June 2013 Epidemics and AIDS Update

1. People doing well on HIV therapy have a mortality risk identical to that of HIV-negative peers
2. 2012: half a million sexually transmitted infections in England
3. High rates of gonorrhea among people living with HIV in the US
4. Female sex workers frequently offered larger fees by their clients in return for sex without a condom
6. NIH scientists discover how HIV kills immune cells
7. The Immune System, HIV, and Aging
8. Am I mad or is it the meds?
9. Dentist in Springettsbury Put Patients at Risk for Hepatitis, HIV, State Says
10. Studies showing how bird flu viruses could adapt to humans offer surveillance and vaccine strategies
11. Spanish researchers writing in cell describe the 9 hallmarks of aging
12. 3 out of 20 scopes used to examine GI tracts and colons improperly cleaned
13. Vitamin D deficiency may help spread of hepatitis B throughout liver
14. How do immune cells detect infections?
15. Unusual Antibodies in Cows Suggest New Ways to Make Medicines for People
16. Non-Invasive First Trimester Blood Test Reliably Detects Down's Syndrome and Other Genetic Fetal Abnormalities
17. Wolbachia Bacteria Evolved to Infect Stem Cell Niches Through Successive Generations of Their Hosts
18. Vaccinating Children Against HPV?
19. Gut Bacteria Play Key Role in Vaccination
20. Association of Eumycetoma and Schistosomiasis
21. Sodium Reduction in Populations Insights From the Institute of Medicine Committee
22. Examining the Health Effects of Fructose
23. How AIDS Invented Global Health
24. New Danish results spark interest for future HIV cure research
25. Low CD4 cell count increases the risk of several cancers after starting HIV therapy
26. Drug Policies Fuel Deadly Hepatitis C Epidemic
27. The 'Elastic Band' Circumcision Device that could Reduce HIV Infection Rate by 60%
28. Saliva proteins may protect older people from influenza
29. University of Toronto breakthrough allows fast, reliable pathogen identification
30. Chlamydia Protein Has an Odd Structure, Scientists Find
31. Why Fruit Ripens and Spoils: Thousands of Plant Genes Activated by Ethylene Gas
32. Scientists discover why leprosy disappeared from Europe
33. WHO says MERS virus death toll hits 33
34. Study Gauges Value of Technology in Schools
35. More Than Half of Young HIV-Infected Americans Are Not Aware of Their Status
36. HIV convicts freed to die
37. 'I don't want to be only person cured of HIV'
38. A Shot in the Arm for Old Antibiotics
39. HIV-Derived Antibacterial Shows Promise Against Drug-Resistant Bacteria
40. Whooping Cough Has Lifelong Health Impact, Study Finds
41. New Way to Improve Antibiotic Production
42. New HIV infections among children have been reduced by 50% or more in seven countries in sub-Saharan Africa
43. Calcium and vitamin D help hormones help bones
44. Virtual skin model reveals secrets of skin aging
45. Reading DNA, Backward and Forward: Biologists Reveal How Cells Control the Direction in Which the Genome Is Read
46. Researchers Strike Gold With Nanotech Vaccine
47. Flu Shot Effective Regardless of Circulating Flu Strain, Research Finds
48. Link shown between Crohn's disease and virus
49. Seniors Are Not Just Wrinkly Adults
50. Sharing the Load
51. Distinct Neural Pathway for Itchiness
People doing well on HIV therapy have a mortality risk identical to that of HIV-negative peers

Michael Carter
Published: 05 June 2013

HIV-positive people taking antiretroviral therapy who have an undetectable viral load and a CD4 cell count above 500 cells/mm³ have a mortality risk comparable to that seen in the general population, investigators report in the online edition of AIDS. Researchers looked at mortality rates among participants enrolled in two large, randomised controlled trials – the SMART and ESPRIT studies.

“We identified no evidence for a raised risk of death compared with the general population in HIV-infected individuals on ART [antiretroviral therapy] with an undetectable viral load, who maintained or had recovery of CD4+ T-counts to at least 500 cells/mm³,” write the authors.

There have been significant improvements in HIV treatment and care in recent years. Antiretroviral therapy has become more powerful, less toxic and easier to take. Data from cohort studies suggests that people doing well on treatment – often defined as the maintenance of an undetectable viral load and a CD4 cell count above 500 cells/mm³ – have a life expectancy similar to that of age- and sex-matched HIV-negative individuals.

An international team of investigators wanted to further explore the impact of successful antiretroviral therapy on mortality risk. They therefore examined data obtained from participants enrolled in the SMART study (CD4 cell-guided treatment interruptions) and ESPRIT trial (HIV therapy with or without interleukin-2, or IL-2). Both were randomised controlled trials, meaning that mortality data were rigorously collected.

The study population involved 3280 people. To be eligible, participants were required to have a recent undetectable viral load (below 400 copies/ml in the SMART study and below 500 copies/ml in the ESPRIT trial) and a CD4 cell count above 350 cells/mm³. Participants from the SMART study all came from the continuous-treatment arm. Participants from the ESPRIT trial received antiretroviral therapy without IL-2.

Most participants were men (80%) and were recruited in the United States (53%). The median age at baseline was 43 years. As regards viral hepatitis, 4% were co-infected with hepatitis B and 8% with hepatitis C. Injecting drug users were excluded from the study.

The participants contributed a total of 12,357 person-years of follow-up. The median length of follow-up was three years.

There were 62 deaths. This meant that the overall mortality rate was 5 per 1000 person-years. AIDS-related deaths were rare (n = 2, 3%). The most common causes of death were cardiovascular disease and sudden death (n= 19, 31%), non-AIDS cancers (n = 12, 19%), accident, suicide or violence (n = 11, 18%), hepatitis co-infections (n = 6, 10%) and liver disease (n = 5, 8%).

The investigators compared the mortality rates seen in people with HIV to those expected in the matched HIV-negative population to produce a standardised mortality ratio (SMR). Overall, HIV was associated with a modest increase in mortality risk (SMR = 1.24).

There were 28 deaths among participants with a CD4 cell count between 350 and 499 cells/mm³, compared to an expected 16 in the general population (SMR = 1.77).

However, there was no evidence of an increased mortality risk for people with a CD4 cell count above 500 cells/mm³ (SMR = 1.00).

“In our study, individuals who had current or recent CD4+ T-cell counts above 500 cells/mm³ had no evidence of increased overall mortality compared with the general population,” comment the authors. “In contrast, those with CD4+ T-cell counts between 350 to 499 cells/mm³ had evidence of higher mortality rates.”

The investigators believe that much of the excess mortality seen in their patients would have been avoided with “timely diagnosis of HIV and initiation of ART”.

But there was even good news with respect to late diagnosis. The investigators found that participants with a CD4 cell count below 200 cells/mm³ at the time of diagnosis had only a very modest increase in their mortality risk, provided their CD4 cell count increased to above 500 cells/mm³ while taking HIV therapy (SMR = 1.18).

There have been significant improvements in HIV treatment since the initiation of the SMART study in 2002 and the ESPRIT trial in 2000. This could mean that modern antiretroviral therapy reduces mortality risk to an even greater extent than that seen in the present analysis.
However, the authors urge caution when interpreting their findings in the context of debates about the best time to start antiretroviral therapy. They believe this “needs to be assessed in randomized trials, such as the ongoing START trial, which is randomizing people with CD4+ T-cell count of at least 500 cells/mm³, to immediate ART versus deferral to CD4+ T-cell count reaching 350 cells/mm³”.

Reference

2012: half a million sexually transmitted infections in England
Roger Pebody
Published: 05 June 2013

There were just under half a million new diagnoses of sexually transmitted infections (STIs) in 2012, according to data released by Public Health England today. As in previous years, there were particularly high rates in gay men and in young heterosexual adults, with some urban areas having a much greater burden of disease than other parts of the country.

More encouragingly, rates of genital warts are down in young women – apparently because of HPV vaccination.

The total number of diagnoses is a little higher than the previous year (from 428,255 to 448,422 in 2012). Chlamydia remained the most commonly diagnosed infection (206,912 diagnoses), but there were also many diagnoses of genital warts (73,893), non-specific genital infection (59,942), genital herpes (32,021) and gonorrhoea (25,525). In comparison, the number of syphilis infections was much lower (2978).

Gay men
Gay men have a disproportionate burden of some STIs. In sexual health clinics, 79% of men diagnosed with syphilis and 58% of men diagnosed with gonorrhoea are gay men and other men who have sex with men (MSM).

The headline figures suggest dramatic increases in gonorrhoea and chlamydia infections in recent years in MSM. For example, there were 4578 diagnoses of gonorrhoea in 2010, 7465 in 2011 and 10,205 in 2012.

However, the way in which these infections are diagnosed has changed in recent years, with more sensitive tests probably contributing to the increasing number of infections identified. Nucleic Acid Amplification Tests (NAATs) are now recommended and more tests are performed on samples from the throat and rectum, rather than only testing genital samples.

Nonetheless, the Public Health England epidemiologists judge that “ongoing high levels of unsafe sex among MSM are likely contributing to increased transmission”. Moreover, gonorrhoea rates are of particular concern due to the increasing prevalence of drug-resistant gonorrhoea that does not respond to existing antibiotics.

Young people
Young people aged 15 to 24 years experience the highest rates of STIs. Among heterosexual people diagnosed in sexual health clinics, 64% of those with chlamydia were in this age group, as were 54% of those with genital warts, 55% with gonorrhoea, and 43% with genital herpes.

While chlamydia screening has reached large numbers of young people (1.7 million tests in 2012, equivalent to around 35% of young women and 16% of young men being tested during the year), Public Health England points to different testing rates in different parts of the country. It believes that regional differences in the number of chlamydia diagnoses are primarily driven by variations in the availability of screening (rather than risk behaviour). PHE urges local areas with lower rates of diagnoses to improve their promotion and delivery of chlamydia screening.

Ethnicity
There are higher rates of STIs in people of black ethnicity, compared to other ethnic groups. In black people, there were approximately 2292 diagnoses for each 100,000 people in the population. This contrasts with 535 diagnoses per 100,000 people of white ethnicity, 380 per 100,000 in people of Asian ethnicity, and 1580 per 100,000 people of mixed ethnicity.

Public Health England says that infections in black people are especially concentrated in individuals living in deprived urban areas.

HPV vaccination and genital warts
Encouragingly, the report suggests that HPV vaccination could be having an impact on infection with genital warts. While overall diagnoses in the under 25s are greater than a decade ago, there has been a
recent decline in cases of genital warts in women aged 15 to 19 (falling by 22% from 11,276 in 2009 to 8,770 in 2012).

The authors say that several factors could contribute to this decline. However, they say there is new evidence that the vaccine Cervarix (which was designed only to protect against HPV 16 and 18, the types associated with cervical and anal cancers) does in fact also have a modest protective effect against HPV 6 and 11 (the types associated with genital warts).

Cervarix was provided in England from 2008 to 2012, when it was replaced by Gardasil (which offers strong protection against all four types of HPV). Hopefully the new vaccine will bring down genital warts rates further.

Data from Australia, where Gardasil has been provided to young women and girls since 2007, suggest that this is possible — in four years, genital warts declined by 93% in women under 21, and by 82% in heterosexual men under 21 (who benefit from their female partners’ lack of infection). During the same time period, rates stayed stable in those aged over 30 and in gay men, who did not participate in the vaccination programme.

High rates of gonorrhoea among people living with HIV in the US

Call for the integration of HIV and STI surveillance data

Michael Carter
Published: 06 June 2013

Combining HIV and gonorrhoea surveillance databases has revealed a high prevalence of gonorrhoea among people living with HIV in four US settings. Published in the online edition of the Journal of Acquired Immune Deficiency Syndromes, the research showed that between 2000 and 2008, approximately 5% of gonorrhoea cases involved people with HIV. Rates of gonorrhoea fell among the general population, but incidence of the infection increased among people with HIV. The investigators believe that combining databases “could allow for enhanced prevention among persons with HIV infection and acute STDs [sexually transmitted infections]”.

There are approximately 50,000 new HIV infections in the US each year. Prevention efforts are more likely to succeed if they are targeted to those with the highest risk. The presence of an untreated sexually transmitted infection can increase the risk of HIV transmission. Investigators therefore wanted to see if combining HIV and gonorrhoea surveillance databases allowed for the identification of people with HIV who had been diagnosed with gonorrhoea.

Surveillance data were obtained from four health jurisdictions: New York City, Washington DC, Miami/Dade County and Arizona.

Approximately 206,000 cases of gonorrhoea were diagnosed in these four areas between 2000 and 2008. The rate of diagnoses fell significantly over the course of the study in three sites: by 14% in New York City; by 21% in Arizona and by 10% in Washington DC. However, Miami experienced a 10% increase in gonorrhoea incidence.

A total of 9,471 (4.6%) gonorrhoea cases involved people diagnosed with HIV. The rate differed between the four jurisdictions (New York City, 5.5%; Washington DC, 7.3%; Miami, 4%; Arizona, 2%).

In contrast to the overall fall seen in three study sites, the proportion of gonorrhoea diagnoses involving people with HIV increased significantly in all jurisdictions over the period of the study: from 3% in 2000 to 7% in 2008 in New York City; from 6.4 to 6.7% in Washington DC; from 2 to 4% in Miami; and from 0.7 to 3% in Arizona.

In each jurisdiction, the majority of people co-infected with HIV and gonorrhoea were men. The rate was 87% in New York City; 76% in both Washington DC and Miami; and 97% in Arizona. The investigators believe these findings indicate “many gonorrhoea–HIV co-infections are occurring in MSM [men who have sex with men] populations”. Despite their high risk, the authors note that the proportion of HIV-positive MSM having an annual gonorrhoea screen is low, “ranging from 14-18% for urethral screening and from 2-8.5% for oral/rectal screening”.

“Matching STD and HIV surveillance registries allowed us to identify and describe persons who acquired gonorrhoea subsequent to HIV diagnosis in 4 diverse jurisdictions”, comment the authors. “HIV care providers should prioritize HIV-infected patients with STDs for prevention strategies such as: initiation of antiretroviral therapy and adherence support; behavioural counselling; partner testing and referral; routine STD screening; and possibly pre-exposure prophylaxis (PrEP) for HIV for their uninfected sex partners.”
They conclude, “public health programmes with interest in prioritizing high-risk HIV-infected persons should consider the use of real-time data integration and analysis to identify STD/HIV co-infected persons and consider re-structuring priorities for partner service delivery for those who might not otherwise receive public health interventions”.

**Reference**

**Female sex workers frequently offered larger fees by their clients in return for sex without a condom**

Michael Carter
Published: 07 June 2013

Client demand for unprotected sex is contributing to the HIV epidemic among female sex workers, according to Canadian research published in the online edition of the *Journal of Acquired Immune Deficiency Syndromes*. Investigators in Vancouver found that approximately three-quarters of sex workers were offered more money by clients for sex without a condom and that 19% accepted this money. Transgender women were more likely to accept extra money for unsafe sex, as were women who experienced client violence and users of methamphetamine.

“Our study confirms the high demand by clients for unprotected sex among SWs [sex workers] in an urban Canadian setting,” write the authors. “These findings are consistent with other studies, which have suggested that clients looking for unprotected sex may seek out SWs who are particularly vulnerable to coercion.”

The investigators were concerned that within the context of commercial sex work, the responsibility to initiate condom use is usually placed with the sex worker. However, a growing body of research has shown that poverty, unstable housing, violence and policing policies have a significant impact on the ability of sex workers to use condoms. Clients of sex workers may also have an important role in determining the use of condoms.

To see if this is the case, the investigators designed a cross-sectional study involving 490 female sex workers. Recruitment to the study took place between February 2010 and October 2011. Participants were offered comprehensive HIV and STI testing and counselling and completed questionnaires. These included sections relating to their social and economic background, sex working patterns, experience of violence and use of recreational drugs. They were also asked if in the previous six months, a client had offered them extra money for sex without a condom, and if they had accepted this money and had unprotected sex with the client. The investigators conducted a series of analyses to see if there were any factors associated with being offered or accepting extra money for sex without a condom.

The women had a median age of 35 years and the median age at first sex work was 20 years. A quarter identified as belonging to a sexual minority (e.g. lesbian, transgender). Overall, 54% reported soliciting for clients independently (e.g. through online advertising), 26% in indoor sex environments (e.g. brothels, massage parlours) and 71% in outdoor environments (e.g. streets). The investigators comment that this shows “the substantial overlap in terms of sex work solicitation environments”. There was an 11% HIV prevalence and 10% of women had a sexually transmitted infection (STI).

A total of 356 women (73%) reported being offered more money by clients for sex without a condom; 75 of these women reported accepting this money and agreeing to unprotected sex.

Factors associated with being offered more money for sex without a condom included use of 'speedballs' (AOR = 6.93; 95% CI, 1.60-29.94); a higher number of weekly clients (AOR = 1.03; 95% CI, 1.01-1.06, a 3% increase in odds for each extra client); difficulty accessing condoms (AOR = 2.72; 95% CI, 1.09-6.77); and having clients who visited other sex workers (AOR = 1.83; 95% CI, 1.19-2.84).

Accepting money for unsafe sex was associated with belong to a sexual minority (AOR = 2.72; 95% CI, 1.35-5.46); experience of client violence (AOR = 2.18; 95% CI, 1.10-4.34); and use of methamphetamine (AOR = 2.95; 95% CI, 1.27-6.87).

Older women were significantly less likely to report accepting more money for unprotected sex (AOR = 0.96%; 95% CI, 0.93-1.00, a 4% decrease in odds for each year). “Older women with longer duration in sex work may be more experienced in negotiations with clients and more comfortable refusing demands for higher fees,” write the authors.

Women who worked indoors (as opposed to outdoors) were also significantly less likely to accept a larger fee in return for unsafe sex (AOR = 0.15; 95% CI, 0.04-0.54). The authors suggest this is because...
“women who work in indoor settings can have more control over negotiations with clients regarding
sexual transactions and can charge increased fees, potentially reducing the need to agree to clients’
demands for unsafe sex.”

The authors conclude their study “provides strong evidence of the importance of acknowledging the
role of clients in the spread of HIV/STIs”. They call for a review of “policies relating to the criminalization
and regulation” of sex work.

Reference
Deering KN et al. Client demands for unsafe sex: the socio-economic risk environment for HIV among street and off-street

By Omololu Ogunmade, 5 June 2013
The Director General of the National Agency for the Control of AIDS (NACA), Professor John Idoko,
Tuesday disclosed that with 3.4 million Nigerians living with HIV/AIDS, Nigeria has become the second
largest country where the disease has afflicted so many people.

Idoko, who made this disclosure during a public hearing on a bill seeking an end to discrimination
against HIV victims, said the ailment was more prevalent in 13 states.

Idoko, who noted that only 18 per cent of HIV positive women received prophylaxis treatment against
mother-child transmission, noted that only 18 per cent of the 170 million population in the country had
gone for HIV test, adding that more than 40 per cent of HIV positive persons do not know their status.

"Most successful initiatives recognise the role of legislation as the tool against stigma and
discrimination," he said

He said if the bill is passed into law, it would strengthen legal protection for vulnerable groups and
ensure their greater access to prevention, treatment and care.

Chairman, Senate Committee on Health, Senator Ifeanyi Okowa (Delta North), described the HIV
pandemic as one of the greatest challenges to health, development, economy and social progress in the
world today.

"In the countries that are worst affected, including our dear country Nigeria, the impact of HIV and
AIDS have eroded decades of development goals and gains, stultifying economies and destabilising
societies.

"There is no doubt that HIV is expected to continue to be a leading cause of mortality and morbidity
in many countries and population, including Nigeria.

"We must begin to be proactive in the implementation of action plans that are workable and friendly
and advocacy must be carried out at all levels of the society.

"HIV poses a serious obstacle to the attainment of decent work and sustainable development and its
effects are concentrated among the most productive age group.

"The HIV problem has been made worse by the violation of their fundamental rights at the work
place, schools, communities and the larger society on the basis of real or the perceived status, particularly
through discrimination directed at persons living with or affected by HIV and AIDS," Okowa said.

While declaring the public hearing open, Senate President David Mark said stigmatisation has been
the bane of adopting measures to prevent the spread of HIV because people fail to disclose their status.

NIH scientists discover how HIV kills immune cells
Findings have implications for HIV treatment
WHAT:
Untreated HIV infection destroys a person’s immune system by killing infection-fighting cells, but
precisely when and how HIV wrecks this destruction has been a mystery until now. New research by
scientists at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of
Health, reveals how HIV triggers a signal telling an infected immune cell to die. This finding has
implications for preserving the immune systems of HIV-infected individuals.

HIV replicates inside infection-fighting human immune cells called CD4+ T cells through complex
processes that include inserting its genes into cellular DNA. The scientists discovered that during this
integration step, a cellular enzyme called DNA-dependent protein kinase (DNA-PK) becomes activated.
DNA-PK normally coordinates the repair of simultaneous breaks in both strands of molecules that
comprise DNA. As HIV integrates its genes into cellular DNA, single-stranded breaks occur where viral
and cellular DNA meet. Nevertheless, the scientists discovered, the DNA breaks during HIV integration
surprisingly activate DNA-PK, which then performs an unusually destructive role: eliciting a signal that
causes the CD4+ T cell to die. The cells that succumb to this death signal are the very ones mobilized to
fight the infection.

