was published in Japan during World War II, apparently part of Japan's biological weapons research. The Central Intelligence Agency (CIA) confiscated the paper after the war. Young GA Jr, Underahl NR, Carpenter LE. **Vitamin D intake and susceptibility of mice to experimental swine influenza**

virus infection. Proc Soc Exp Biol Med. 1949 Dec;72(3):695–7. Underahl NR, Young GA. **Effect of dietary intake of fat-soluble vitamins on intensity of experimental swine influenza virus infection in mice.** Virology. 1956 Jun;2(3):415–29.

Yet another study revealed that when you give flu shots to hemodialysis patients, those taking activated vitamin D develop significantly better immunity. Antonen JA, Hannula PM, Pyhala R, Saha HH, Ala-Houhala IO, Pasternack AI. **Adequate seroresponse to influenza vaccination in dialysis patients.** Nephron. 2000 Sep;86(1):56–61.

Will normal vitamin D levels protect your family against the flu? No one knows. It would be nice if we had a report from a big hospital that happened to experience a flu outbreak —with some of the patients having been on vitamin D and some not. Would the patients on vitamin D be less likely to get the flu?

In the meantime, it seems to me the smart thing to do is to take enough real vitamin D—which is vitamin D3 (cholecalciferol)—or get enough UVB light so as to achieve a 25-hydroxyvitamin D level of about 50 ng/mL. Of course, it is a good idea to maintain this level year-round, even if you don't fear the coming influenza pandemic. 50 ng/mL is the normal human level and protects the owner from a myriad of chronic diseases. Hollis BW. **Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D.** J Nutr. 2005 Feb;135(2):317–22. Peterlik M, Cross HS. **Vitamin D and calcium deficits predispose for multiple chronic diseases.** Eur J Clin Invest. 2005 May;35(5):290–304.

Also, don't depend on high levels in the summer being stored and used in the winter. Vieth believes that the intracellular kinetics of vitamin D metabolism is such that declining vitamin D blood levels may cause rapidly declining intracellular levels. That is, declining levels in the autumn may be as dangerous as low levels in the winter. Vieth R. **Enzyme kinetics hypothesis to explain the U-shaped risk curve for prostate cancer vs. 25-hydroxyvitamin D in nordic countries.** Int J Cancer. 2004 Sep 1;111(3):468; author reply 469.

How Much Vitamin D?

So how much vitamin D should one take? Professor Robert Heaney believes healthy blood levels may require up to 4,000 units a day for those with no sun exposure. Most people need to take more in the winter than the summer. Larger people and African Americans need more than little people and caucasians. Sunphobes need more than those who enjoy God's invention. Heaney RP. **The Vitamin D requirement in health and disease.** J Steroid Biochem Mol Biol. 2005 Oct;97(1–2):13–9.

Children over 50 pounds need up to 2,000 units a day. Those under 50 pounds, should receive about 1,000 units a day. The only way to know for certain how much one needs is to have a 25-hydroxyvitamin D blood test. The test should be conducted in the late winter, when vitamin D levels are lowest, as well as at the beginning of fall, when vitamin D levels are highest. This will indicate how much to take to keep stable levels. Or, adults can simply take 4,000 units a day, every day, excluding those days spent in the sun during late spring, summer, and early fall.

It might be a good idea to keep pharmacological doses (50,000 units) of vitamin D next to your antivirals and to take one of these 50,000 unit capsules at the first sign of the flu, although there is not yet one study to support such a practice. It might help tame those unchained macrophages, possibly saving one's life. Or, it might not help at all. One can purchase these 50,000 IU capsules from LifeSpan Nutrition. Single administrations of 10 times that amount have repeatedly been found to be safe and are routinely used in Europe as stoss therapy for vitamin D deficiency.

Maybe vitamin D could end up helping one's family survive the coming influenza pandemic, or maybe not. Let's gamble. Ever heard of the vitamin D variation of Pascals wager?

Pascal's (Vitamin D) Wager

"If one erroneously believes vitamin D is effective against influenza, they lose nothing, whereas if one correctly believes vitamin D is effective against influenza, it may result in saving their life. But if one correctly disbelieves in vitamin D, they gain nothing, whereas if one erroneously disbelieves in vitamin D, the mistake could prove fatal."

John Jacob Cannell MD Executive Director