According to the scientists, these new findings suggest that treating HIV-infected individuals with
drugs that block early steps of viral replication—up to and including activation of DNA-PK and
integration—not only can prevent viral replication, but also may improve CD4+ T cell survival and
immune function. The findings also may shed light on how reservoirs of resting HIV-infected cells develop
and may aid efforts to eliminate these sites of persistent infection.

**ARTICLE:**
A Cooper et al. HIV-1 causes CD4 cell death through DNA-dependent protein kinase during viral integration. *Nature*
DOI:10.1038/nature12274 (2013).

**The Immune System, HIV, and Aging**
June 3, 2013
By Richard Jefferys and Tim Horn

**From the Introduction**
Little more than a decade ago, it was almost inconceivable that the issue of aging with HIV infection
would emerge as an important concern. But it has now become clear that combination antiretroviral
therapy (ART) can suppress virus replication for many years—likely for life—in most people who can
access the drugs, and the opportunistic infections that were once the primary causes of illness have largely
evanesced everywhere treatment is available. Morbidity and mortality from HIV infection has plummeted,
and the survival of HIV-positive individuals is edging ever closer to that of comparable HIV-negative
people. With the specter of AIDS having finally been chased from the near horizon, attention has turned
to health problems that may lie further down the road.

Looming largest are illnesses typically associated with aging. Examples include cardiovascular,
kidney, and liver disease; bone loss and increased fracture risk; frailty; cognitive impairment; and cancer.
Evidence is accumulating that the risk of these conditions is elevated in HIV-positive individuals and, in
some cases, they may be occurring at a younger age, on average, than is typically observed among
comparable HIV-negative populations. As the proportion of older individuals living with HIV grows, there
is an urgent need to understand how a broad array of factors may be contributing to this phenomenon;
these factors include inflammation, immune dysregulation, polypharmacy, long-term drug toxicities, and
coinfections and comorbidities that are disproportionally prevalent among people with HIV, such as
hepatitis B and C, current or former substance-use disorders, stress, and depression.

It is important to emphasize that the reported elevations in risk for aging-associated diseases among
people with HIV (compared to their HIV-negative counterparts) are typically relatively small. There are
also inconsistencies between studies and as yet unresolved controversies regarding the extent to which
HIV infection is an independent risk factor for specific illnesses. So while there is cause for vigilance and
concern, there is no reason to panic, and it is likely that many HIV-positive people will not face a
significant additional hazard of aging-associated conditions. As a general recommendation, HIV-positive
individuals should consider the lifestyle factors that are now known or expected to maximize health once a
person reaches old age; these include daily exercise, a healthy diet, maintaining low blood pressure and
cholesterol, and avoiding substance abuse and excess fat gain.

The purpose of this brief report is to outline current scientific knowledge regarding the immunologic
connections between HIV and aging, and provide an introduction to some of the unresolved questions
that are being addressed—or need to be addressed—by research.

**Am I mad or is it the meds?**
Jun 6
Posted by *ukpositivelad*
It’s 00:50 and once again I can’t sleep.
My insomnia has kept me up for the best part of three days in a row now, my mind is tired, my body is
exhausted and yet I still can’t sleep.

I go to the bathroom to top up my water glass and I catch a glimpse of myself in the mirror, I look like
death warmed up – my skin pale, bags under my eyes so big you could carry your shopping in them, and
I’m breaking out in spots -my body has had enough but my HIV meds won’t let me sleep.

This has been going on for months upon months now, sleeping only three or four nights a week, the
rest sat up trying to keep myself busy until it’s time to go to work. Sadly it’s become something of a routine
– a routine that’s causing me to burn out.
I wish I could say that insomnia was the biggest of my concerns, but sadly it gets worse, over the last few weeks things have been going bump in the night. I’m hearing and seeing things that aren’t there. It started off as little things, a thud in the hallway, a shadow out the corner of my eye – but progressively they’re getting more and more significant – I’ve heard the front door being hammered only for no-one to be there, giant spiders on the ceiling, I’ve even seen myself sat in my desk chair.

I’m reasonably sure that it’s not a inherent problem with my mind, so much as the medication – the hallucinations only happen after I’ve taken my meds and on nights I can’t sleep. So I think it’s pretty reasonable to conclude that they’re side effects that I’d normally sleep through – but in my perma-awake state I have to endure. What I’m not sure, however, is why they’ve only started now – nearly 18 months after I started this combination therapy.

I’ve asked my doctors to change my HIV meds before based on my sleeping issues but they’ve told me to wait it out, I’m hoping when I see them on the 17th that they’ll take the news of hallucinations and even less sleep slightly more seriously. Either that or they’ll lock me up, and if they do I hope they have wine.

Dentist in Springettsbury Put Patients at Risk for Hepatitis, HIV, State Says

York Daily Record (06.06.2013) By Sean Adkins

The Pennsylvania Department of Health is advising patients of York County dentist Dr. Jacqueline A. Marcin, D.M.D. that they might be at risk for infection. In April, the state’s board of dentistry temporarily suspended Marcin’s license after an investigation found that her practice did not sterilize some of its equipment properly. The state department of health is recommending that Marcin’s current and former patients get tested for HIV, hepatitis B, and hepatitis C. The patients may have undergone dental procedures that Marcin performed directly, such as tooth removals, fillings, and denture fittings.

Secretary of Health Michael Wolf expressed his concern for Marcin’s patients and stated that, "We have not received any related reports of disease transmission or illness at this time," but he added that the health department recommended testing as a precautionary measure for Marcin’s current or former patients. They should call the toll-free hotline, at 1–855–265–4613.

Studies showing how bird flu viruses could adapt to humans offer surveillance and vaccine strategies

Bird flu viruses are potentially highly lethal and pose a global threat, but relatively little is known about why certain strains spread more easily to humans than others. Two studies published by Cell Press June 6th in the journal *Cell* identify mutations that increase the infectivity of H5N1 and H7N9 viruses through improved binding to receptors in the human respiratory tract. The findings offer much-needed strategies for monitoring the emergence of dangerous bird flu strains capable of infecting humans and for developing more effective vaccines.

"Avian influenza viruses evolve rapidly, and there are many subtypes of these viruses that we need to be concerned about because, in many cases, humans do not have immunity to these newer strains," says senior study author Ram Sasisekharan of the Singapore-MIT Alliance for Research and Technology. "Our findings can be put to use to monitor the evolution of H5N1 and H7N9 viruses in the field as well as in the clinic if and when there is an outbreak."

In the past 10 years, the H5N1 virus has infected nearly 600 individuals in several outbreaks around the world, killing about 60% of those infected. And over the past few months, a lethal subtype of the H7N9 virus has been found in at least 131 people, mostly in mainland China. Although these viruses do not normally infect humans, over time they can adapt to humans and gain the ability to spread more easily from person to person, underscoring the importance of finding out which mutations could enhance the ability of these viruses to infect humans.

To address this question, Sasisekharan and his team analyzed the structure of the H5N1 and H7N9 viruses, focusing on hemagglutinin (HA)—a type of viral protein that binds to cell receptors in the respiratory tract of hosts. They characterized the set of HA mutations required to increase the preference of the viruses for human receptors, discovering that only a single amino acid change in the HA sequence is necessary for this to occur. Moreover, they found that distinct HA mutations are evolving in the H7N9 virus indicating that currently recommended H7 vaccines would not be effective against this newly emerged virus.

"Right now, there is no vaccine to protect against the H7N9 virus, and our findings could guide efforts to develop effective vaccine strategies," Sasisekharan says.
Spanish researchers writing in cell describe the 9 hallmarks of aging
The authors contend that by understanding and combating aging we can also fight cancer and other diseases of most incidence in the developed world
For some species, living twice as long in good health depends on no more than a few genes. When this fact was revealed by studies on worms three decades ago, it ushered in a golden age of ageing studies that has delivered numerous results, but also sown some confusion. The prestigious journal Cell is now publishing an exhaustive review of the subject that aims to set things straight and "serve as a framework for future studies. All the molecular indicators of ageing in mammals – the nine signatures that mark the advance of time – are set out in its pages. And the authors also indicate which can be acted upon in order to prolong life, while debunking a few myths like the belief that antioxidants can delay aging.

The authors are Spanish scientists Maria Blasco (Spanish National Cancer Research Centre, CNIO), Carlos Lopez-Otin (University of Oviedo), and Manuel Serrano (CNIO), along with Linda Partridge (Max Planck Institute for Biology of Ageing) and Guido Kroemer (Paris Descartes University). Their inspiration came from a classic 2000 paper; The Hallmarks of Cancer, also published in Cell, which marked a watershed in cancer research. Blasco, Serrano and Partridge contacted Cell proposing a similar effort to systematically review and organize the state of knowledge on aging; Lopez-Otin and Kroemer had also come to the conclusion that this kind of analysis was much needed, and decided to share their ideas and efforts to get the project off the ground.

"The current situation of aging research exhibits many parallels with that of cancer research in previous decades," reads the opening paragraph of the resulting paper, titled The Hallmarks of Aging. "The aging field has been notoriously more abundant in theories than experimental evidence," says Blasco; "this review doesn’t discuss theories, but molecular and genetic evidence." For Lopez-Otin "the time had come to set out in organized, understandable fashion the molecular keys to what is still a little known process, despite the thousands of scientific papers published on the subject every year."

The paper's connection with cancer goes beyond formal parallelisms. Because one of the main conclusions of The Hallmarks of Aging is that by understanding and combating aging we can also fight against cancer and the other diseases of most incidence in the developed world. The relationship is clear: aging is the result of the lifelong accumulation of DNA damage, and it is this same process that causes cancer, diabetes, cardiovascular disease and neurodegenerative conditions like Alzheimer's.

"Aging is the cause of the diseases that afflict us as we get older," Blasco explains. "Identifying the molecular markers of aging will help us find the cause of other diseases like cancer. The implications are enormous." As the article puts it, "cancer and aging share common origins," and can be regarded as "two different manifestations of the same underlying process."

"IT'S NOT ABOUT NOT HAVING WRINKLES"
For Serrano, this removes the "frivolity" with which aging research is often approached: "It's not about not having wrinkles or living to be a hundred at any cost, but about prolonging disease-free life." In Cell the scientists are explicit about their final goal, which is "to identify pharmaceutical targets to improve human health during aging."

Another milestone of the paper is that it not only defines the nine molecular hallmarks of aging but orders them into primary hallmarks – the triggers; those that make up the organism's response to these triggers; and the functional defects resulting. This hierarchy is important, because different effects can be achieved by acting on one or other of these processes. By acting on just one mechanism, if it numbers among the primaries, we can delay the aging of many organs and tissues.

There are four primary causes of aging: genomic instability; the shortening of telomeres; epigenetic alterations; and loss of proteostasis.

Genomic instability refers to the defects the genes accumulate over time, due to intrinsic or extrinsic causes. The shortening of telomeres – the protective caps over the ends of chromosomes – is one such defect, but so important a one that it stands as a hallmark in its own right. Epigenetic alterations are the result of lived experience – our exposure to the environment.

Loss of proteostasis has to do with the non-elimination of defective proteins, whose accumulation promotes age-related diseases. With Alzheimer's, for instance, neurons die because plaques form of a protein that should have been eliminated.
The organism responds to these triggers with mechanisms that try to correct the damage, but which can themselves turn deleterious if they become exacerbated or chronic. This is the case of cellular senescence: the cell is induced to stop dividing, and thus prevent cancer, when too many defects are built up, but if the effect is overdone, the tissues — and the body — age.

This double-edged sword is also present in two processes at the heart of the debate on aging theories: the so-called oxidative damage, linked to the famous free radicals; and metabolism-derived mechanisms, relating, in turn, to the evidence — though not yet in humans — that calorie restriction prolongs life.

**FREE RADICALS: A DOUBLE-EDGED SWORD**

Everything suggests that the secret to living longer is a lot more complex than simply taking antioxidants or cutting out food. Free radicals may be harmful in large quantities, but their presence also triggers a protective response. As for antioxidants, the authors are adamant: there is no genetic evidence that enhancing antioxidant defenses can delay aging. And while the organism may deploy protective strategies to cope with nutrient scarcity — presumably the reason why calorie restriction appears to work —, these too "in excess and during time, can become pathological," they affirm.

The third group of hallmarks comes into play when the body cannot compensate the damage caused by the two preceding groups. One is the exhaustion of tissue stem cells, which cease to discharge their regenerating function; another is errors in intercellular communication, which give rise, for instance, to inflammation — a process whose chronic form is associated with cancer.

Among the next big challenges is to understand the connections between hallmarks. And, of course, to investigate ways to bring these processes under control. The authors run through the list of already identified therapeutic targets and propose some solutions to slow down aging.

One therapeutic strategy tested successfully in mice is to stop the telomeres from shortening. "The process can be halted and even reversed in mice," remarks Blasco, an expert in the area, who is convinced that, by and large, "we still have ample room for manoeuver to combat aging and enjoy more years of both life and health."

For Lopez-Otin, "We have diverse opportunities to extend longevity in the not too distant future. Treatments aimed at reducing or correcting the genomic damage that occurs with time are still a distant prospect, but those focusing on metabolic regulation systems may be much more achievable. We don't aspire to immortality, just to the possibility of making life a little better for us all."

**Reference article:**

**3 out of 20 scopes used to examine GI tracts and colons improperly cleaned**

**Scopes at 5 US hospitals analyzed for presence of ‘bio dirt’**

Fort Lauderdale, Fla., June 7, 2013 - Three out of 20 flexible gastrointestinal (GI) endoscopes used for screening were found to harbor unacceptable levels of "bio dirt" -- cells and matter from a patient's body that could pose potential infection risk -- according to a study of endoscopes used at five hospitals across the U.S.

In an abstract to be presented at the **40th Annual Conference** of the Association for Professionals in Infection Control and Epidemiology (**APIC**), researchers in the 3M Infection Prevention Division analyzed 275 flexible duodenoscopes, gastroscopes, and colonoscopes and found that 30 percent, 24 percent, and 3 percent respectively did not pass a cleanliness rating.

"Three out of 20 is an unexpectedly high number of endoscopes failing a cleanliness criterion," said Marco Bommarito, PhD, lead investigator and lead research specialist, 3M Infection Prevention Division. "Clearly, we’d like no endoscopes to fail a cleanliness rating."

In the last several years there have been reports of improperly cleaned endoscopes at healthcare facilities across the country, including the Veterans Administration, in which thousands of patients required testing for HIV, as well as hepatitis B and C. According to the Centers for Disease Control and Prevention, who published guidelines for reprocessing endoscopes in 2008, more healthcare-associated outbreaks have been linked to contaminated endoscopes than to any other medical device. In addition, cross-contamination from flexible endoscopes has been identified by the ECRI Institute, an independent organization that researches patient safety and quality, as a leading health hazard.²

Annually between 15 and 20 million endoscopy procedures are conducted with reusable endoscope devices to screen various components of a patient’s GI tract. These devices allow healthcare providers to investigate the surface of this organ and identify issues such as polyps or colon cancer. Duodenoscopes,
gastroscopes, and colonoscopes examine the duodenum – or the first section of the small intestine, the stomach, and the colon, respectively.

After an endoscope is used for a procedure it is sent for cleaning before being reused with another patient. This reprocessing involves two steps: first, manual cleaning with an enzymatic cleaner and flushing by a hospital technician and second, soaking the device in a high-level disinfectant. The first step is vital to ensure that the disinfection process is effective. After manual cleaning is completed, the technician visually inspects the instrument to ensure cleanliness. However, this study has found that contamination can remain on the device and may be invisible to the naked eye.

In the study, after the manual cleaning step of the decontamination and disinfection process, cleaning technicians at five hospitals across the U.S. were asked to flush the scopes with sterile water, and this sample was analyzed by researchers for adenosine triphosphate (ATP) – a marker of bio contamination. The amount of ATP, in relative light units (RLUs), was measured with a hand-held luminometer. Based on previously published clinical data, a threshold for "pass/fail" was set at 200 RLUs.3,4 Any instruments with more than 200 RLUs were identified as a cleaning failure.

"The cleaning protocols for flexible endoscopes need improvement, such as guidelines tailored to the type of scope or identifying if there is a critical step missing in the manual cleaning process, and documented quality control measures" said Dr. Bommarito. "These types of improvements could have a positive impact on patient safety."

Vitamin D deficiency may help spread of hepatitis B throughout liver
Researchers from Germany have found that low levels of vitamin D are associated with high levels of hepatitis B virus (HBV) replication. Findings published online in Hepatology, a journal of the American Association for the Study of Liver Diseases, suggest seasonal fluctuations in vitamin D and HBV levels point to a link in these variables among patients with chronic HBV.

While highly effective vaccines are available, HBV still remains one of the most significant infectious diseases worldwide. In fact, the World Health Organization (WHO) states that HBV is 50 to 100 times more infectious than human immunodeficiency virus (HIV). Furthermore WHO reports that two billion individuals have been infected with HBV, which is responsible for nearly 600,000 deaths each year. In the U.S. the Centers for Disease Control and Prevention (CDC) estimates that up to 1.4 million Americans are living with chronic HBV.

"Vitamin D helps maintain a healthy immune system and there is evidence of its role in inflammatory and metabolic liver disease, including infection with hepatitis C virus (HCV)," explains lead investigator Dr. Christian Lange from Johann Wolfgang Goethe University Hospital in Frankfurt. "However, the relationship between vitamin D metabolism and chronic HBV infection remains unknown and is the focus of our present study."

Between January 2009 and December 2010, the team recruited 203 patients with chronic HBV who had not previously received treatment for their infection. Levels of 25-hydroxyvitamin D were measured from each participant. Patients co-infected with HCV, HIV, or hepatitis D; those with excessive alcohol use; and those with liver cancer or other malignancies were excluded.

Results show that 34% of participants had severe vitamin D deficiency (less than 10 ng/mL), 47% with vitamin D insufficiency (between 10-20 ng/mL) and 19% had normal levels of vitamin D (greater than 20 ng/mL). Further analyses indicate that the concentration of HBV in the blood, known as viral load, was a strong indicator of low vitamin D levels. In patients with HBV DNA less than 2000 IU/mL or more, the levels of vitamin D were 17 and 11 ng/mL, respectively.

Researchers also determined that patients with the hepatitis B antigen (HBsAg) had lower levels of vitamin D than HBsAg negative participants. Inverse seasonal fluctuations between vitamin D and HBV levels were noted, which further suggests a relationship between the two variables.

"Our data confirm an association between low levels of vitamin D and high concentrations of HBV in the blood," concludes Dr. Lange. "These findings differ from previous research of patients with chronic hepatitis C, which found no connection between vitamin D levels and concentration of HCV in the blood." The authors propose further investigation of vitamin D as a therapeutic intervention for controlling HBV.

Full citation: "Low Vitamin D Serum Concentration is Associated with High Levels of Hepatitis B Virus (HBV) Replication in Chronically Infected Patients." Harald Farnik, Jorg Bojunga, Annemarie Berger, Regina Allwinn, Oliver Waidmann, Bernd Kronenberger, Oliver T. Keppler, Stefan Zeuzem, Christoph Sarrazin and Christian M. Lange. Hepatology; (DOI: 10.1002/hep.26488) Published Online: May 22, 2013.
How do immune cells detect infections?

McGill researchers use computer simulations to shed light on how immune cells may identify foreign antigens

How do immune cells manage to sort through vast numbers of similar-looking proteins within the body to detect foreign invaders and fight infections?

"For immune cells, singling out foreign proteins is like looking for a needle in a haystack – where the needle may look very much like a straw, and where some straws may also look very much like a needle," notes McGill University physics professor Paul François.

Understanding how immune cells tackle this formidable challenge is important, because it could provide crucial insights into the understanding of immune diseases, from AIDS to auto-immune disorders.

In a study published May 21 in the journal Physical Review Letters, François and McGill graduate student Jean-Benoît Lalanne used computational tools to examine what kind of solutions immune systems may use to detect small concentrations of foreign antigens (characteristic of potentially harmful infections) in a sea of "self-antigens" normally present at the surface of cells.

The researchers' computer simulations yielded a surprisingly simple solution related to the well-known phenomenon of biochemical adaptation – a general biochemical mechanism that enables organisms to cope with varying environmental conditions.

To find solutions, the computer uses an algorithm inspired by Darwinian evolution. This algorithm, designed previously within the François research group, randomly generates mathematical models of biochemical networks. It then scores them by comparing properties of these networks to predefined properties of the immune system. Networks with best scores are duplicated in the next generation and mutated, and the process is iterated over many simulated "generations" until networks reach a perfect score.

In this case, almost all solutions found were very similar, sharing a common core structure or motif.

"Our approach provides a simpler theoretical framework and understanding of what happens" as immune cells sort through the "haystack" to detect foreign antigens and trigger the immune response, François says. "Our model shares many similarities with real immune networks. Strikingly, the simplest evolved solution we found has both similar characteristics and some of the blind spots of real immune cells we studied in a previous collaborative study with the groups of Grégoire Altan-Bonnet (Memorial Sloan Kettering, New York), Eric Siggia (Rockefeller University, New York) and Massimo Vergassola (Pasteur Institute, Paris)."

To access the abstract of the paper: http://prl.aps.org/abstract/PRL/v110/i21/e218102

Unusual Antibodies in Cows Suggest New Ways to Make Medicines for People

June 6, 2013 — Humans have been raising cows for their meat, hides and milk for millennia. Now it appears that the cow immune system also has something to offer. A new study led by scientists from The Scripps Research Institute (TSRI) focusing on an extraordinary family of cow antibodies points to new ways to make human medicines.

"These antibodies' structure and their mechanism for creating diversity haven't been seen before in other animals' antibodies," said Vaughn V. Smider, assistant professor of cell and molecular biology at TSRI and principal investigator for the study, which appears as the cover story in the June 6, 2013 issue of the journal Cell.

Defense Against Infection

Antibodies, part of our immune system, are large proteins that resemble lobsters -- with a tail and two identical arms for grabbing specific targets (called "antigens," often parts of bacteria or viruses). At the business end of each arm is a small set of protein loops called complementarity-determining regions or CDRs, which actually do the grabbing. By rearranging and mutating the genes that code for CDRs, an animal's immune system can generate a vast and diverse population of antibodies -- which collectively can bind to just about any of the body's foreign invaders.

In humans and in many other mammals, most of an antibody's specificity for a target is governed by the largest CDR region, CDR H3. Researchers have been finding hints that an unusually long version of this domain can sometimes be the key to a successful defense against a dangerous infection. For example, in a study reported in Nature last August, Ian A. Wilson, who is Hansen Professor of Structural Biology and chair of the Department of Integrative Structural and Computational Biology at TSRI, and
collaborators isolated an anti-HIV antibody with a long CDR H3 region -- twice normal length -- which allows it to grab a crucial structure on the virus and thereby neutralize the infectivity of most HIV strains.

Waithaka Mwangi, assistant professor in the Texas A&M College of Veterinary Medicine and Biomedical Sciences (CVM) and an author on the Cell paper, suggests thinking of these long CDRs as a probe on a thin extended scaffold that can fit narrow crevices to reach and bind unique hidden pathogen determinants that ordinary antibodies cannot.

**Learning from Nature**

Reports on these antibodies recently caught the interest of Smider, whose area of research includes finding new ways to generate therapeutic antibody proteins. "We started thinking about how we could make these long CDR3s that are so rare in humans, and we knew from the literature that cows make even longer ones all the time," he said.

To investigate, Smider assembled a collaboration that included the TSRI laboratories of Wilson and Peter G. Schultz, who is the Scripps Family Chair Professor of Chemistry, as well as researchers at CVM. Michael F. Criscitiello, assistant professor at the CVM and a co-author of the paper, noted that to contribute to the groundbreaking study and noted researchers at CVM offered key immunology proficiency with -- and access to -- cows. "Such collaborations bring together specialists in diverse fields and certainly facilitate future research," added Terje Raudsepp, associate professor at the CVM and another of the study's authors.

The team performed a detailed structural and sequence analysis of these unusually long CDR H3 cow antibodies, to gain insight into how they are made naturally -- and how such structures might be engineered in the laboratory.

First author Feng Wang, at the time a postdoctoral research associate with Schultz and Smider at TSRI, led the effort to purify long CDR H3 cow antibodies -- which represent about 10 percent of the cow antibody repertoire -- and analyze their corresponding gene sequences. Co-first author Damien C. Ekiert, at the time a graduate student in the Wilson laboratory at TSRI, was able to crystallize the long CDR H3 antibody samples and determine the 3D atomic structures of two representative antibodies by X-ray crystallography.

Although the structure of the long CDR H3 protein in Wilson's human anti-HIV antibody had seemed unusual, the corresponding structure in the cow antibodies turned out to be unique in the known world of animal antibodies: a long "stalk" element topped by an antigen-binding "knob." Sequencing of the DNA that codes for the knob region revealed an unusual abundance of cysteine -- a sulfur-containing amino acid that is apt to bond to a nearby cysteine on the same protein chain, thus forming a loop.

**Efficient Way to Evolve**

Analyses of these DNA sequences also indicated that, in the cow B-cells where these antibodies are made, the knob-coding gene segments are extraordinarily likely to develop point mutations that either add or subtract cysteines. The effect of these tiny mutations is to create or remove -- often radically -- antigen-grabbing loops on the structure. "This is a very efficient way to evolve new protein folds," said Wang. Indeed, it seems to be the principal way in which the cow immune system creates a diverse set of these long CDR H3 antibodies.

In the cows, binding of these antibodies to viruses is almost entirely done by the knob on the long CDR H3, which shows that these antibodies do have an important function in the immune system. "For the very first time we have an ultra-long CDR3 antibody binding to an actual pathogen," said Mwangi.

One question that remains is why the cow immune system evolved to make such antibodies. Smider suspects that it has to do with cows' unusual, four-chambered, grass-fermenting stomach, with its extensive collection of bacteria and other microorganisms. "If some of these escape from the stomach and get into the bloodstream or other tissues, there could be some pretty serious infections; so that's our starting hypothesis for why cows have this unusual immune defense," he said.

The stalk-and-knob structure of the CDR H3 loops on these antibodies, which resemble structures found in some insect poisons and other proteins, also suggest that they evolved to grab a particular type of target. "What comes to mind are ion channel or pore structures in the walls of cells," Smider said. "In any case, we're hoping to find out whether any of the structures targeted by these knobs exist on microorganisms that cause human disease."

**Toward Real World Applications**

Smider, Schultz, and Wang, who now has his own laboratory at the California Institute for Biomedical Research (CALIBR), hope to harness the potential power of long CDR H3 antibodies for a wide variety of human -- and perhaps also veterinary -- medical applications. "One approach we're taking is to immunize
cows with antigens of interest to see if we can recover antibodies that neutralize the antigens using these elongated CDR H3 proteins,” said Wang.

Another approach, said Smider, is to generate extensive "libraries" of long CDR H3 antibodies in the laboratory and select for those antibodies that have a desired effect. Fabrus Inc, a company founded by Smider and whose scientists were collaborators on the study, is building these libraries for therapeutic discovery. CALIBR, founded by Schultz to translate scientific findings into medicines, also is investigating the possibility of replacing the knob region of such antibodies with known therapeutic proteins to increase their stability and potency.

"It's somewhat rare in science that you find something so unexpected and then have the opportunity to study it in depth -- and then get to develop real biomedical applications from it," Smider said. Other contributors to the study, "Reshaping Antibody Diversity," were Insha Ahmad of the TSRI Department of Cellular and Molecular Biology, Wenli Yu of the TSRI Department of Integrative Structural and Computational Biology, Yong Zhang of the TSRI Department of Chemistry, Ali Torkamani of the TSRI Department of Molecular and Experimental Medicine, Omar Bazirgan of Fabrus Inc and Terje Raudsepp, Waithaka Mwangi and Michael F. Criscitiello of the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University.

**Journal Reference:**

---

**Non-Invasive First Trimester Blood Test Reliably Detects Down's Syndrome and Other Genetic Fetal Abnormalities**

June 7, 2013 — New research has found that routine screening using a non-invasive test that analyzes fetal DNA in a pregnant woman’s blood can accurately detect Down’s syndrome and other genetic fetal abnormalities in the first trimester. Published early online in Ultrasound in Obstetrics & Gynecology, the results suggest that the test is superior to currently available screening strategies and could reshape standards in prenatal testing.

Current screening for Down’s syndrome, or trisomy 21, and other trisomy conditions includes a combined test done between the 11th and 13th weeks of pregnancy, which involves an ultrasound screen and a hormonal analysis of the pregnant woman’s blood. Only chorionic villus sampling and amniocentesis can definitely detect or rule out fetal genetic abnormalities, but these are invasive to the pregnancy and carry a risk of miscarriage.

Several studies have shown that non-invasive prenatal diagnosis for trisomy syndromes using fetal cell free (cf) DNA from a pregnant woman’s blood is highly sensitive and specific, making it a potentially reliable alternative that can be done earlier in pregnancy.

An Ultrasound in Obstetrics & Gynecology study by Kypros Nicolaides, MD, of the Harris Birthright Research Centre for Fetal Medicine at King’s College London in England, and his colleagues is the first to prospectively demonstrate the feasibility of routine screening for trisomies 21, 18, and 13 by cfDNA testing. Testing done in 1005 pregnancies at 10 weeks had a lower false positive rate and higher sensitivity for fetal trisomy than the combined test done at 12 weeks. Both cfDNA and combined testing detected all trisomies, but the estimated false-positive rates were 0.1% and 3.4%, respectively.

"This study has shown that the main advantage of cfDNA testing, compared with the combined test, is the substantial reduction in false positive rate. Another major advantage of cfDNA testing is the reporting of results as very high or very low risk, which makes it easier for parents to decide in favor of or against invasive testing," the authors wrote.

A second Ultrasound in Obstetrics & Gynecology study by the group, which included pregnancies undergoing screening at three UK hospitals between March 2006 and May 2012, found that effective first-trimester screening for Down’s syndrome could be achieved by cfDNA testing contingent on the results of the combined test done at 11 to 13 weeks. The strategy detected 98% of cases, and invasive testing was needed for confirmation in less than 0.5% of cases.

"Screening for trisomy 21 by cfDNA testing contingent on the results of an expanded combined test would retain the advantages of the current method of screening, but with a simultaneous major increase in detection rate and decrease in the rate of invasive testing," the authors concluded.
Journal References:

Wolbachia Bacteria Evolved to Infect Stem Cell Niches Through Successive Generations of Their Hosts
June 6, 2013 — Wolbachia are intracellular bacteria that infect invertebrates at pandemic levels, including insects that cause such devastating diseases as Dengue fever, West Nile virus, and malaria. While Wolbachia-based technologies are emerging as promising tools for the control of the insect vectors of these deadly diseases, the processes underlying Wolbachia’s successful propagation within and across species remain elusive.

A new study by Boston University researchers sheds light on some of these processes by providing evidence that a new study by Boston University researchers sheds light on some of these processes by providing evidence that Wolbachia target the ovarian stem cell niches of its hosts—a strategy previously overlooked to explain how Wolbachia thrive in nature. Wolbachia target the ovarian stem cell niches of its hosts—a strategy previously overlooked to explain how Wolbachia thrive in nature.

The study, “Evolutionarily conserved Wolbachia-encoded factors control pattern of stem-cell niche tropism in Drosophila ovaries and favor infection,” has been published in the current issue of PNAS Early Edition.

Although Wolbachia are mainly vertically transmitted (from the parental generation of the species to the offspring), there is also evidence of extensive horizontal transmission (from one individual to another in the same generation). The study shows that both vertical and horizontal transmission occurs through “Because Wolbachia are maternally transmitted, their presence in the germ line is essential for their vertical propagation to the next generation,” says Michelle Toomey, Boston University PhD student who, with Kanchana Panaram, a former postdoctoral fellow in the Frydman Lab at the Department of Biology, are the study’s co-first authors. “However, Wolbachia are often found in several somatic tissues as well, and this distribution varies among different Wolbachia—host associations.”

The study indicates it is easier for Wolbachia to reach the germ line through the stem cell niches during vertical transmission and probably during horizontal transmission as well.

“Wolbachia represent the first reported case of bacteria living in a stem cell niche. The data presented in this study provide the foundation for future methodologies toward the identification of genetic pathways mediating Wolbachia’s stem-cell niche tropism in hosts,” says Horacio Frydman, assistant professor of biology. Understanding the basis of Wolbachia targeting of specific tissues in the host and its consequences toward bacterial transmission will provide further insight into their extremely successful propagation and help identify new Wolbachia-based vector control approaches.

Journal Reference:

Vaccinating Children Against HPV?
June 7, 2013 — The Human papillomavirus, or HPV, and its link to certain cancers has been in the headlines recently, reigniting the debate whether it is appropriate to vaccinate children against the virus.

Both the Centers for Disease Control and Prevention (CDC) and the American College of Pediatrics now recommend that both girls and boys be vaccinated against HPV. Robert I. Haddad, MD, disease center leader of Dana-Farber Cancer Institute’s head and neck oncology program, says the recommendations are well founded. "We are clearly seeing an epidemic of HPV-related head and neck cancer -- the numbers are rising dramatically. HPV is a cause of many cancers, so it is really important to support endeavors to vaccinate."

HPV has more than 100 strains, including HPV-16 and 18, which are aggressive, high-risk, sexually transmitted, and have been linked to certain types of cervical or head and neck cancers.

According to Haddad, HPV infection is a major cause of oropharyngeal cancer, which effects the base of the tongue, the tonsils, and the walls of the pharynx. This year, about 14,000 people in the United States will be diagnosed with oropharyngeal cancer. Most of them will be young , between 40 and 50 years old, and three out of four will be male.
"A decade ago, patients with head and neck cancer were smokers or heavy drinkers. Now, only 20
percent are smokers or drinkers, and the other 80 percent have an oropharynx cancer caused by an HPV
infection," says Haddad.

Because HPV is predominately transmitted through sexual contact, the CDC recommends vaccinating
girls and boys at ages 11 or 12. The vaccine is given in three doses several months apart.

"I advise my patients with HPV-related cancers to vaccinate their children against HPV -- both boys
and girls," says Haddad. "There is a misconception that only girls should be vaccinated and that is the
wrong approach. We strongly believe that both boys and girls should be vaccinated against HPV."

In June 2006, The US Food and Drug Administration approved the use of the vaccine, Gardasil
(Merck), for girls ages 9 to 26. The vaccine protects against four strains of HPV, including HPV-6 and -11,
as well as the high risk strains HPV-16 and 18, which are a known cause of cervical, oropharyngeal, anal,
and vaginal cancers. The CDC followed suit recommending the three dose vaccine become a routine
immunization for girls. Gardasil was licensed for use in boys in October 2009. The CDC voted to approve
it for boys in 2011.

More information can be found on Dana-Farber’s Insight blog post -- Should Boys and Girls Be
Vaccinated Against HPV? (http://blog.dana-farber.org/insight/2013/06/should-boys-and-girls-be-
vaccinated-against-hpv/)

**Gut Bacteria Play Key Role in Vaccination**

June 5, 2013 — The bacteria that live in the human gut may play an important role in immune response to
vaccines and infection by wild-type enteric organisms, according to two recent studies resulting from a
collaborative effort between the University of Maryland School of Medicine Institute for Genome Sciences
and the Center for Vaccine Development. The first study, published online in *PLOS ONE*, examines the
impact of an oral typhoid vaccination on the microbiota, or populations of bacteria, in the human gut. The
second study, also published online in *PLOS ONE* looks in monkeys at the impact in the gut microbiota of
vaccines against Shigella, as well as exposure to wild-type Shigella, another group of bacteria that, like S.
Typhi, gain access to the host via the oral route. These studies find that higher diversity in the gut
microbiota, i.e., more types of bacteria in the gut, affect the characteristics and magnitude of the immune
responses to the vaccines and, in the case of exposure to wild-type Shigella, appear to be more resistant to
infection. This research provides a window into how vaccines and resistance to enteric pathogens work. It
also helps scientists understand more about how the “good” bacteria in the body affect human health, a
growing area of research known as the human microbiome.

"Our research raises the intriguing possibility that the gut microbiota may play an important role in
response to vaccines and susceptibility to enteric pathogens, or bacteria that affect the intestinal tract," says
the senior author on both papers, Claire M. Fraser, Ph.D., Professor of the Departments of Medicine
and Microbiology and Immunology and director of the Institute for Genome Sciences (IGS) at the
University of Maryland School of Medicine. "The results are preliminary and more research is needed. In
future studies, we plan to expand the subject pool and add metagenomic analysis. Metagenomics, also
known as community or environmental genomics, will allow us to look at the function of the gut
microbiota and how it is changing under various vaccination schedules. This research provides a
fascinating window into the human microbiome, and how the bacteria in our bodies impact our health.
Both S. Typhi and Shigella are still devastating to populations in certain parts of the world. We hope that
this work might one day help to provide relief to those areas that still suffer from these diseases."

The first study analyzed the impact of an oral typhoid vaccination with an attenuated Salmonella
enterica serovar Typhi (S. Typhi) on the human gut microbiota. While typhoid is not considered endemic
in Western countries today, it is estimated that there are over 20 million illnesses associated with typhoid
worldwide, particularly in south-central and south-east Asia. Scientists at the Center for Vaccine
Development and other institutions have long been working to develop an improved oral vaccine to
prevent the disease. Differences in the effectiveness of experimental vaccines have been attributed to
heterogeneous immunogenicity among subjects, host genetics, nutrition, socioeconomic status and other
factors. Researching the impact of the composition of intestinal microbiota is a new approach made
possible by state-of-the-art advances in high-throughput sequencing technologies. The cutting edge
facilities at the University of Maryland Institute for Genome Sciences generate huge quantities of data far
more quickly than older technology. Similarly, advanced instrumentation and immunological techniques
at the Center for Vaccine Development have, and continue to provide significant insights into the immune
responses that are likely to correlate with protection.
The typhoid study involved an interdisciplinary team of scientists: experts in infectious diseases, enteric pathogens, microbiology, immunology and genomic analysis. The team found preliminary evidence that the gut microbiota might play a role in how individuals respond to vaccination. The study is noteworthy for its longitudinal analysis, and tracking data across ten discrete time points (pre- to 56 days post-immunization). The scientists found that more diversity in the gut microbiota may enable more robust immune responses to the vaccine.

The second study, also led by this interdisciplinary team at the University of Maryland School of Medicine, similarly found evidence that the diversity of the gut microbiota was related to responsiveness and protection against Shigella dysenteriae 1. The research examined cynomolgus macaques that had been immunized with attenuated Shigella vaccines and/or challenged with wild-type S. dysenteriae 1. The scientists found that those animals that showed high diversity in their gut microbiota were more resistant to Shigella infection than those with lower diversity.

"These studies were performed to evaluate the hypothesis that the gut microbiota composition may impact the response to vaccination or exposure to enteric pathogens in humans and non-human primates. Salmonella and Shigella were chosen because of their great importance to Public Health. Since they gain access to the host when they are ingested, we would expect many factors in the gut microenvironment, including the presence of a defined microbiota, to play a key role in the immune response to vaccination and resistance to infection," says Marcelo B. Sztein, MD, Professor in the Departments of Pediatrics, Medicine and Microbiology and Immunology and Associate Director for Immunologic Studies at the Center for Vaccine Development, University of Maryland School of Medicine. "This area will continue to be a target for our research as we try to learn more about these pathogens, how they affect the body and how we can prevent infection with these sometimes deadly illnesses."

Journal References:

Association of Eumycetoma and Schistosomiasis

Jaap J. van Hellemond, Alieke G. Vonk, Corné de Vogel, Rob Koelewijn, Norbert Vaessen, Ahmed H. Fahal, Alex van Belkum, Wendy W. J. van de Sande mäll

Author Summary

Eumycetoma is a mutilating fungal disease of mainly the foot and is found in (sub)tropical regions such as Sudan. At the moment it is not understood why some people develop eumycetoma and others not. In the regions where eumycetoma is prevalent many other infections are also found. These infections could alter the immune system which makes people more or less susceptible in obtaining another infection. One of the infections with such an effect is Schistosomiasis. In Africa, eumycetoma is found in regions were schistosomiasis is prevalent. In this study we show that eumycetoma patients more often have antibodies against *Schistosoma* species, than healthy controls from the same region. In contrast, eumycetoma patients did not have more often antibodies against *Toxoplasma* species. This might implicate that schistosomiasis predisposes eumycetoma development. If schistosomiasis indeed predisposes eumycetoma development, eradicating *Schistosoma* in a population could also lower the number of eumycetoma cases in that area, which in the end could lead to intervention strategies not only for schistosomiasis but also for eumycetoma.


Sodium Reduction in Populations Insights From the Institute of Medicine Committee

Brian L. Strom, MD, MPH; Cheryl A. M. Anderson, PhD, MPH, MS; Joachim H. Ix, MD, MAS


Published online June 6, 2013

The recent Institute of Medicine (IOM) report regarding dietary sodium has generated considerable interest and debate, as well as misinterpretation by advocates on both sides. Further discussion is necessary to inform the public and the health care community and to inform public health strategies for sodium reduction.
Dietary sodium intake averages approximately 3400 mg/d in US adults, far in excess of the Dietary Guidelines for Americans (DGA) recommendation of less than 2300 mg/d for those older than 2 years and less than 1500 mg/d for certain high-risk subgroups, including African Americans, individuals with hypertension, diabetes, or chronic kidney disease (CKD), or those older than 50 years. In contrast, the 2005 IOM Panel on Dietary Reference Intakes (DRI) for Water, Potassium, Sodium, Chloride, and Sulfate found insufficient evidence to derive a “recommended dietary allowance” for sodium. Instead, an “adequate intake” of 1500 mg/d of dietary sodium was determined, reflecting the minimum needed to achieve a diet adequate in essential nutrients and to cover sweat losses. Additionally, the 2005 IOM panel established a “tolerable upper intake level,” using projections from available data on the effects on blood pressure, that consumption up to 2300 mg/d was unlikely to cause harm.

Based on the strength of the blood pressure data, various US (eg, American Heart Association [AHA]) and international (eg, World Health Organization [WHO]) organizations published recommendations for sodium consumption. Although these recommendations were somewhat different from the DGA, there was general agreement that sodium consumption is excessive worldwide and should be reduced. Despite these recommendations, more than 90% of US adults consume more than 2300 mg of sodium per day, and among the high-risk subgroups more than 98% consume more than 1500 mg of sodium per day.

A substantial body of evidence supports efforts to reduce sodium intake. This evidence links excessive dietary sodium to high blood pressure, stroke, and cardiovascular disease (CVD). However, effects of sodium on blood pressure cannot always be disentangled from effects of total dietary modification, and effects of other electrolytes on blood pressure remain unresolved. Concerns have been raised that a very low sodium intake may adversely affect lipids, insulin resistance, renin, and aldosterone levels and potentially may increase risk of CVD and stroke. Some studies link sodium intakes of less than 1500 mg/d to increased risk of CVD, at least in subpopulations. Thus, debate emerged about the sodium intake target that best improves health outcomes.

In response, the US Centers for Disease Control and Prevention commissioned the IOM to convene an expert committee to examine the designs, methods, and conclusions of literature published since the 2005 DRI report. Specifically, the committee was asked to review and assess potential benefits and adverse outcomes of reducing sodium intake in the population, particularly in the range of 1500 to 2300 mg/d, with emphasis on the high-risk subgroups. The committee was asked to focus on studies of direct health outcomes (vs surrogate end points such as blood pressure), to comment on implications for population-based strategies to reduce sodium intake, and to identify methodologic gaps and ways to address them. The committee’s full report is published elsewhere.

**Sodium And Direct Health Outcomes**

The committee searched literature published through 2012 for relevant publications. Information also was gathered from an open public workshop. Although not its primary emphasis, the committee summarized studies published since 2003 evaluating intermediate markers, particularly blood pressure. Focusing on CVD outcomes, the committee’s assessment of evidence was guided by factors such as study design, quantitative measures of dietary sodium intake, confounder adjustment, and number and consistency of available studies.

**Findings And Conclusions**

**General US Population.** Studies linking dietary sodium intake with direct health outcomes were highly variable in methodological quality; limitations included overreporting or underreporting of sodium intake. However, when considered collectively, the evidence on direct health outcomes indicates a positive relationship between higher levels of sodium intake and risk of CVD, consistent with the known effects of sodium intake on blood pressure. Furthermore, in some studies, the association between sodium and CVD outcomes persisted after adjusting for blood pressure, suggesting that associations between sodium and CVD may be mediated through other factors (eg, effects of other electrolytes) or through pathways other than blood pressure.

Studies evaluating sodium intake in the range of 1500 to 2300 mg/d demonstrate evidence of blood pressure lowering, but no studies have examined sodium intake in that range in the general population and direct CVD outcomes. The committee found that studies on direct health outcomes were of inconsistent quality and insufficient quantity to conclude whether sodium intake of less than 2300 mg/d was associated with either a greater or lesser risk of CVD.

**Population Subgroups.** The committee reviewed multiple randomized trials conducted by a single team that indicated low sodium intake (up to 1840 mg/d) may lead to greater risk of adverse events in patients with heart failure (HF) with reduced ejection fraction who received aggressive therapeutic regimens. Because these therapeutic regimens were different from standard US practice, trials using...
regimens that more closely resemble standard US clinical practice are needed. Of note, due to allegations of duplicate publication in 2 of these trials, a meta-analysis including them was recently retracted, after the IOM report’s completion. Another recently published small randomized trial involving patients with acute decompensated HF showed no benefit on weight or clinical stability from a combination of sodium and fluid restriction.

The committee reviewed 2 related studies in individuals with prehypertension that suggested benefit from lowering sodium intake to 2300 mg/d and perhaps lower, although these studies were based on small numbers of persons with sodium intake in the less than 2300 mg/d range. In contrast, for patients with diabetes, CKD, or preexisting CVD, the committee found no evidence of benefit and some evidence suggesting risk of adverse health outcomes at sodium intake of 1500 to 2300 mg/d. In studies that explored statistical interactions, race, age, hypertension, and diabetes did not modify associations of sodium with health outcomes. The committee concluded that, with the exception of heart failure, evidence of both benefit and harm is not strong enough to indicate that these subgroups should be treated differently from the general US population. Thus, the committee also concluded that evidence on direct health outcomes does not support recommendations to lower sodium intake within these subgroups to or even less than 1500 mg/d.

**Implications For Population-Based Strategies To Gradually Reduce Sodium Intake**

Although not asked to specify targets for dietary sodium, the committee noted factors that precluded establishing these targets. These include lack of consistency in methods for defining sodium intakes at both high and low ends of typical intakes and extreme variability in intake levels across studies. The committee could only consider sodium intake levels within the context of each individual study because there were impediments to calibrating sodium assessment measures across studies.

After release of the IOM report, several news outlets highlighted disagreement among health agencies about targets for dietary sodium intake and reported that experts disagreed about the importance of blood pressure. Focusing the debate on specific targets misses the larger conclusion with which all are in agreement and may hinder implementation of important public health policy. Rather than focusing on disagreements about specific targets that currently affect less than 10% of the US population (ie, sodium intake of <2300 mg/d vs <1500 mg/d), the IOM, AHA, WHO, and DGA are congruent in suggesting that excess sodium intake should be reduced, and this is likely to have significant public health effects. Accomplishing such a reduction will require efforts to decrease sodium in the food environment and provide individual consumers more choice in their dietary consumption of sodium.

**References**


8 Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis [retraction]. heart.bmj.com/content/early/2013/03/12/heartjnl-2012-302337.extract. Accessed May 23, 2013


**Examining the Health Effects of Fructose**

David S. Ludwig, MD, PhD


Published online June 3, 2013

In the 1990s, excessive fat consumption was commonly believed to be the main cause of obesity. High sugar consumption was often considered to be innocuous and possibly protective against obesity by displacing dietary fat. A decade later, the American Heart Association linked intake of added sugars to
weight gain and recommended substantial decreases in consumption to a daily maximum of 100 kcal for women and 150 kcal for men. Some experts now argue that sugar comprises the single most important cause of the worldwide epidemics of obesity and diabetes, primarily through the effects of fructose at prevailing levels of consumption. This Viewpoint examines the physiological effects of common sugars and argues against a narrow public health focus on fructose.

Fructose Vs Glucose
Fructose, a 6-carbon sugar, is more than twice as sweet as its isomer glucose. Most caloric sweeteners contain approximately equal amounts of these 2 sugars, either linked covalently in sucrose (table sugar) or as monosaccharide mixtures in high-fructose corn syrup and honey. Pure glucose, as found in unmodified corn syrup, has relatively little sweetness, and pure fructose may cause malabsorption in some people, limiting its practical use.

Despite chemical similarities, the metabolism of these 2 sugars differs markedly, and this difference underlies recent health concerns. Following consumption, glucose potently stimulates insulin secretion, promoting glycogen synthesis in the liver and glucose uptake by tissues throughout the body. In contrast, fructose does not directly elicit insulin secretion and is taken up almost exclusively by the liver. Moreover, unlike glucose, the metabolism of fructose is not tightly regulated by liver cell energy state. Consequently, fructose rapidly undergoes glycolysis, fueling de novo lipogenesis under some conditions. This newly synthesized lipid may accumulate locally, causing fatty liver and hepatic insulin resistance, or be exported, increasing serum triglycerides, systemic insulin resistance, and fat deposition in adipose tissue. Fructose metabolism may also up-regulate hepatic signal transduction pathways involved in inflammation and drive uric acid production, possibly contributing to hypertension and endothelial dysfunction. Consistent with these mechanisms, feeding studies have demonstrated marked metabolic aberrations—including insulin resistance, dyslipidemia, higher blood pressure, and increased visceral adiposity—among obese individuals consuming fructose compared with glucose.

However, these feeding studies have been criticized for providing unrealistically high amounts of fructose, typically exceeding the 95th percentile of consumption by 50% or more. A recent meta-analysis found no adverse effects of isocaloric substitution of fructose and glucose at average consumption levels for body weight, lipids, blood pressure, uric acid, or insulin levels and found possible benefit for glucose tolerance and glycemic control in diabetes. The monosaccharide feeding studies have also been criticized because humans virtually always consume fructose together with glucose, as in sucrose, high-fructose corn syrup, or honey, not in isolation.

Another argument against fructose having uniquely harmful effects involves the glycemic index, a measure of how food affects blood glucose in the postprandial period. Glucose and most commonly consumed starch foods (all starches are polymers of glucose) have a high glycemic index, whereas fructose has an exceptionally low value. If the effects of fructose on health predominated, and the various forms of glucose were innocuous, then the glycemic index should have a null or inverse association with disease risk. However, systematic reviews and meta-analyses have linked a high glycemic index diet to the same adverse effects as fructose, including obesity and diabetes.

In light of these considerations, a critical scientific question is whether replacement of fructose-containing sweeteners at prevailing consumption levels with glucose (as a monosaccharide or as starch) would provide health benefits. If so, a specific public health focus on fructose may be warranted. If not, then broader measures targeting all highly processed carbohydrate foods would be indicated. However, no modern controlled feeding studies adequately address this question, but research dating back to the 1970s is informative. In 1 study, 9 men and women, aged 37 to 62 years, living in a metabolic ward consumed a high-sugar diet (containing 70% of carbohydrate as sucrose, an average of about 675 kcal/d) or a sucrose-free diet (containing wheat and potato starch), each for 4 weeks. Upon repeated measurements, fasting blood glucose was slightly higher (3 mg/dL) for the sucrose condition but no differences between diets were found in body weight, glucose tolerance, fasting and stimulated insulin, cholesterol, triglycerides, or nonesterified fatty acids.

Digestion Rate, Not Dose
Fruit is the primary natural source of fructose. Most fruits have about 10 g of fructose, as monosaccharide or sucrose, per 80-kcal serving, comprising at least half the total sugar content. If fructose were toxic at high dosage, then individuals consuming large amounts of fruit might experience adverse effects. However, observational studies report inverse associations between fruit consumption and body weight or risk of obesity-associated diseases, with no evident upper threshold for protection, although some studies do not adequately distinguish between fruits and vegetables.
In possibly the only interventional study of its kind, 17 Bantu and white adults in South Africa, aged 20 to 64 years, consuming a Western diet were instructed to eat primarily fruit (20 servings per day for the typical participant) supplemented with nuts to satisfy basic macronutrient requirements. Despite the extraordinarily high fructose content of this diet, presumably about 200 g/d, the investigators reported no adverse effects (and possible benefit) for body weight, blood pressure, and insulin and lipid levels after 12 to 24 weeks. Nevertheless, findings from this study must be interpreted cautiously because of important design limitations, including lack of an active control group.

The absence of harm from high fruit consumption likely relates to the slow digestion rate of whole fruit compared for example with a sugar-sweetened beverage, producing portal fructose concentrations that do not exceed hepatic metabolic capacity. Although soluble fiber helps to reduce sugar absorption rates from the digestive tract (primarily by increasing luminal viscosity), the physical form and cellular structure of whole fruit probably have a greater effect, by sequestering sugar away from the absorptive surface of the small intestine. In addition, the high micronutrient and antioxidant content of fruit may protect against hepatic inflammation and systemic insulin resistance.

**Conclusions**

Few modern studies have compared the long-term effects of glucose, fructose, and starch under physiologically relevant condition, and such research should assume high priority. The available evidence suggests 3 key points. First, fructose in its primary natural form (whole fruit) is not associated with adverse effects up to the limits of human consumption. Second, excessive intake of refined sugar plays a significant role in the epidemics of obesity and related diseases, in part because large amounts of rapidly absorbed fructose can overwhelm hepatic biochemical pathways. Third, rapidly absorbed forms of glucose—present in both sugar and high glycemic index starch—also contribute importantly to these diseases, especially considering their much greater caloric contribution to typical diets than fructose. Therefore, the recommendation to replace fructose with glucose lacks an evidence basis. Rather, public health efforts should focus on reducing intakes of all highly processed carbohydrates, not just refined sugar.

**References**


**Perspective**

**How AIDS Invented Global Health**

Allan M. Brandt, Ph.D.


Over the past half-century, historians have used episodes of epidemic disease to investigate scientific, social, and cultural change. Underlying this approach is the recognition that disease, and especially responses to epidemics, offers fundamental insights into scientific and medical practices, as well as social and cultural values. As historian Charles Rosenberg wrote, “disease necessarily reflects and lays bare every aspect of the culture in which it occurs.”

Many historians would consider it premature to write the history of the HIV epidemic. After all, more than 34 million people are currently infected with HIV. Even today, with long-standing public health campaigns and highly active antiretroviral therapy (HAART), HIV remains a major contributor to the
burden of disease in many countries. As Piot and Quinn indicate in this issue of the *Journal* (pages 2210–2218), combating the epidemic remains a test of our expanding knowledge and vigilance. Nonetheless, the progress made in addressing this pandemic and its effects on science, medicine, and public health have been far-reaching (see timeline ). The changes wrought by HIV have not only affected the course of the epidemic: they have had powerful effects on research and science, clinical practices, and broader policy. AIDS has reshaped conventional wisdoms in public health, research practice, cultural attitudes, and social behaviors. Most notably, the AIDS epidemic has provided the foundation for a revolution that upended traditional approaches to “international health,” replacing them with innovative global approaches to disease. Indeed, the HIV epidemic and the responses it generated have been crucial forces in “inventing” the new “global health.”

This epidemic disrupted the traditional boundaries between public health and clinical medicine, especially the divide between disease prevention and treatment. In the 1980s, before the advent of antiretroviral therapies, public health officials focused on controlling social and behavioral risk factors; prevention was seen as the only hope. But new treatments have eroded this distinction and the historical divide between public health and clinical care. Clinical trials have shown that early treatment benefits infected patients not only by dramatically extending life expectancy, but by significantly reducing the risk of transmission to their uninfected sexual partners. Essential medicines benefit both patients and populations, providing a critical tool for reducing fundamental health disparities. This insight has encouraged the integration of approaches to prevention and treatment, in addition to behavioral change and adherence.

The rapid development of effective antiretroviral treatments, in turn, could not have occurred without new forms of disease advocacy and activism. Previous disease activism, for example, had established important campaigns supporting tuberculosis control, cancer research, and the rights of patients with mental illness. But AIDS activists explicitly crossed a vast chasm of expertise. They went to Food and Drug Administration meetings and events steeped in the often-arcane science of HIV, prepared to offer concrete proposals to speed research, reformulate trials, and accelerate regulatory processes. This approach went well beyond the traditional bioethical formulations of autonomy and consent. As many clinicians and scientists acknowledged, AIDS activists, including many people with AIDS, served as collaborators and colleagues rather than constituents and subjects, changing the trajectory of research and treatment. These new models of disease activism, enshrined in the Denver Principles (1983), which demanded involvement “at every level of decision-making,” have spurred new strategies among many activists focused on other diseases. By the early 2000s, AIDS activists had forged important transnational alliances and activities, establishing a critical aspect of the “new” global health.

Furthermore, HIV triggered important new commitments in the funding of health care, particularly in developing countries. With the advent of HAART and widening recognition of HIV’s potential effect on the fragile progress of development in resource-poor settings, HIV spurred substantial increases in funding from sources such as the World Bank. The growing concern in the United Nations and elsewhere that the epidemic posed an important risk to global “security” elicited new funding from donor countries, ultimately resulting in the establishment of the Global Fund to Fight AIDS, Tuberculosis, and Malaria. In 2003, it was joined by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), which, with bipartisan support, initially pledged $15 billion over 5 years. Since PEPFAR’s inception, Congress has allocated more than $46 billion for treatment, infrastructure, and partnerships that have contributed to a 25% reduction in new infections in sub-Saharan Africa.

HIV has also attracted remarkable levels of private philanthropy, most notably from the Bill and Melinda Gates Foundation. HIV funding led to new public–private partnerships that have become a model for funding of scientific investigation, global health initiatives, and building of crucial health care delivery infrastructure in developing countries. These funding programs have fomented contentious debates about priorities, efficiency, allocation processes, and broader strategies for preventing and treating many diseases, especially in poorer countries. Nonetheless, they offered new approaches to identifying critical resources and evaluating their effect on the burden of disease. The success of future efforts will depend on maintaining and expanding essential funding during a period of global economic recession, as well as new strategies for evaluating the efficacy of varied interventions.
AIDS also spurred another related debate that continues to roil global health — about the cost of essential medicines. Accessibility of effective and preventive treatments has relied on the availability of reduced-cost drugs and their generic equivalents. A recent decision by the Indian Supreme Court upheld India’s right to produce inexpensive generics, despite the multinational pharmaceutical industry’s claims for stronger recognition of patents.

Another central aspect of the new activism was an insistence that the AIDS epidemic demanded the recognition of basic human rights. Early on, lawyers, bioethicists, and policymakers debated the conditions under which traditional civil liberties could be abrogated to protect the public from the threat of infection. Such formulations reflected traditional approaches to public health and the “police powers” of the state, including mandatory testing, isolation, detention, and quarantine. Given the stigma attached to HIV infection at the time, as well as ungrounded fears of casual transmission, affected people often suffered the double jeopardy of disease and discrimination. As a result, Jonathan Mann, the first director of the World Health Organization’s Global Program on AIDS, explained, “To the extent that we exclude AIDS infected persons from society, we endanger society, while to the extent that we maintain AIDS infected persons within society, we protect society. This is the message of realism and of tolerance.” Mann argued that HIV could never be successfully addressed if impositions on human rights led people to hide their infections rather than seek testing and treatment. Only policy approaches that recognized and protected human rights (including the rights to treatment and care, gender equality, and education) would permit successful clinical and population-based interventions.

These complementary innovations are at the core of what we now call “global health” — which has demonstrated its capacity to be far more integrative than traditional notions of international health. It draws together scientists, clinicians, public health officials, researchers, and patients, while relying on new sources of funding, expertise, and advocacy. This new formulation is distinct, first of all, in that it recognizes the essential supranational character of problems of disease and their amelioration and the fact that no individual country can adequately address diseases in the face of the movement of people, trade, microbes, and risks. Second, it focuses on deeper knowledge of the burden of disease to identify key health disparities and develop strategies for their reduction. Third, it recognizes that people affected by disease have a crucial role in the discovery and advocacy of new modes of treatment and prevention and their equitable access. Finally, it is based on ethical and moral values that recognize that equity and rights are central to the larger goals of preventing and treating diseases worldwide.

For more than the past decade, major academic medical centers, schools of public health, and universities have created global health programs and related institutes for multidisciplinary research and education. Thus, the institutionalization of this formulation is not only affecting services worldwide, but also changing the training of physicians, other health professionals, and students of public health. When the history of the HIV epidemic is eventually written, it will be important to recognize that without this epidemic there would be no global health movement as we know it today.

May 23, 2013
New Danish results spark interest for future HIV cure research
As mentioned in our previous CATIE News story, Danish scientists have been studying potential ways of curing HIV infection with the experimental cancer drug panobinostat. Interim results of their clinical trial of this drug will be presented later this year at an international conference. In the meantime, Danish scientists have also been doing some other interesting cure research that may have gone underappreciated. This other research is the focus of this CATIE News story. Before getting into the details of their work, a bit of background is necessary.

A lesson from history
In the late 1800s, New York surgeon William Coley began experiments to assess the impact of inducing bacterial infections on the course of certain cancers in people. Specifically, he deliberately caused serious skin infections with Streptococcus and later other bacteria. This idea was based on observation that some patients with cancer experienced unexpected remission of their disease when they also developed certain bacterial infections. However, the consequences of serious bacterial infections in the pre-antibiotic era could be dangerous. Eventually Dr. Coley and colleagues used injections of heat-killed bacteria (a mixture known as Coley’s toxins). This resulted in limited success in carefully selected patients with certain cancers. Bear in mind that clinical trials in that era were not underpinned by rigorous statistics and they generally lacked a randomized, controlled design.
Side effects
The initial effect of the therapy was to cause symptoms of a severe flu-like illness. Within an hour of injection of the vaccine, patients experienced severe but temporary chills, followed by a high fever. These and other symptoms cleared within 12 to 24 hours after injection. Some patients were given daily therapy with this vaccine, others received it every other day for weeks or months and then the administration was gradually reduced and ended, depending on the response of the cancer.

Researchers in the late 20th century suspected that these bacterial vaccines worked by stimulating the body to produce a mix of chemical messengers, called cytokines, which alerted the immune system to the presence of cancer. Furthermore, these cytokines also strengthened the ability of cells of the immune system to destroy some cancers.

Weakened strains of bacteria
After Dr. Coley’s death, general interest in his bacterial vaccines waned. Today, some scientists are aware of the potential of Dr. Coley’s work. Bacterial extracts are now used as part of the treatment for some cases of bladder cancer. In this instance, doctors use weakened strains of bacteria related to those that cause TB (tuberculosis). The strain of bacteria used is called BCG. This works by stimulating the immune system resident in the bladder and helping it attack this cancer. BCG is also used to make a vaccine to prevent TB. However, this vaccine is not highly effective at preventing TB and is seldom used in high-income countries today.

In the 1980s, Japanese researchers working with BCG found that exposing cells of the immune system to bacterial DNA improved their ability to attack cancerous tissue. In the 1990s, doctors in Japan conducted a clinical trial of bacterial DNA to treat patients with cancer. Their overall results were promising, with 43% of 75 patients demonstrating a response. However, due to the difficulty of creating uniform and safe concentrations of extracts of DNA derived from BCG, the Japanese Ministry of Health and Welfare rejected a request to license such therapy.

Pattern recognition
In the mid-1990s, physician-investigator Arthur Krieg, MD, and other scientists were trying to understand precisely how bacterial extracts, such as those used by Dr. Coley, could have such a profound impact on the immune system and cancer cells. In experiments in the lab, scientists exposed cells of the immune system to tiny pieces of nucleic acids (strips of DNA) arising from bacterial infections. This exposure to bacterial nucleic acids caused cells to produce a protective immune response. Further research found that a segment of the tiny pieces of nucleic acid were common to many bacteria and triggered a protective response by the immune system when it encountered different species of bacteria. This occurred because the immune system recognized a pattern in the nucleic acid of bacteria via specialized receptors. These receptors are called TLRs (toll-like receptors).

Recognizing viruses and cancer
TLRs act as part of the body’s warning system for invasion by germs. Different TLRs serve to recognize different patterns in different types of germs. One type of TLR called TLR9 is particularly important. Researchers have found that TLR9 plays a role in helping the immune system sense viral infections such as HIV, HBV (hepatitis B virus) and HPV (human papilloma virus). All three viruses can cause varying degrees of immune dysfunction in people and have been associated with an increased risk for the development of different cancers. Furthermore, these particular viral infections weaken the ability of TLR9 to alert the immune system to the presence of viruses and tumours. Partly as a result of weakened TLR9 activity, and likely other immunologic dysfunction associated with these viral infections, the immune system is not able to contain and eradicate these viruses and the tumours they cause.

CpG—A refined approach
As mentioned earlier, exposure to bacterial extracts such as Coley’s toxins can cause unpleasant symptoms. A more refined approach to eliciting a protective immune response uses artificially created strings of DNA that mimic patterns found in bacterial and viral DNA. These artificial strings of nucleic acids are called CpG.

Researchers in several countries have tested the general safety and preliminary effectiveness of CpG 7909 (also known as agatolimod, PF-3512676, ProMune). This compound interacts with TLR9 and appears to boost its function, activating the immune system to better sense and fight viral infections and possibly some tumours. Several clinical trials have been done with CpG 7909 in HIV-negative patients with cancer. Several small clinical trials and two large phase III clinical trials (enrolling a total of about 1,600 patients with advanced lung cancer receiving chemotherapy) have been performed with CpG 7909 in HIV-negative patients. In these trials the drug appeared to be generally safe; however, there appeared to be limited anti-cancer effect.
CpG 7909—Tested in HIV-positive volunteers in Canada
In the past decade, a team of scientists at the Ottawa Hospital Research Institute tested CpG 7909 in HIV-positive people. In their experiments, the researchers used very small doses of this CpG together with a hepatitis B vaccine. The team found that this compound, when combined with the vaccine, increased the immune system’s response to the vaccine and this response lasted a long time. The use of CpG 7909 was generally safe, with side effects (redness and swelling at the injection site) being temporary.

The new Danish study
Several years ago, a team of researchers at Aarhus University in Denmark conducted a randomized, placebo-controlled study to compare the effect of a pneumonia vaccine with or without CpG 7909 in 97 HIV-positive people who were taking combination anti-HIV therapy (commonly called ART or HAART). In this study, repeated injections of 1 mg of CpG 7909 at the start and in the third and ninth months of the trial significantly increased the immune response to the vaccine.

However, the Danish team did some additional research. After the study was completed they reanalyzed stored blood samples from a subset of participants. The purpose of this reanalysis was to assess the impact that exposure to CpG 7909 may have had on the proportion of HIV-infected cells in the blood. The reason for this investigation was that laboratory studies done several years before with cells and HIV found that several CpGs had the ability to both stimulate HIV replication from resting infected cells and to interfere with HIV’s ability to cause new infections.

The team found that the proportion of HIV-infected cells fell by 12% after each injection of CpG. This finding suggests that regular exposure to CpG 7909 can reduce the burden of HIV-infected cells in the body. This burden is called the “reservoir” by scientists and, in theory, a smaller reservoir should make curing HIV ultimately easier over the long term. However, separate clinical trials will be needed to assess this possibility, as none of the participants who received CpG injections were cured.

In contrast, among participants who received placebo, the proportion of HIV-infected cells remained about the same. Furthermore, participants who received injections of CpG appeared to have killer T-cells (called CD8+ cells) with increased anti-HIV activity. There was no detectable increase in HIV antibodies in participants.

According to the researchers, CpG 7909 was “generally well tolerated,” with mild side effects at the injection site (pain, swelling, redness, bruising). In some cases there were also temporary flu-like symptoms (such as fever, joint pain, chills and fatigue) and in 76% of participants, these were judged to be of “moderate to severe” intensity. Exposure to CpG did not reduce CD4+ cell counts. In some cases, there were very small and temporary increases in HIV viral load. But no participant had their viral load become detectable (that is, rise above the 50 copies/ml mark) for more than two consecutive blood tests. Further analyses found that CpG 7909 did not cause any toxicity to major organ-systems such as the bone marrow, liver or kidneys.

Caution needed
The results from the Danish reanalysis are modest yet promising. However, they need to be interpreted cautiously, at least for the following reasons:

• Reanalyzing data from a study designed for a different purpose can, at best, yield interesting results. However, such reanalysis cannot produce definitive results. The findings from the Danish study can be used to design a clinical trial to assess the impact of CpG 7909 on changes in the proportion of HIV-infected cells, perhaps with more participants and over a longer period.

• The reanalysis had additional gaps: The study was not formally designed to assess the impact on the immune system’s ability to detect and destroy HIV-infected cells. Therefore, the scientists are not certain how repeated exposure to CpG 7909 apparently reduced the burden of HIV-infected cells.

What is clear is that no one has yet been cured of HIV by repeated exposure to CpG 7909 over a period of 10 months. Also, such a cure—with this or any other therapy—is not imminent. Rather, much more study is required of this exciting compound, perhaps in combination with other experimental drugs in HIV-positive people who are taking ART.

Problems with access to CpG 7909
CpG 7909 was developed by the Coley Pharmaceutical Group, which was then acquired by the pharmaceutical company Pfizer in 2011, along with all of the rights for commercially testing and using CpG 7909 in people. Pfizer is developing a new CpG molecule that recently entered clinical trials, but they have not been providing this to outside groups for testing. CpG 7909 is in cancer vaccines being developed by GlaxoSmithKline as well as in several other cancer vaccines being developed by university-based scientists. Although clinical trials with CpG 7909 are ongoing in HIV-negative people, Pfizer has not
continued Coley’s policy of providing the compound to academic researchers for their research. Until this situation changes, it is not likely that CpG 7909 will be tested in clinical trials in HIV-positive people.

**Not giving up**

Although the Danish scientists cannot currently access CpGs for clinical trials in people, they are not giving up on cure research. They have at least another approach to a potential cure for HIV. In collaboration with other scientists in Australia, Sweden and the United States, they are testing a drug that will hopefully help to drive HIV out of hiding. This approach has the potential to reduce the burden of HIV-infected cells in the body and make future attempts at a cure perhaps easier. The drug being tested is an experimental cancer therapy called panobinostat, made by the pharmaceutical company Novartis. Panobinostat belongs to a class of drugs called HDAC inhibitors. Interim results from their study of panobinostat will be released later this year. To find out more about HDAC inhibitors and their potential and challenges for curing HIV, see *TreatmentUpdate 196*.

**Cure research in context**

The journey toward a cure will not be easy and many challenges lie ahead. Some of the challenges are known, others may only become known as experiments proceed. As with any great scientific endeavour, there will be setbacks. The initial wave of cure research experiments over the next five to 10 years should be viewed as exploratory and their results highly preliminary. This research will seek to answer important scientific questions that can then be used to build a foundation toward a cure. In the meantime, research funding agencies need to show patience and sustained funding as hardworking scientists struggle against the many challenges that lie in their path as they search for avenues to explore in the quest for an HIV cure.

—Sean R. Hosein

**Acknowledgement**

We thank Ole Søgaard, MD, and colleagues at Aarhus University, Denmark, and Arthur Krieg MD, RaNA Therapeutics, Cambridge, Massachusetts, for their helpful comments, research assistance and expert review.

**References:**

Low CD4 cell count increases the risk of several cancers after starting HIV therapy

Michael Carter
Published: 12 June 2013

A large US study has provided important new insights into the incidence and timing of cancers among people taking antiretroviral therapy. Published in the online edition of Clinical Infectious Diseases, the study showed that incidence of AIDS-defining cancers was highest in the six months after starting HIV therapy and then fell dramatically.

In contrast, after the first year of HIV treatment, annual rates of non-AIDS defining cancers increased by approximately 7%, an increase attributed to ageing. A lower CD4 cell count at the time antiretroviral treatment was started was a risk factor for several cancers.

The investigators believe their findings show the importance of early antiretroviral therapy and the integration of "aggressive" cancer screening into routine HIV care.

Cancers are an important cause of serious illness and death in people living with HIV. However, the timing and incidence of malignancies after starting antiretroviral therapy has received little attention.

A team of investigators in the United States therefore examined the records of approximately 11,500 people who started triple-drug HIV therapy between 1996 and 2011. Trends in cancer incidence were monitored for up to ten years after treatment initiation. The investigators also sought to identify factors associated with a cancer diagnosis.

The investigators divided cancers into several categories: AIDS-defining cancers (Kaposi’s sarcoma, non-Hodgkin’s lymphoma and cervical cancer); non-AIDS-defining cancers; lymphomas; cancers related to human papillomavirus (HPV); other virus-related cancers; and virus-unrelated cancers.

The patients were racially diverse and overwhelmingly male (80%). The median age for starting antiretroviral therapy was 38 years. Most people were immuno suppressed when they started treatment, median CD4 cell count being just 202 cells/mm³. The majority of people (47%) started treatment with a regimen based on a protease inhibitor and 42% started treatment with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combination.

Patients were followed for a median of three years and 10% of patients contributed ten years of follow-up.

There were 457 cancer diagnoses during 46,318 person-years of follow-up. This provided an incidence rate of 987 cases per 100,000 person-years.

Overall incidence of AIDS-defining cancers was similar to the incidence rate for non-AIDS-defining cancers (515 vs 466 per 100,000 person-years).

Kaposi’s sarcoma was the most common AIDS-defining cancer, with an incidence rate of 304 cases per 100,000 person-years. The most common non-AIDS-defining malignancy was anal cancer (69 cases per 100,000 person-years). Among women, the most common non-AIDS cancer was breast cancer (128 cases per 100,000 person-years).

The timing of cancer diagnosis varied according to whether the malignancy was AIDS-defining or non-HIV-related.

Incidence of Kaposi’s sarcoma was especially high in the first six months after HIV therapy was started (1342 cases per 100,000 person-years). Incidence then fell dramatically during the second six months of therapy (348 cases per 100,000 person-years). Incidence of the cancer then remained at low rates throughout the rest of follow-up (164 cases per 100,000 person-years).

A similar trend was observed for lymphomas (both non-Hodgkin and Hodgkin). Incidence was highest in the first six months after treatment initiation (660 cases per 100,000 person-years) and then fell sharply in the next six months (260 cases per 100,000 person-years).

In contrast, incidence of all non-AIDS-defining cancers increased with longer duration of follow-up. The increase was 7% for each additional year of treatment. Incidence climbed from 416 cases per 100,000 person-years after the first year of therapy to 615 cases per 100,000 person-years after ten years of treatment.

"This increase is likely a consequence of increasing cancer incidence with advancing age, as noted in the general population", write the authors.

Each ten-year increase in age was associated with a doubling in the risk of non-lymphoma cancers and HPV-related cancers (adjusted HR = 2.33; 95% CI, 1.97-2.74).

CD4 cell count at the time HIV therapy was started was also associated with subsequent cancer risk.
Immune suppression at the time of treatment initiation was an especially strong predictor of Kaposi’s sarcoma. The pattern of a high incidence of this malignancy in the first six months of treatment followed by a steep decline was seen only in people with a baseline CD4 cell count below 200 cells/mm$^3$ ($p = 0.002$). People with a CD4 cell count above this level when they started therapy had a low incidence of Kaposi’s sarcoma throughout follow-up.

A low CD4 cell count was also associated with the development of lymphomas and diagnosis with HPV-related cancers.

The investigators found no evidence that overall cancer incidence declined over time, therefore suggesting "incremental improvements in antiretroviral therapy during the modern antiretroviral therapy era have not had dramatic effects on cancer incidence". They believe this finding "emphasizes the continued need for cancer screening and prevention measures in the HIV population...for instance increased HPV vaccination and anal pap smear screening may help prevent anal cancer, one of the most common malignancies in this population."

The authors also believe their study further supports efforts to reduce rates of late HIV diagnosis.

**Reference**


**Drug Policies Fuel Deadly Hepatitis C Epidemic**

*Human Rights Watch* (05.30.2013)

Based on a Global Commission on Drug Policy report, the global advocacy organization Human Rights Watch urged governments around the world to reform drug control policies that resulted in increased risk of hepatitis C for injecting drug users. The commission released the report prior to the 23rd International Harm Reduction Conference held June 9–12 in Vilnius, Lithuania, which borders Eastern European and Central Asian regions that are home to the "world’s fastest growing hepatitis C and HIV epidemics."

The report stated that instead of reducing the supply of illegal drugs, "repressive drug policies" encouraged organized crime, violence, and jailing of drug users, and created the potential for a worldwide hepatitis C epidemic. The report noted that punitive laws deterred drug users from obtaining sterile syringes and from seeking drug treatment and health services. Incarcerated drug users often continued using drugs and spreading HIV and hepatitis C since prisons seldom offered prevention and treatment.

Instead of the current law enforcement policies, the report recommended that nations redirect funding toward public health approaches that “maximize” hepatitis C prevention and treatment. Drug users rarely had access to comprehensive, integrated harm reduction services that could lower hepatitis C and HIV rates and prevent coinfection. Elements of harm reduction included patient education, opioid substitution therapy, sterile syringes, testing, and treatment. Human Rights Watch reported that more than 60 percent of injection drug users (10 million) had hepatitis C, and most of the 3 million HIV-infected drug users—more than 90 percent in some countries—also had hepatitis C. Coinfection with hepatitis C complicates HIV treatment, but studies have shown that hepatitis C treatment increased adherence to HIV treatment among drug users.

The full report, "The Negative Impact of the War on Drugs on Public Health: The Hidden Hepatitis C Epidemic," was published online at http://www.globalcommissionondrugs.org/hepatitis/.

**The 'Elastic Band' Circumcision Device that could Reduce HIV Infection Rate by 60%**

*Daily Mail (London)* (06.03.2013) By Emma Innes

The World Health Organization has approved the PrePex circumcision device, a new nonsurgical method of male circumcision that uses an elastic band. The technique did not involve general anesthesia and was believed to be safer than surgery. The New York Times reported that nurses could insert the disposable device in approximately four minutes. The device did not require sterile conditions, was inexpensive compared to surgery, and was easy to ship and store. The manufacturer claimed the technique involved no needles or blood loss, and the patient could return to his daily routine immediately. The procedure did not require stitches or sutures. Expectations were that PrePex would slow the spread of HIV in sub-Saharan Africa, because circumcised males were approximately 60 percent less likely to become infected.

**Saliva proteins may protect older people from influenza**

Spit. Drool. Dribble. Saliva is not normally a topic of polite conversation, but it may be the key to explaining the age and sex bias exhibited by influenza and other diseases, according to a new study.
Published in ACS' Journal of Proteome Research, it provides new insights into why older people were better able to fight off the new strains of "bird" flu and "swine" flu than younger people. Zheng Li and colleagues explain that saliva does more than start the process of digesting certain foods. Saliva also contains germ-fighting proteins that are a first-line defense against infections. Scientists already knew that levels of certain glycoproteins — proteins with a sugar coating that combat disease-causing microbes — differ with age. Li's team took a closer look at how those differences affected vulnerability to influenza.

Their tests of 180 saliva samples from men and women of various ages suggested that seniors, who fought off the bird flu better than the younger groups, might thank their saliva. Glycoproteins in saliva of people age 65 and over were more efficient in binding to influenza than those in children and young adults. The research "may provide useful information to help understand some age-related diseases and physiological phenomenon specific to women or men, and inspire new ideas for prevention and diagnosis of the diseases by considering the individual conditions based primarily on the salivary analysis," the scientists state.

University of Toronto breakthrough allows fast, reliable pathogen identification

TORONTO, ON – Life-threatening bacterial infections cause tens of thousands of deaths every year in North America. Increasingly, many infections are resistant to first-line antibiotics. Unfortunately, current methods of culturing bacteria in the lab can take days to report the specific source of the infection, and even longer to pinpoint the right antibiotic that will clear the infection. There remains an urgent, unmet need for technologies that can allow bacterial infections to be rapidly and specifically diagnosed.

Researchers from the University of Toronto have created an electronic chip with record-breaking speed that can analyze samples for panels of infectious bacteria. The new technology can report the identity of the pathogen in a matter of minutes, and looks for many different bacteria and drug resistance markers in parallel, allowing rapid and specific identification of infectious agents. The advance was reported this month in the journal Nature Communications.

"Overuse of antibiotics is driving the continued emergence of drug-resistant bacteria," said Shana Kelley (Pharmacy and Biochemistry), a senior author of the study. "A chief reason for use of ineffective or inappropriate antibiotics is the lack of a technology that rapidly offers physicians detailed information about the specific cause of the infection."

The researchers developed an integrated circuit that could detect bacteria at concentrations found in samples, along with whether the pathogen possessed drug resistance," explained Chemistry Ph.D. student Brian Lam, the first author of the study.

One key to the advance was the design of an integrated circuit that could accommodate a panel of many biomarkers. "The team discovered how to use the liquids in which biological samples are immersed as a 'switch' — allowing us to look separately for each biomarker in the sample in turn," said Ted Sargent (Electrical and Computer Engineering), the other senior author of the report.

"The solution-based circuit chip rapidly and identifies and determines the antibiotic resistance of multiple pathogens — this represents a significant advance in biomolecular sensing," said Paul S. Weiss, Kavli Chair in NanoSystems Science and Director of the California NanoSystems Institute at UCLA.

Ihor Boszko, Director of Business Development at Xagenic, a Toronto-based in vitro diagnostics company said the breakthrough could have significant practical implications. "This kind of highly sensitive, enzyme-free electrochemical detection technology will have tremendous utility for near patient clinical diagnostics. Multiplexing of in vitro diagnostic approach adds the capability of simultaneously testing for multiple viruses or bacteria that produce similar clinical symptoms. It also allows for simple and cost effective manufacturing of highly multiplexed electrochemical detectors, which will certainly have a significant impact on the availability of effective diagnostic tools."

Other authors of the paper were Jagotamoy Das (Chemistry), Richard Holmes (Pharmacy) and Ludovic Live and Andrew Sage (Institute of Biomaterials & Biomedical Engineering). The paper, "Solution-based circuits enable rapid and multiplexed pathogen detection," can be found at http://www.nature.com/ncomms/2013/130612/ncomms3001/full/ncomms3001.html.

Chlamydia Protein Has an Odd Structure, Scientists Find

June 11, 2013 — A protein secreted by the chlamydia bug has a very unusual structure, according to scientists in the School of Medicine at The University of Texas Health Science Center San Antonio. The
discovery of the protein's shape could lead to novel strategies for diagnosing and treating chlamydia, a sexually transmitted disease that infects an estimated 2.8 million people in the U.S. each year.

The protein, Pgp3, is secreted by *Chlamydia trachomatis*, the bacterium that causes chlamydia. Pgp3's shape is very distinguishable -- sort of like an Eiffel Tower of proteins. "From a structural standpoint, the protein is very odd indeed," said X-ray crystallographer P. John Hart, Ph.D., the Ewing Halsell President's Council Distinguished Chair in the Department of Biochemistry at the San Antonio medical school. "This long and slender molecule contains a fusion of structural motifs that resemble those typically found in viral and not bacterial proteins." Dr. Hart is co-lead author of the research, which is described in the *Journal of Biological Chemistry* (JBC).

The Pgp3 protein is a chlamydial virulence factor that is hypothesized to enhance the bug's ability to initially infect its human host and then evade host defenses. "Although my lab has worked on this protein for many years and gained a great deal of knowledge on it, we still don't know what roles it may play in chlamydial pathogenesis (disease development)," said co-lead author Guangming Zhong, M.D., Ph.D., professor of microbiology at the Health Science Center. "With the structural information uncovered in this paper, we can now test many hypotheses."

This is the second chlamydial virulence factor that Dr. Zhong's laboratory has identified; the first was a protein called CPAF. Structural studies have played an important role in understanding CPAF's functions in chlamydial infections, Dr. Zhong said.

**Chlamydia's toll**

According to the U.S. Centers for Disease Control and Prevention (CDC), more than 1.4 million new cases of chlamydia were reported in 2011 across the 50 states and the District of Columbia. But the CDC says as many cases go unreported because most people with chlamydia have no symptoms and do not seek testing. If left untreated, chlamydia can permanently damage a woman's reproductive system. This can lead to ectopic pregnancy, pelvic inflammatory disease and infertility.

The disease burden of chlamydia worldwide is magnitudes greater, with new cases numbering in the dozens of millions per year. The World Health Organization estimates that 499 million new cases occur annually of four curable sexually transmitted diseases -- chlamydia, syphilis, gonorrhea and trichomoniasis. This estimate is for cases in adults aged 15-49.

Chlamydia infection induces inflammatory pathology in humans, and Pgp3 may contribute to the pathology by activating inflammation via one of its structural features uncovered in the crystal structure, said Dr. Zhong, who has worked with Dr. Hart on the Pgp3 project for nearly four years.

**Journal Reference:**

**Why Fruit Ripens and Spoils: Thousands of Plant Genes Activated by Ethylene Gas**
June 11, 2013 — It's common wisdom that one rotten apple in a barrel spoils all the other apples, and that an apple ripens a green banana if they are put together in a paper bag. Ways to ripen, or spoil, fruit have been known for thousands of years -- as the Bible can attest -- but now the genes underlying these phenomena of nature have been revealed.

In the online journal eLIFE, a large international group of scientists, led by investigators at the Salk Institute for Biological Studies, have traced the thousands of genes in a plant that are activated once ethylene, a gas that acts as a plant growth hormone, is released.

This study, the first such comprehensive genomic analysis of ethylene's biological trigger, may lead to powerful practical applications, the researchers say. Ethylene not only helps ripen fruit, it also regulates growth and helps defends a plant against pathogens, among a variety of other functions.

Teasing out the specific genes that perform each of these discrete functions from the many genes found to be activated by ethylene might allow scientists to produce plant strains that slow down growth when needed, accelerate or prevent ripening, retard rotting or make plants more resistant to disease, says the senior investigator, Joseph R. Ecker, head of Salk's Plant Molecular and Cellular Biology Laboratory.

"Now that we know the genes that ethylene ultimately activates, we will be able to identify the key genes and proteins involved in each of these branch pathways, and this might help us manipulate the discrete functions this hormone regulates," Ecker says.

By all accounts, it took a Herculean effort to decode the genetic pathways that ethylene activates -- one that involved four institutions and 19 researchers, many of whom normally work in human biology. For example, Ecker invited the expertise of Carnegie Mellon University computer scientist Ziv Bar-Joseph, transcriptional expert Timothy Hughes from the University of Toronto, as well as computational biologist Trey Ideker and genomicist Bing Ren from the University of California, San Diego.

The study also represents a milestone for Ecker, who has devoted his career to understanding the power exerted by plant-based ethylene.

"I have been trying, for several decades, to understand how a simple gas -- two carbons and four hydrogens -- can cause such profound changes in a plant," Ecker says. "Now we can see that by altering the expression of one protein, ethylene produces cascading waves of gene activation that profoundly alters the biology of the plant."

Although the plant they studied is the Arabidopsis thaliana, related to cabbage and mustard, ethylene functions as a key hormone in all plants, he adds.

The researchers looked at what happens in Arabidopsis after ethylene gas causes activation of EIN3, a master transcription factor -- a protein that controls gene expression -- that Ecker had discovered and cloned in 1997. EIN3 and a related protein, EIL1, are required for the response to ethylene gas; without these proteins, ethylene has no effect on the plant.

"We wanted to know how ethylene is actually doing its job," Ecker says. "Once the plant responds to ethylene by activating EIN3, what happens? What genes are turned on? And what are those genes doing?"

Using a technique known as ChIP-Seq, the researchers exposed Arabidopsis to ethylene and identified all the regions of the plant genome that bound to EIN3, which required using next-generation sequencing. They then used genome-wide mRNA sequencing to identify those targeted genes whose expression actually changes due to interaction with EIN3. "Not all genes targeted by EIN3 have changes in their gene expression," Ecker says.

They found that thousands of genes in the plant responded to EIN3. Then the investigators discovered two interesting things. First, when EIN3 is activated by ethylene, it goes back to control the genes in the pathway that were used to activate the EIN3 transcription factor in the first place. "That tells us that a plant making a critical master regulator like EIN3 wants to keep that production pathway under very tight control," Ecker says. "We had not expected this, and now this gives us a strategy to understand genetic control of other plant hormones."

The second discovery is that EIN3 targets all other hormone signaling pathways in the plant. Ecker offers an analogy to understand the reasons why: "Imagine you are in a recording studio and you have one of those tables in front of you that have all of those switches. If you start pushing up the dials for one sound effect, you probably turn down the dial for other sound."
"If ethylene tells a plant to stop growing, it has to control other hormones that are telling the plant to grow," he says. "We found that about half of the genomic targets of the EIN3 protein are found in other hormone signaling pathways."

Control of those hormones by EIN3 is very complex and is accomplished in a 24-hour period during which four cascading waves of transcriptional regulation takes place, Ecker says. In addition to gaining insight into how ethylene genetically controls diverse functions within a plant, he adds that findings from the study provides a template by which to decode the workings of other plant hormones -- none of which have been as well studied as ethylene.

"Learning how plants coordinate hormone responses is essential to understanding their regulation of growth and development, be it in seed germination, fruit ripening, or responding to drought, insects, or pathogens," says Katherine Chang, the first author of the paper and researcher in Ecker's lab. "In this way, mapping interconnections between the hormone pathways may have implications in agriculture."

**Journal Reference:**

---

**Scientists discover why leprosy disappeared from Europe**

By David Ferguson
Friday, June 14, 2013 13:10 EDT

Ancient DNA isolated from the mass grave of a 15th century leper colony has given scientists a clue as to why the one-time scourge of humanity has all but vanished from western Europe. According to NPR's Shots Health News blog, a paper published Thursday in *Science* magazine explained that human beings themselves changed to overcome the once-prevalent skin disease.

Leprosy, also known as Hanson's disease, afflicted as many as 1 in 30 citizens of Western Europe at its height in the 15th century. In Medieval woodcuts and drawings, lepers are represented almost as frequently as Christ and the Virgin Mary. But then, in the era after the Crusades, the disease mysteriously all but vanished from the continent.

Scientists wondered whether the bacteria that causes leprosy, *Mycobacterium leprae*, had mutated into some less virulent form, or whether Europeans developed immunity. According to the study published in *Science*, it wasn't the bacteria that mutated, it was the people.

Stewart Cole of the Ecole Polytechnique Fédérale de Lausanne, one of the study's lead authors, told NPR that his team extracted DNA from the mass grave of a Medieval leper colony. DNA of any kind of is extremely difficult to extract from bones, but the team met with success when they were able to remove a small amount of tissue from a 600-year-old rotted tooth.

The material they found was "a mixture of human DNA, microorganisms and contaminating DNA from other bones and surrounding soil," said Cole, but they were able to fully reconstruct a 600-year-old strain of leprosy and map its genome, only to find that it is essentially identical to living leprosy infecting people in the developing world today.

Cole told NPR, "If the explanation of the drop in leprosy cases isn’t in the pathogen, then it must be in the host, that is, in us."

The scientists believe that a certain gene that makes people highly resistant to leprosy spread through the population of Europe, gradually conveying a kind of mass immunity.

Today, leprosy infections are treated with antibiotics and can be handled quickly and effectively if caught early. Stigma associated with the disease often keeps people in the developing world from seeking help for the malady until it has run amok in the system, causing irreversible damage.

Cole told NPR that understanding a disease's history can inform scientists’ and physicians’ approaches to treating and managing present and future diseases.

“Having information about the specific genes and proteins in the disease can help to determine preventative and therapeutic strategies, as well as possible drug resistances,” he said.

---

**WHO says MERS virus death toll hits 33**

By Agence France-Presse
Friday, June 14, 2013 7:18 EDT

The global death toll from the SARS-like virus MERS has risen to 33, after two new fatalities in Saudi Arabia, the World Health Organization (WHO) said on Friday.
Spokeswoman Fadela Chaib said the Saudi health ministry had informed the UN agency of three new laboratory-confirmed cases, one of them fatal, and the death of a patient already diagnosed with the disease.

“Globally, from September 2012 to date, WHO has been informed of a total of 58 laboratory-confirmed cases of infection with MERS-CoV, including 33 deaths,” Chaib told reporters.

Until last month, the disease was known simply as novel coronavirus, before being renamed Middle East Respiratory Syndrome Coronavirus, or MERS-CoV, as cases initiated in that region.

There have now been 44 confirmed cases in Saudi Arabia, 28 of them fatal, according to WHO figures. WHO logs cases by country of infection, rather than of death, and its Saudi toll includes one individual who died in Britain.

One person has died in France after being infected in Dubai, and a patient died in Munich, Germany who was transferred there after first being treated in Abu Dhabi.

There have also been two cases in Jordan, both of them fatal. Qatar has seen two, with those patients treated in Britain and Germany.

Two patients caught the disease in Britain from a person who had been to the Middle East, one of whom died.

Tunisia has seen two non-fatal cases and Italy two — one of whom caught the virus in Jordan and gave it to a contact in Italy.

France has recorded one infection, a man who is thought to have caught the disease while sharing a hospital room with the deceased patient who had got it in Dubai.

The virus is a member of the coronavirus family, which includes the pathogen that causes Severe Acute Respiratory Syndrome (SARS).

SARS sparked global panic in 2003 after it jumped to humans from animals in Asia and killed 800 people.

Like SARS, MERS appears to cause a lung infection, with patients suffering from a temperature, cough and breathing trouble. But it differs in that it also causes rapid kidney failure.

Health officials have expressed concern about the high proportion of deaths relative to cases, warning that MERS could spark a new global crisis if it mutates into a form that spreads more easily.

June 13, 2013

Study Gauges Value of Technology in Schools

By Motoko Rich

With school districts rushing to buy computers, tablets, digital white boards and other technology, a new report questions whether the investment is worth it.

In a review of student survey data conducted in conjunction with the federal exams known as the National Assessment of Educational Progress, the nonprofit Center for American Progress found that middle school math students more commonly used computers for basic drills and practice than to develop sophisticated skills. The report also found that no state was collecting data to evaluate whether technology investments were actually improving student achievement.

“Schools frequently acquire digital devices without discrete learning goals and ultimately use these devices in ways that fail to adequately serve students, schools, or taxpayers,” wrote Ulrich Boser, a senior fellow at the Center for American Progress and the author of the report.

The analysis of the N.A.E.P. data found that 34 percent of eighth graders who took the math exams in 2011 used computers to “drill on math facts” while less than a quarter worked with spreadsheets or geometric figures on the computer. Only 17 percent used statistical programs.

The federal survey data showed striking differences among racial groups and income levels. More than half of the black students who took the eighth-grade math exam in 2011 said they used computers to work on math drills, while only 30 percent of white students said they did.

Similarly, 41 percent of students eligible for free and reduced lunches said they used computers for math drills, compared with 29 percent of students whose families earn too much for them to qualify for the lunches.

In high school science classrooms, the use of technology evidently has not advanced much past the 1980s. According to the report, 73 percent of students who took the 12th-grade National Assessment science exam said they regularly watched a movie or video in class.

Such data, Mr. Boser said, suggested that technology “doesn’t seem to have dramatically changed the nature of schooling.”
Experts who study the effectiveness of instructional technology say there is potential for some digital programs to improve teaching. John Pane, a senior scientist at the RAND Corporation, said good technology allowed students to work at their own pace and independently while teachers worked with smaller groups.

Mr. Pane conducted a study, financed by the federal Department of Education, of an algebra software program created by Carnegie Learning, a math curriculum developer. He found that high school students who used the program, which was designed to accompany a teacher-led curriculum, showed gains on their state-standardized math tests that were nearly double the gains of a typical year’s worth of growth using a more traditional high school math curriculum.

Whether those gains came from the use of technology or changes in the curriculum, he said, was hard to say. But Steve Ritter, chief scientist at Carnegie Learning, said one of the benefits of the technology was that it used the principles of cognitive science to help students gain a deeper understanding of concepts rather than simply drill math problems.

“We’re not just seeing whether they got the answer right or wrong,” Mr. Ritter said, “but why they got it right or wrong.”

More Than Half of Young HIV-Infected Americans Are Not Aware of Their Status

Too many young people continue to become infected and few are tested for HIV

Young people between the ages of 13 and 24 represent more than a quarter of new HIV infections each year (26 percent) and most of these youth living with HIV (60 percent) are unaware they are infected, according to a Vital Signs report from the Centers for Disease Control and Prevention. The most-affected young people are young gay and bisexual men and African-Americans, the report says.

The analysis looks at the latest data on HIV infections, testing, and risk behaviors among young people and was published in advance of World AIDS Day, Dec. 1.

Overall, an estimated 12,200 new HIV infections occurred in 2010 among young people aged 13-24, with young gay and bisexual men and African-Americans hit harder by HIV than their peers. In 2010, 72 percent of estimated new HIV infections in young people occurred in young men who have sex with men (MSM). By race/ethnicity, 57 percent of estimated new infections in this age group were in African-Americans.

“That so many young people become infected with HIV each year is a preventable tragedy,” said CDC Director Thomas R. Frieden, M.D., M.P.H. “All young people can protect their health, avoid contracting and transmitting the virus, and learn their HIV status.”

According to CDC experts, a number of factors contribute to the high levels of HIV in young people and vary by population. HIV prevalence is higher in some communities than in others, which can increase the likelihood that a person will be exposed to infection with each sexual encounter. Previous research has also found that other factors can increase risk of infection, such as higher levels of unrecognized and untreated infection, as well as social and economic factors, such as poverty, lack of access to health care, stigma, and discrimination.

Despite recommendations from CDC and the American Academy of Pediatrics that call for routine HIV testing of youth in medical settings, the analysis shows that 35 percent of 18-24 year olds have been tested for HIV, while only 13 percent of high school students (and 22 percent of sexually experienced students) have ever been tested.

Partially as a result of lower testing levels, HIV-infected people under the age of 25 are significantly less likely than those who are older to get and stay in HIV care, and to have their virus controlled at a level that helps them stay healthy and reduce their risk of transmitting HIV to partners.

CDC also examined risk behaviors among high school students in 12 states and nine large urban school districts, and found that young MSM reported engaging in substantially higher levels of risk behavior than their heterosexual male peers:

- Young MSM were more likely to report having had sex with four or more partners or ever injecting illegal drugs.
- Among students who were currently sexually active, young MSM were more likely to have used alcohol or drugs before their last sexual experience, and were less likely to have used a condom.
- Young MSM were also less likely to report having been taught about HIV or AIDS in school.

“We can and must achieve a generation that is free from HIV and AIDS,” said Kevin Fenton, M.D., director, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC. “It will take a concerted effort at all levels across our nation to empower all young people, especially young gay and
bisexual youth, with the tools and resources they need to protect themselves from HIV infection.” These efforts are underway as part of the National HIV/AIDS Strategy.

CDC works with partners across the country to help prevent HIV and other STDs among young people. These efforts include encouraging HIV education and testing, funding the delivery of targeted testing and prevention services for youth at greatest risk, and working to address the social and environmental factors that can place some youth at increased risk. CDC also provides data and support to help communities develop effective school- and community-based HIV and STD prevention efforts.

**HIV convicts freed to die**

Denise Williams  |  18 June, 2013 00:01

**HIV-positive inmates released from prison are handed a virtual death sentence - there is no obligation on the Department of Correctional Services to ensure that they continue to receive, and take, medication.**

This worrying admission was made to parliament’s joint standing committee on HIV and Aids last week.

The department also said that 100 babies of women prisoners, who might have contracted HIV, were not receiving life-saving treatment.

Briefing the committee, the department’s director of health care services, Maria Mabena, said 21000 of the 152000 prison population had tested positive for HIV.

The department’s admission that, though counselling is offered and information on referral clinics provided, there was no guarantee that prisoners would receive treatment once released, equates to a death sentence for many.

"There is a discharge plan." He said one of several plans was for released inmates to make an appointment for specialist treatment.

"We also issue a referral letter to the nearest clinic and the prisoners are given a month's prescription. But after that there is a gap, we don't know if they went [to the clinic].

"When they don't go, [the spread of HIV/Aids] would be exacerbated," Mabena said.

The department said that it could not test a child for HIV without the mother's consent.

"[Of] 100 babies, none is on prevention of mother-to-child transmission treatment. They [the babies] might have it [HIV] but they have not been tested because we do not force them [the mothers].

"There are women who do not go to the clinics. Testing is not mandatory," she said.

Oversight committee co-chairman Bevan Goqwana said it was troubling that there was a fatal lapse in the treatment plan.

"The way the health department is working with correctional services, it needs to be enforced. We will be writing to both.

"Getting a treatment for a month and there's nothing after that? There are serious problems," he said.

He said often people did not persevere with their treatment because they felt better, or, in many instances, could not pay for the medicines or afford to travel to a clinic.

"When you don’t have treatment and you have not been referred properly to a particular place and you don’t have money ... you are going to stop your treatment and start vagabonding and infecting other people," he said.

Yogan Pillay, the Health Department's deputy director-general for strategic health programmes, acknowledged that his department's working relationship with Correctional Services should be strengthened.

"I would say that there are people who are falling through the gaps," he said.

Pillay said a mother's consent was necessary before a child could be tested for HIV.

"We don’t routinely test any child ... The idea is for parents to trust us and, if they think [the child might have HIV], to get the child tested.

"Most moms will do the best they can for their kids," he said.

'I don't want to be only person cured of HIV’

Timothy Ray Brown, a native of Seattle who was the first person cured of the AIDS virus, is joining with scientists at the Fred Hutchinson Cancer Research Center to help extend the cure to others.

By Sandi Doughton, Seattle Times science reporter
The Cure Agenda for HIV/AIDS

Timothy Ray Brown will join scientists from the Fred Hutchinson Cancer Research Center on Wednesday in a free, public event called “From One to Many: The Cure Agenda for HIV/AIDS at Fred Hutch.” The 7 p.m. event is at the Pigott Building, Seattle University, 901 12th Ave. It will be preceded by a social hour at 6 p.m.

Early reports identified him only as “the Berlin patient.” But Timothy Ray Brown, the first person cured of HIV, was born and raised in Seattle.

Now, Brown is returning to his hometown to help boost efforts at the Fred Hutchinson Cancer Research Center and elsewhere to extend the cure to others.

“I don’t want to be the only person in the world cured of HIV,” Brown said in an interview. “I want there to be a lot more like me.”

During his visit, Brown will participate in a science forum at the Hutch and a free, community event Wednesday at Seattle University, where he was once a student. Seattle is also the first stop on his national fundraising tour for The Timothy Ray Brown Foundation, devoted to the search for a cure.

“I really believe that there is going to be a cure for everyone within my lifetime,” said Brown, 47.

His own cure was a grueling procedure that required a combination of serendipity and scientific innovation difficult to duplicate.

Diagnosed with HIV in 1995, Brown kept the disease mostly in check with a regimen of drugs. Then in 2006, while living in Berlin, he began to feel so weak he could barely ride his bicycle to work.

German doctors diagnosed a highly lethal form of leukemia.

Brown’s first stroke of luck was coming under the treatment of bone-marrow transplant expert Dr. Gero Hütter.

Hütter knew that about one in 100 Northern Europeans carry a genetic mutation that blocks the AIDS virus from getting into their immune cells, shielding them from infection. Since a bone-marrow transplant basically involves killing off the patient’s defective immune system with radiation and chemotherapy, and replacing it with one from a donor, Hütter wondered if using a donor with the protective mutation might rid Brown of HIV at the same time it cured his leukemia.

Out of more than 2.5 million people in Germany’s donor registry, Hütter found 267 tissue matches to Brown — and one person who also carried the mutation. But the benefits from the first transplant didn’t last, and Brown’s cancer came roaring back.

The donor, a German man living in the United States whom Brown has never met, agreed to a second transplant. Hütter warned Brown there was a high likelihood the procedure would kill him — and it nearly did.

“I became delirious. I couldn’t walk and I was incontinent,” Brown recalled. When a physical therapist told him to lift his left leg, he lifted the right. “I couldn’t tell the difference anymore.”

Brown spent most of 2008 in the hospital. But every time Hütter tested him for HIV, the tests came up blank. Today, Brown no longer takes drugs for HIV, and no tests have detected virus anywhere in his body.

Most AIDS experts agree that his cure is real, though some suspect virus may still be lurking in some cells. Brown himself didn’t believe he was cured until Hütter published a paper about the case in the New England Journal of Medicine in 2009.

“At that point I thought, medical scientists are accepting it, so it must be true,” Brown said.

In April, a 12-year-old boy with HIV received a transplant in Minnesota using umbilical-cord blood from a newborn with the protective mutation — but it’s too early yet to know if the procedure provided a cure.

Clearly, though, it’s not the kind of operation that can be widely replicated, said Hutch researcher Dr. Keith Jerome.
Jerome and his colleagues hope to develop a streamlined version of Brown’s cure. “The long-term goal is to make this simple enough that it doesn’t require hospitalization,” Jerome said.

With a $20 million grant from the National Institutes of Health (NIH), the Hutch scientists are tweaking patients’ own stem cells to make them resistant to HIV.

To do that, they use special enzymes developed by California-based Sangamo BioSciences to induce artificial mutations that mimic those in people who are naturally immune to the virus.

“It’s an engineering tour de force,” Jerome said. “In some ways, it seems like science fiction that we can actually modify a spot in the genome and leave everything else alone.”

The treated stem cells would then be infused back into the patient, where the hope is they would proliferate and replace the patient’s HIV-plagued immune system.

The research is still in an early stage, but the scientists hope to start clinical trials soon.

In a sign of the growing optimism about a cure, two other labs also received major NIH grants at the same time as the Hutch. Scientists at the University of California, San Francisco, are working to rev up patients’ immune systems to fight the virus. At the University of North Carolina, the focus is on drugs that will roust out hidden pockets of infection.

Other scientists think early, aggressive treatment of HIV might be able to eliminate the virus. That’s what happened with a baby in Mississippi who was born infected. Doctors immediately administered high doses of drugs. More than two years later, the child seems to be HIV-free.

Brown, who now lives in Las Vegas, says he’s healthy and plans to spend much of the summer in Seattle, where his mother still lives. After coming out as gay in the 1980s, he was an AIDS activist in Seattle long before his diagnosis.

Brown said his foundation will push for more cure research funding, a cause that convinced him to step back into the spotlight.

“I realized I couldn’t really effect change and advocate for a cure for other people until I came forward, so that’s what I did.”

A Shot in the Arm for Old Antibiotics
June 19, 2013 — Slipping bacteria some silver could give old antibiotics new life, scientists at the Wyss Institute for Biologically Inspired Engineering at Harvard University reported June 19 in Science Translational Medicine.

Treating bacteria with a silver-containing compound boosted the efficacy of a broad range of widely used antibiotics and helped them stop otherwise lethal infections in mice. It helped make an antibiotic-resistant strain of bacteria sensitive to antibiotics again. And it expanded the power of an antibiotic called vancomycin that is usually only effective in killing pathogens called Gram-positive bacteria, such as Staph and Strep. Silver allowed vancomycin for the first time to penetrate and kill Gram-negative bacteria, a group that includes microbes that can cause food poisoning and dangerous hospital-acquired infections.

Silver also proved useful for two types of stubborn infections that usually require repeated rounds of antibiotic treatment and multiple visits to the clinic: dormant bacteria that lie low during antibiotic treatment and rebound to cause recurrent infections, and microbial slime layers called biofilms that coat catheters and prosthetic joints.

"The results suggest that silver could be incredibly valuable as an adjunct to existing antibiotic treatments," said Jim Collins, Ph.D., a pioneer of synthetic biology and Core Faculty member at the Wyss Institute, who is also the William F. Warren Distinguished Professor at Boston University, where he leads the Center of Synthetic Biology.

In recent years more disease-causing bacteria have grown resistant to common antibiotics, with serious public health consequences. Yet drug companies have struggled for years to develop new types of antibiotics that target these tough bacteria. That has led scientists to re-examine older methods that were used to fight infection well before penicillin use took off in the 1940s. Silver treatment, which has been used since antiquity to prevent and heal infections, is one of them.

Despite silver’s long history of use in the clinic, no one understood fully how it killed bacteria. To find out, Ruben Morones-Ramirez, Ph.D., a postdoctoral fellow at the Wyss Institute who left recently to become a professor at Universidad Autónoma de Nuevo Leon in Mexico, treated normal and mutant strains of E. coli bacteria with a silver compound. Then he observed them under the electron microscope and ran a series of biochemical tests.
He found that silver compounds cause bacteria to produce more reactive oxygen species -- chemically reactive molecules that damage the bacterial cell's DNA and enzymes, as well as the membrane that encloses the cell. Silver also made the bacteria's cell membrane leakier.

Although silver was used alone as a therapy in the past, the scientists suspected that both changes might make cells more vulnerable to conventional antibiotics -- and they did. A small amount of silver made E. coli bacteria between 10 and 1000 times more sensitive to three commonly used antibiotics: gentamycin, ofloxacin, and ampicillin.

"If you know the mechanism, you can have much more success making combinatorial therapies," Morones-Ramirez said.

In mice, silver also helped antibiotics fight E. coli-induced urinary-tract infections. It made a previously impervious strain of E. coli sensitive to the antibiotic tetracycline.

And it allowed vancomycin to save the lives of 90 percent of mice with life-threatening cases of peritonitis -- inflammation caused by infections of the abdominal space surrounding the internal organs. Without silver, only 10 percent of the mice survived.

The scientists also did a series of toxicity studies, showing that the doses of silver needed to help antibiotics kill bacteria were far below what could harm the mice. Nor did they harm cultured human cells, suggesting that oral and injectable silver could be safe for humans as well.

"Doctors desperately need new strategies to fight antibiotic-resistant infections, and Jim and his team have uncovered one that's incredibly versatile, and that could be put to use quickly in humans," said Don Ingber, M.D., Ph.D., Wyss Institute Founding Director.

"We're keen to explore how smart drug-delivery nanotechnologies being developed at the Wyss could help deliver effective but nontoxic levels of silver to sites of infection," Collins said.

Journal Reference:
J. R. Morones-Ramirez, J. A. Winkler, C. S. Spina, J. J. Collins. Silver Enhances Antibiotic Activity Against Gram-Negative Bacteria. Science Translational Medicine, 2013; 5 (190): 190ra81 DOI: 10.1126/scitranslmed.3June 19, 2013 — A team of researchers at the University of Pittsburgh has developed antibacterial compounds, derived from the outer coating of HIV, that could be potential treatments for drug-resistant bacterial infections and appear to avoid generating resistance. These new agents are quite small, making them inexpensive and easy to manufacture.

The first of many probable applications will likely be the chronic bacterial infections in the lungs of cystic fibrosis patients "that frequently develop resistance to all standard antibiotics, and are the leading cause of death in these patients," says senior author Ronald Montelaro.

The lead compound shows powerful antibacterial activity against clinical isolates of diverse pathogenic bacteria that are resistant to most antibiotics. These agents, called engineered cationic antimicrobial peptides (eCAPs) "may be applicable to treatment of other respiratory infections, topical infections, and systemic infections," says Montelaro.

The genesis of the new agent was basic research on HIV envelope protein structure and function, says Montelaro. As part of this research, "we identified highly conserved unique protein sequences that were predicted by computer modeling to assume structures characteristic of natural antibacterial peptides. Since antibacterial peptides specifically target and disrupt the integrity and function of bacterial membranes, we thought that these similar peptide sequences in the HIV envelope protein might contribute to toxicity and death in infected cells by altering cell membranes."

The team engineered the original HIV peptides for greater effectiveness and smaller size, the latter to reduce manufacturing expenses. The engineering involved modifying amino acid content (they contain just two different amino acids), peptide length, charge, and hydrophobicity. The current paper describes the third generation peptides. The lead agent contains just 12 amino acid residues.

"Another potential application is biodefense, where eCAPs may be used as a rapid postexposure aerosol treatment in individuals after exposure to aerosolized pathogens, where the goal of immediate treatment would be to rapidly reduce bacterial dose from a lethal to a nonlethal or subclinical level," says Montelaro.

Journal Reference:
HIV-Derived Antibacterial Shows Promise Against Drug-Resistant Bacteria

June 19, 2013 — A team of researchers at the University of Pittsburgh has developed antibacterial compounds, derived from the outer coating of HIV, that could be potential treatments for drug-resistant bacterial infections and appear to avoid generating resistance. These new agents are quite small, making them inexpensive and easy to manufacture.

The research was published in the June 2013 issue of the journal *Antimicrobial Agents and Chemotherapy*.

The first of many probable applications will likely be the chronic bacterial infections in the lungs of cystic fibrosis patients "that frequently develop resistance to all standard antibiotics, and are the leading cause of death in these patients," says senior author Ronald Montelaro.

The lead compound shows powerful antibacterial activity against clinical isolates of diverse pathogenic bacteria that are resistant to most antibiotics. These agents, called engineered cationic antimicrobial peptides (eCAPs) "may be applicable to treatment of other respiratory infections, topical infections, and systemic infections," says Montelaro.

The genesis of the new agent was basic research on HIV envelope protein structure and function, says Montelaro. As part of this research, "we identified highly conserved unique protein sequences that were predicted by computer modeling to assume structures characteristic of natural antibacterial peptides. Since antibacterial peptides specifically target and disrupt the integrity and function of bacterial membranes, we thought that these similar peptide sequences in the HIV envelope protein might contribute to toxicity and death in infected cells by altering cell membranes."

The team engineered the original HIV peptides for greater effectiveness and smaller size, the latter to reduce manufacturing expenses. The engineering involved modifying amino acid content (they contain just two different amino acids), peptide length, charge, and hydrophobicity. The current paper describes the third generation peptides. The lead agent contains just 12 amino acid residues.

"Another potential application is biodefense, where eCAPs may be used as a rapid postexposure aerosol treatment in individuals after exposure to aerosolized pathogens, where the goal of immediate treatment would be to rapidly reduce bacterial dose from a lethal to a nonlethal or subclinical level," says Montelaro.

**Journal Reference:**

Whooping Cough Has Lifelong Health Impact, Study Finds

June 18, 2013 — People born during whooping cough outbreaks are more likely to die prematurely even if they survive into adulthood, research at Lund University in Sweden has found. Women had a 20% higher risk of an early death, and men a staggering 40%. Women also suffered more complications during and after pregnancy, with an increased risk of miscarriage as well as infant death within the first month of life.

"The results show the importance of following up patients with exposure to whooping cough in childhood, particularly pregnant women," says Luciana Quaranta, the PhD candidate at Lund University behind the findings.

The landmark study used a globally unique database, the Scanian Economic Demographic Database, based on data from Sweden’s extensive population registers. Quaranta mapped five communities between 1813 and 1968, in an effort to understand how conditions at birth, such as socioeconomic status and exposure to infectious diseases, affect us later in life.

Whooping cough, or pertussis, was widely considered to have been all but eradicated in many developed countries until recently. The UK, the US and Australia have all seen outbreaks of the disease in the past two years.

New Way to Improve Antibiotic Production

June 17, 2013 — An antibiotic has been found to stimulate its own production. The findings, to be published in PNAS, could make it easier to scale up antibiotic production for commercialisation.

Scientists Dr Emma Sherwood and Professor Mervyn Bibb from the John Innes Centre were able to use their discovery of how the antibiotic is naturally produced to markedly increase the level of production.

"We have shown for the first time that an antibiotic with clinical potential can act as signalling molecule to trigger its own synthesis," said Professor Bibb.
The antibiotic called planosporicin is produced by a soil bacterium called *Planomonospora alba*. When nutrients become limited, a small amount of the antibiotic is produced. The antibiotic is then able to trigger a mechanism which coordinates its own production throughout the bacterial population resulting in high levels.

"A frequent stumbling block in developing a natural product for commercialisation is being able to provide enough material for clinical trials," said Professor Bibb.

"Our work shows with the right understanding it is possible to increase productivity very dramatically in a targeted and knowledge-based manner."

With knowledge of this signalling mechanism in hand, the scientists were able to increase production by overexpressing two positively acting regulatory genes and deleting one that acts negatively.

Planosporicin is similar to the antibiotic NAI-107 that is about to enter clinical trials for *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) infections. The knowledge gained from this study is being used to increase NAI-107 production.

Commercial manufacturers of antibiotics may be able to use the results to reduce production times and therefore reduce costs. Bacteria often have to be grown for days and sometimes weeks before they start to make effective amounts of an antibiotic. Sherwood and Bibb were able to trigger production essentially from the beginning of growth.

**Journal Reference:**
Emma J. Sherwood and Mervyn J. Bibb. The antibiotic planosporicin coordinates its own production in the actinomycete *Planomonospora alba*. *PNAS*, June 17, 2013 DOI: 10.1073/pnas.1305392110

**New HIV infections among children have been reduced by 50% or more in seven countries in sub-Saharan Africa**

*New report also shows that access to treatment remains unacceptably low for children—only 3 in 10 children in need of treatment have access in most of the ‘Global Plan’ priority countries.*

**GENEVA, 25 June 2013—A new report** on the Global Plan towards elimination of new HIV infections among children by 2015 and keeping their mothers alive (Global Plan) has revealed a marked increase in progress in stopping new infections in children across the Global Plan priority countries in Africa.

The report outlines that seven countries in sub-Saharan Africa—Botswana, Ethiopia, Ghana, Malawi, Namibia, South Africa and Zambia—have reduced new HIV infections among children by 50% since 2009. Two others—the United Republic of Tanzania and Zimbabwe—are also making substantial progress. It highlights that there were 130 000 fewer new HIV infections among children across the 21 Global Plan priority countries in Africa—a drop of 38% since 2009.

“The progress in the majority of countries is a strong signal that with focused efforts every child can be born free from HIV,” said Michel Sidibé, Executive Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS). “But in some countries with high numbers of new infections progress has stalled. We need to find out why and remove the bottlenecks which are preventing scale-up.”

With a 76% decline since 2009, Ghana showed the greatest decline in the rate of new infections among children and South Africa showed a 63% decline (24 000 fewer new HIV infections in 2012 than in 2009). However, the pace of decline in some of the Global Plan priority countries has been slow and in Angola, new HIV infections have even increased. New infections among children in Nigeria—which has the largest number of children acquiring HIV (nearly 60 000 new HIV infections among children in 2012)—remained largely unchanged since 2009. Without urgent action in Nigeria the global target for 2015 may not be reached.

More pregnant women living with HIV were receiving antiretroviral medicines to prevent HIV from being transmitted to their children and for their own health in 2012 than in 2009, with coverage levels exceeding 75% in many countries. Increased coverage has reduced HIV transmission rates from mother to child in most countries. Botswana and South Africa have reduced transmission rates to 5% or below.

“We have the tools required to reach the Global Plan’s goals, and recent data show that we are moving ever closer to their realization,” said Ambassador Eric P. Goosby, U.S. Global AIDS Coordinator. “This month, as U.S. Secretary of State John Kerry announced, the one millionth baby will be born HIV-free due to PEPFAR’s support. Now, we must all continue working together to see the day when no children are born with HIV, which is within our reach,” he added.

The report however also reveals that only half of all breastfeeding women living with HIV or their children receive antiretroviral medicines to prevent mother-to-child transmission of HIV. It outlines that breastfeeding is critical to ensuring child survival and strongly emphasizes the urgent need to provide antiretroviral therapy during the breastfeeding period.
More than half of the children eligible for treatment in South Africa and Swaziland now have access. Chad, Ethiopia, Ghana, Kenya, Malawi, Nigeria, South Africa, United Republic of Tanzania and Zimbabwe have doubled the numbers of children accessing treatment from 2009 to 2012. While the report outlines that the number of children requiring HIV treatment will reduce as new HIV infections decline, urgent steps need to be taken to improve early diagnosis of HIV in children and ensure timely access to antiretroviral treatment.

The number of pregnant women living with HIV receiving antiretroviral therapy for their own health has increased since 2009. In Botswana, Ghana, Malawi, Namibia, South Africa, Swaziland and Zambia, more than 75% of the pregnant women eligible receive antiretroviral therapy and more than 50% in Kenya, Lesotho, the United Republic of Tanzania and Zimbabwe. Increasing access to antiretroviral therapy for pregnant women living with HIV for their own health is critical.

The Global Plan towards elimination of new HIV infections among children by 2015 and keeping their mothers alive is an initiative spearheaded by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the United States Presidents Emergency Plan for AIDS Relief (PEPFAR) which was unveiled in June 2011 at the UN General Assembly High Level Meeting on AIDS. It has two main targets for 2015: a 90% reduction in the number of children newly infected with HIV and a 50% reduction in the number of AIDS-related maternal deaths. The Plan focuses on the 22* countries which account for 90% of new HIV infections among children.

This second progress report presents the progress made by the 21 countries in sub-Saharan Africa and some of the challenges they face in meeting the agreed targets for 2015.

* Angola, Botswana, Burundi, Cameroon, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Uganda, United Republic of Tanzania, Swaziland, Zambia and Zimbabwe.

PEPFAR
The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) is the U.S. Government initiative to help save the lives of those suffering from HIV/AIDS around the world. This historic commitment is the largest by any nation to combat a single disease internationally, and PEPFAR investments also help alleviate suffering from other diseases across the global health spectrum. PEPFAR is driven by a shared responsibility among donor and partner nations and others to make smart investments to save lives. Learn more at www.pepfar.gov.

UNICEF
UNICEF works in more than 190 countries and territories to help children survive and thrive, from early childhood through adolescence. The world’s largest provider of vaccines for developing countries, UNICEF supports child health and nutrition, good water and sanitation, quality basic education for all boys and girls, and the protection of children from violence, exploitation, and AIDS. UNICEF is funded entirely by the voluntary contributions of individuals, businesses, foundations and governments. For more information about UNICEF and its work visit www.unicef.org Follow us on Twitter and Facebook

UNAIDS
The Joint United Nations Programme on HIV/AIDS (UNAIDS) leads and inspires the world to achieve its shared vision of zero new HIV infections, zero discrimination and zero AIDS-related deaths. UNAIDS unites the efforts of 11 UN organizations—UNHCR, UNICEF, WFP, UNDP, UNFPA, UNODC, UN Women, ILO, UNESCO, WHO and the World Bank—and works closely with global and national partners to maximize results for the AIDS response. Learn more at unaids.org and connect with us on Facebook and Twitter.

Calcium and vitamin D help hormones help bones
CLEVELAND, Ohio (June 26, 2013)—Should women take calcium and vitamin D supplements after menopause for bone health? Recommendations conflict, and opinions are strong. But now, an analysis from the major Women’s Health Initiative (WHI) trial throws weight on the supplement side—at least for women taking hormones after menopause. The analysis was published online today in Menopause, the journal of The North American Menopause Society.

Among the nearly 30,000 postmenopausal women in the hormone trial, some 8,000 took supplemental calcium (1,000 mg/day) and vitamin D (400 mg/day), and some 8,000 took look-alike placebos. These women came from all the hormone groups in the study—those who took estrogen plus a progestogen (required for women with a uterus), those who took estrogen alone, and those who took the hormone look-alike placebos. The researchers looked at how the rates of hip fracture differed among
women who took hormones and supplements, those who took hormones alone, and those who took neither.

The supplements and hormones had a synergistic effect. Women using both therapies had much greater protection against hip fractures than with either therapy alone. Taking supplements alone wasn't significantly better than taking no supplements and no hormones. The benefit of hormone therapy was strong in women who had a total calcium intake (supplements plus diet) greater than 1,200 mg/day. Similarly, the benefit was strong in women who had higher intakes of vitamin D, but the individual effect of each one could not be determined because the two supplements were given together.

The effects translated into 11 hip fractures per 10,000 women per year among the women who took both hormones and supplements compared with 18 per 10,000 women per year among those who took hormones only, 25 per 10,000 women per year among those who took supplements alone, and 22 among those who got neither therapy.

These results suggest, said the authors, that women taking postmenopausal hormone therapy should also take supplemental calcium and vitamin D. Although they couldn't specify how much, they noted that the benefits seem to increase with increasing total intake of calcium and vitamin D. The dose will depend on keeping side effects, such as constipation from too much calcium, to a minimum, they said.

That differs from the recommendation of the US Preventive Services Task Force (USPSTF), made earlier this year. USPSTF stated there was no basis for recommending calcium and vitamin D supplements to prevent fractures. But now, with a study this large, there may well be.

The study will be published in the February 2014 print edition of Menopause.

**Virtual skin model reveals secrets of skin aging**

We constantly grow new skin and slough off the old. Until now, scientists have never agreed on exactly how this works, but new research from the University of Sheffield may provide the answer.

Engineers and biologists at the University of Sheffield have shown how a recent theory-- that skin has 'sleeping' stem cells which can be woken up when required-- best explains how our skin constantly regrows. The research-- conducted in collaboration with The Procter & Gamble Company (P&G), makers of Olay, and published in Nature Scientific Reports-- has implications for combating the effects of aging and perhaps even skin cancer.

The Sheffield/P&G team developed an "in silico" (computer) model of human skin biology, capturing how the outer layers of the skin are developed and maintained over time. This model simulation or "virtual" skin was then used to test the three most popular theories of how skin cells function to regenerate our skin, the largest human organ, over a three-year period. When the simulation was run according to two of the theories, the virtual skin failed to fully regenerate. Only one theory enabled the virtual skin to still be in good shape after three years, as Dr. Xinsha Li (University of Sheffield Faculty of Engineering) and Dr. Arun Upadhyay (P&G), the lead co-authors explained in their research.

"The theory which seems to fit best says that skin has a population of 'sleeping' stem cells, which sit in the lowest layer of the skin but don't constantly divide to make new cells," Dr. Li said. "However, these sleeping cells can be called into action if the skin is damaged, or if the numbers of other types of more mature skin cells decrease, ensuring that the skin can be constantly regenerated under all conditions."

The model showed that we gradually lose these sleeping stem cells over time-- which would explain why our ability to regenerate our skin reduces as we age. "Each time we wake up these cells, to heal a wound or replenish stocks of other cells, a few of them don't go back into sleep mode, so the population slowly reduces," says Dr. Li. "This explains why older skin is slower to heal and in part why our skin changes as we age. By understanding this mechanism better, it might be possible to find ways to combat the effects of aging on our skin."

Computer modelling of skin biology is the latest step in the evolution of skin science. It allows scientists to project the activity of tissues like skin that are difficult to follow in live systems for extended periods. Currently, 3-dimensional cultures of engineered human skin are viable for only a few weeks and clinical studies in humans are only practical for a few months. With the development of in silico models scientists can predict for the first time what happens in skin as it ages year by year even as it ages decade by decade.

"These models permit exploration of hypotheses in very short periods of time, relative to the lab based bench work," says Dr. Upadhyay. "In silico modelling can significantly shorten R&D programs, and help focus subsequent lab or clinical work on the options with the greatest likelihood of succeeding. This is another reason why in silico models are an effective complement to more established research tools and methods."
The ability to follow virtual skin models over decades may be especially important to skin cancer research. Environmental damage caused by UV exposure or chronic wounding can cause sleeping cells to harbor the mutations which cause skin cancers such as basal cell carcinoma, a very aggressive type of skin cancer.

"The stem cells can harbor mutations throughout the years, but with no effect if they're still in sleep mode," explains Dr. Li. "However, when they start to divide to heal a wound for example, this could trigger the cancer. If it's possible to study this phenomenon for long periods of time it may be possible to find ways to prevent the activation of mutated cells and therefore reduce the risk of developing the disease."

Other parts of the body, such as the lung or gut lining and the cornea, also regenerate in the same way as our skin. Research is already underway at the University of Sheffield to look at the healing process of the lung lining following asthma attacks.

This study is an excellent example of how computer modelling can enhance our long-term understanding of complex processes such as skin aging. Dr. Upadhyay, a physicist-turned-computational biologist, drew inspiration from the great physicist Richard Feynman in summarizing the study, noting that, "You really don't understand something until you have built it from scratch. By building the virtual skin model from a few cells into a tissue capable of self-renewal, we have moved a big step in our understanding of stem cells and skin renewal."

**Reading DNA, Backward and Forward: Biologists Reveal How Cells Control the Direction in Which the Genome Is Read**

June 24, 2013 — MIT biologists have discovered a mechanism that allows cells to read their own DNA in the correct direction and prevents them from copying most of the so-called "junk DNA" that makes up long stretches of our genome.

Only about 15 percent of the human genome consists of protein-coding genes, but in recent years scientists have found that a surprising amount of the junk, or intergenic DNA, does get copied into RNA -- the molecule that carries DNA's messages to the rest of the cell.

Scientists have been trying to figure out just what this RNA might be doing, if anything. In 2008, MIT researchers led by Institute Professor Phillip Sharp discovered that much of this RNA is generated through a process called divergent expression, through which cells read their DNA in both directions moving away from a given starting point.

In a new paper appearing in *Nature* on June 23, Sharp and colleagues describe how cells initiate but then halt the copying of RNA in the upstream, or non-protein-coding direction, while allowing it to continue in the direction in which genes are correctly read. The finding helps to explain the existence of many recently discovered types of short strands of RNA whose function is unknown.

"This is part of an RNA revolution where we’re seeing different RNAs and new RNAs that we hadn't suspected were present in cells, and trying to understand what role they have in the health of the cell or the viability of the cell," says Sharp, who is a member of MIT's Koch Institute for Integrative Cancer Research. "It gives us a whole new appreciation of the balance of the fundamental processes that allow cells to function."

Graduate students Albert Almada and Xuebing Wu are the lead authors of the paper. Christopher Burge, a professor of biology and biological engineering, and undergraduate Andrea Kriz are also authors.

**Choosing direction**

DNA, which is housed within the nucleus of cells, controls cellular activity by coding for the production of RNAs and proteins. To exert this control, the genetic information encoded by DNA must first be copied, or transcribed, into messenger RNA (mRNA).

When the DNA double helix unwinds to reveal its genetic messages, RNA transcription can proceed in either direction. To initiate this copying, an enzyme called RNA polymerase latches on to the DNA at a spot known as the promoter. The RNA polymerase then moves along the strand, building the mRNA chain as it goes.

When the RNA polymerase reaches a stop signal at the end of a gene, it halts transcription and adds to the mRNA a sequence of bases known as a poly-A tail, which consists of a long string of the genetic base adenine. This process, known as polyadenylation, helps to prepare the mRNA molecule to be exported from the cell's nucleus.

By sequencing the mRNA transcripts of mouse embryonic stem cells, the researchers discovered that polyadenylation also plays a major role in halting the transcription of upstream, noncoding DNA
sequences. They found that these regions have a high density of signal sequences for polyadenylation, which prompts enzymes to chop up the RNA before it gets very long. Stretches of DNA that code for genes have a low density of these signal sequences.

The researchers also found another factor that influences whether transcription is allowed to continue. It has been recently shown that when a cellular factor known as U1 snRNP binds to RNA, polyadenylation is suppressed. The new MIT study found that genes have a higher concentration of binding sites for U1 snRNP than noncoding sequences, allowing gene transcription to continue uninterrupted.

A widespread phenomenon
The function of all of this upstream noncoding RNA is still a subject of much investigation. "That transcriptional process could produce an RNA that has some function, or it could be a product of the nature of the biochemical reaction. This will be debated for a long time," Sharp says.

His lab is now exploring the relationship between this transcription process and the observation of large numbers of so-called long noncoding RNAs (lncRNAs). He plans to investigate the mechanisms that control the synthesis of such RNAs and try to determine their functions.

"Once you see some data like this, it raises many more questions to be investigated, which I’m hoping will lead us to deeper insights into how our cells carry out their normal functions and how they change in malignancy," Sharp says.

Researchers Strike Gold With Nanotech Vaccine
June 25, 2013 — Scientists in the US have developed a novel vaccination method that uses tiny gold particles to mimic a virus and carry specific proteins to the body’s specialist immune cells.

The technique differs from the traditional approach of using dead or inactive viruses as a vaccine and was demonstrated in the lab using a specific protein that sits on the surface of the respiratory syncytial virus (RSV).

The results have been published today, 26 June, in IOP Publishing’s journal Nanotechnology by a team of researchers from Vanderbilt University.

RSV is the leading viral cause of lower respiratory tract infections, causing several hundred thousand deaths and an estimated 65 million infections a year, mainly in children and the elderly.

The detrimental effects of RSV come, in part, from a specific protein, called the F protein, which coats the surface of the virus. The protein enables the virus to enter into the cytoplasm of cells and also causes cells to stick together, making the virus harder to eliminate.

The body’s natural defence to RSV is therefore directed at the F protein; however, up until now, researchers have had difficulty creating a vaccine that delivers the F protein to the specialised immune cells in the body. If successful, the F protein could trigger an immune response which the body could 'remember' if a subject became infected with the real virus.

In this study the researchers created exceptionally small gold nanorods, just 21 nanometres wide and 57 nanometres long, which were almost exactly the same shape and size as the virus itself. The gold nanorods were successfully coated with the RSV F proteins and were bonded strongly thanks to the unique physical and chemical properties of the nanorods themselves.

The researchers then tested the ability of the gold nanorods to deliver the F protein to specific immune cells, known as dendritic cells, which were taken from adult blood samples.

Dendritic cells function as processing cells in the immune system, taking the important information from a virus, such as the F protein, and presenting it to cells that can perform an action against them—the T cells are just one example of a cell that can take action.

Once the F protein-coated nanorods were added to a sample of dendritic cells, the researchers analysed the proliferation of T cells as a proxy for an immune response. They found that the protein-coated nanorods caused the T cells to proliferate significantly more compared to non-coated nanorods and just the F protein alone.

Not only did this prove that the coated-nanorods were capable of mimicking the virus and stimulating an immune response, it also showed that they were not toxic to human cells, offering significant safety advantages and increasing their potential as a real-life human vaccine.

Lead author of the study, Professor James Crowe, said: "A vaccine for RSV, which is the major cause of viral pneumonia in children, is sorely needed. This study shows that we have developed methods for putting RSV F protein into exceptionally small particles and presenting it to immune cells in a format that physically mimics the virus. Furthermore, the particles themselves are not infectious.”
Due to the versatility of the gold nanorods, Professor Crowe believes that their potential use is not limited to RSV.

"This platform could be used to develop experimental vaccines for virtually any virus, and in fact other larger microbes such as bacteria and fungi.

"The studies we performed showed that the candidate vaccines stimulated human immune cells when they were interacted in the lab. The next steps to testing would be to test whether or not the vaccines work in vivo" Professor Crowe continued.

Journal Reference:

Flu Shot Effective Regardless of Circulating Flu Strain, Research Finds
June 25, 2013 — New research out of St. Michael's Hospital has found that despite popular belief, the flu shot is effective in preventing the flu, even if the virus going around does not match the vaccine.

"It's quite common for people to say they are not going to get the flu shot this year because they've heard it does not match the strain of flu going around," said Dr. Andrea Tricco, the lead author of the paper and a scientist at the Li Ka Shing Knowledge Institute of St. Michael's Hospital. "However, we've found that individuals will be protected regardless of whether the flu strain is a match or not."

The review of the literature analyzed more than 40 years of data, from 1971 to 2011, and included 47 influenza seasons and almost 95,000 healthy people.

Dr. Tricco and colleagues were particularly interested in flu seasons when the flu vaccines were not matched well to circulating strains. They wanted to understand whether the flu vaccines would still be effective when the strains were not a match.

Vaccines work by giving the body an inactive, or non-infective, form of the flu virus so that the body can produce antibodies. When an individual comes into contact with the virus in the future, the body can use the natural antibodies it has created to fight it off.

The study looked at the two most popular vaccine formulations in Canada -- Trivalent inactive vaccine for adults and live-attenuated influenza vaccine for children. They found that both vaccines provided significant protection against matched (ranging from 65 per cent to 83 per cent effectiveness) and mismatched (ranging from 52 per cent to 54 per cent effectiveness) flu strains.

The paper was published online in the journal BMC Medicine today.

"Looking at matches and mismatches can be a difficult process because it's not a yes or no variable," Dr. Tricco said. "Often we're looking at the degree of match between a flu strain and what's included in a vaccine because strains drift from year to year."

Dr. Tricco said that the study's results are mainly applicable to the seasonal flu in otherwise healthy children and adults.

Journal Reference:

Link shown between Crohn's disease and virus
A new study reveals that all children with Crohn's disease that were examined had a commonly occurring virus – an enterovirus – in their intestines. This link has previously not been shown for this chronic inflammatory intestinal disorder. The findings are being published today in the latest issue of the international journal Clinical and Translational Gastroenterology.

These findings need to be confirmed in larger studies, but they are important, as this connection has never been pointed out before. This paves the way for a better understanding of what might be involved in causing the disease, says Alkwin Wanders, one of the scientists behind the study at Uppsala University and Uppsala University Hospital.

In Sweden several thousand adults live with Crohn's disease, and each year about 100 children and adolescents develop the disorder. The disease affects various parts of the gastrointestinal system and causes symptoms such as stomach aches, diarrhoea, and weight loss – in severe cases fistulas, or strictures in the intestines.

The cause of Crohn's disease is not known. Mutations in more than 140 genes have been shown to be associated with the disorder, but this genetic connection is not a sufficient explanation. Many of these genes play key roles in the immune defence, which has prompted theories that the disease might be
caused by impaired immune defence against various microorganisms. In that case, the disease would be a consequence of interplay between heredity and environment.

Recent research has shown that some of the genes that are strongly linked to the disorder are important for the immune defence against a certain type of viruses that have their genetic material in the form of RNA, so-called RNA viruses. Using this as a point of departure, an interdisciplinary research team was established in Sweden to investigate what role this type of virus plays in the disease.

The research team includes the paediatrician Niklas Nyström, the pathologist Alkwin Wanders, virus researchers Gun Frisk and Oskar Skog, the molecular biologist Mats Nilsson, and the geneticist Ulf Gyllensten at Uppsala University and Uppsala University Hospital, along with cell biologists Jonas Fuxe and Tove Berg the paediatrician Yigael Finkel at Karolinska Institutet in Stockholm.

This unique composition, with complementary clinical and scientific expertise, has been extremely fruitful for our studies, says Alkwin Wanders.

In the present study the researchers investigated whether the RNA virus were present in children with Crohn’s disease. They focused in particular on the prevalence of enteroviruses, a group of RNA viruses that are known to infect the intestinal mucous lining.

The results showed significant amounts of enteroviruses in the intestines of all of the children with Crohn’s disease, whereas the control group had no or only minimal amounts of enteroviruses in their intestines. Similar results were obtained using two different methods. Enteroviruses were found not only in intestinal mucous linings but also in so-called nerve cell ganglia in deeper segments of the intestinal wall. Receptors for a group of enteroviruses were also found in both the intestinal mucous linings and nerve cell ganglia, which may explain how the virus can make its way into the nerve system in the intestine.

Another interesting finding is that the enterovirus could be thought to be stored in nerve cells in the intestine and to spread to different parts of the intestine via nerve fibres. This would explain both the fact that the disease is periodic (comes and goes) and the fact that it often affects multiple segments of the intestines, says Alkwin Wanders.

The present study comprises nine children with advanced Crohn's disease and fifteen children with incipient Crohn’s disease symptoms. The research now wants to go on to examine larger groups of patients and more control individuals. They also want to pursue experimental research to investigate the link further.

**Seniors Are Not Just Wrinkly Adults**

June 27, 2013 — Emergency patients over the age of 74 have significantly different and more complex health and social needs than their younger counterparts, even after controlling for illness severity, which has important implications about aging populations and emergency departments of the future. The results of the most extensive international study of the characteristics and outcomes of older emergency patients to be reported to date were published online in *Annals of Emergency Medicine*.

"These patients have complex profiles before they come to the ER, and even more complicated needs once they get there," said lead study author Leonard C. Gray, MD, PhD, of the Centre for Research in Geriatric Medicine at the University of Queensland in Brisbane, Australia. "Dependence on others and geriatric illnesses, such as cognitive impairment and mobility problems, affect the majority of older emergency patients across a wide range of nations with different health systems and cultural contexts. They require specialized care to avoid missed diagnoses, pressure ulcers and a range of other potential problems associated with this particular population."

Researchers examined medical records for 2,282 patients older than 74 in 13 different emergency departments in seven countries (Australia, Belgium, Canada, Germany, Iceland, India and Sweden). Functional and cognitive problems increased dramatically after patients arrived at the emergency department.

More than one-third (37 percent) of patients had a recent fall, prior to coming to the emergency department.

Prior to visiting the emergency department, nearly half (46 percent) were dependent on others in one or more activities of daily living; after coming to the emergency department, only 33 percent were completely independent in all activities. In the emergency department, 26 percent displayed symptoms of cognitive impairment, whereas before coming to the ER only 20 percent had cognitive difficulties. Before coming to the ER, 26 percent of older patients could not walk without supervision; after coming to the ER, that number rose to 49 percent.
"Frailty, confusion and dependence on others make these our most fragile emergency patients," said Dr. Gray. "Specialized training in geriatric care and even specialized layout and procedures can help us provide the best assessment and care. The growing prevalence of older patients in ERs around the world suggests a need for careful scrutiny of current clinical practice and design of emergency departments worldwide."

**Journal Reference:**

**Sharing the Load**

By varying the size of their steps, dynein motor proteins work effectively as teams to carry heavy loads around the cell.

By Dan Cossins | May 1, 2013

![Diagram of dynein motor proteins and phagosomes](image)

**TEAM WORK:** Dynein motor proteins carrying phagosomes along microtubules are weak individually, but strong when working in teams. As a group, dyneins usually take large steps when hauling cargo (1), but as a focused laser beam pulls the cargo in the opposite direction and load increases, the leading proteins shorten their steps (2). This allows trailing dyneins to catch up, meaning the individual proteins bunch together to better share the strain (3). Against even higher loads, dyneins activate "catch bonds," attaching themselves to microtubules to ensure they don’t get ripped off the track (4).**

**GRAPHICS**


Inside every cell is a busy transit system, with motor proteins carrying cargo back and forth on a network of polymerized protein filaments. The motor proteins traveling along these intracellular highways are essential for almost every cellular process. But while much is known about how single motors generate force, how they operate in teams is not clear.

To find out, Roop Mallik of the Tata Institute of Fundamental Research in Mumbai, India, and colleagues used optical tweezers to measure forces exerted in vivo by dyneins and kinesins, two types of motor proteins. With a focused laser beam, they trapped the cargo being carried—in this case, phagosomes containing latex beads—to effectively increase the load, and then measured at single-molecule resolution the forces generated by the motors to overcome this laser-induced resistance.
For kinesins, the stronger of the two proteins, adding a second motor didn’t significantly increase the force produced. But as the number of weaker dynein motors increased, the force generated rose in a linear fashion. “The kinesin motor is very strong individually but doesn’t work well as a team,” says Mallik. “Dynein is a very wimpy kind of motor on its own, but in numbers, these wimps become strong.”

The researchers then noticed that individual dyneins can shorten their step size and therefore slow down as the load they’re carrying increases. This sensitivity to load—not shared by kinesins—means that a dynein motor carrying more load than others in the team moves slowest, allowing the rest of the group to bunch up and therefore distribute the load more equally among individuals.

 “[The authors] have shown that the reason dynein is able to behave well in teams is because it has the flexibility of a gear-like mechanism” that alters step size and speed in response to load, says Richard McKenney, a molecular biologist at the University of California, San Francisco, who was not involved in the study. “This mechanism is distinct to dynein, and likely allows it to participate in so many cellular functions.”

Dyneins appear to have another trick for tackling heavier loads: they activate “catch bonds”—attachments to microtubules that strengthen under increasing force. “This means they can become more tenacious under higher loads,” says Mallik, and do not get ripped off the track.

Taken together, Mallik’s insights suggest that dyneins may be uniquely adapted to work in large teams, allowing for the assembly of appropriately sized collectives to meet specific needs. This could explain the counterintuitive choice of a weak motor protein for the movement of large cellular cargoes such as phagosomes and endosomes, and for the separation of chromosomes, which also requires pulling with a large force.

**Distinct Neural Pathway for Itchiness**

Scientists find the molecule that delivers itchiness signals to the brain via a dedicated, and previously unknown, neural pathway.

By Dan Cossins | May 24, 2013

Researchers have identified a particular neurotransmitter that is responsible for passing itchy sensations from the skin to the brain, and found a new subset of neurons in the spinal cord that transmits those signals, according to a study published this week (May 24) in *Science*. The findings suggest that itchiness has a neural pathway distinct from the one that mediates pain sensation.

Itchiness is triggered by the activation of sensory neurons called TRPV1 cells but these neurons also respond to heat and pain, so researchers were unsure if the sensation of itchiness might be a low level form of pain.

Analyzing proteins expressed by TRPV1 cells in mice, researchers from the National Institute of Dental and Craniofacial Research in Bethesda, Maryland, discovered that a protein called natriuretic polypeptide b (Nppb) was expressed only in a subset of the cells. Nppb-knockout mice did not respond to itch-inducing compounds, suggesting that the protein is required to produce the itch sensation.

The team found Nppb receptors on spinal cord neurons that release a molecule called gastrin-releasing peptide (GRP), a neurotransmitter suspected to relay itch signals from nerve fibers in the skin to spinal cord neurons. GRP could not be found outside the spinal cord, however, suggesting this theory was wrong. Instead, the researchers propose that GRP is released downstream of Nppb-releasing TRPV1 neurons, which are the first neurons to transmit itch signals.

The discovery will not lead to new therapies for people suffering from chronic itchiness any time soon, because neural pathways may not work the same way in humans. But “at least they have a new target,” University of Minnesota neuroscientist Glenn Giesler told *ScienceNOW*. 