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US research shows that HPV vaccination could prevent pre-cancerous anal cell changes in HIV-positive gay men

Michael Carter
Published: 03 January 2013

Vaccination against cancer-associated strains of human *papillomavirus* (HPV) could be highly effective at preventing pre-cancerous anal cell changes in men living with HIV, according to research published in the online edition of the *Journal of Infectious Diseases*.

The cross-sectional study showed that almost all cases of high-grade anal intraepithelial neoplasia (HGAIN) – the cell changes that occur in the anus prior to the development of anal cancer – were caused by strains of HPV covered by licensed or investigational vaccines. The investigators believe their findings “can inform assumptions of HPV vaccine efficacy and cost-effectiveness and decision-analysis models.”

There is a high incidence and prevalence of pre-cancerous anal lesions and anal cancer in HIV-positive gay men. Vaccines that provide a high level of protection against the HPV genotypes with the highest risk of anal and genital cancers have been licensed. Research is currently underway into potential vaccines that provide even broader protection. HPV vaccination is currently targeted at adolescent girls. There has been considerable debate about the efficacy and cost-effectiveness of vaccinating adult, HIV-positive gay men.

Doctors in San Francisco therefore designed a study involving 363 HIV-positive gay men who received care between 2009 and 2010. Each patient was screened for the presence of pre-cancerous anal lesions and provided samples for HPV genotyping. Several HPV genotypes have been associated with pre-cancerous anal cell changes. These include HPV 16/18/31/33/45/52/58. These genotypes are covered by licensed or investigational vaccines.

Multiple HPV genotypes are often present in pre-cancerous lesions. The investigators therefore developed a model that allowed them to calculate the proportion of cases of HGAIN attributable to individual HPV genotypes. “We used this information to predict the potential efficacy of prophylactic HPV vaccines, under the assumption that vaccination would occur before natural infection and seroconversion,” explain the authors.

The study participants had a median age of 53 years. They were highly sexually experienced. The median age at first anal sex was 20 years; 40% reported over 40 lifetime anal sex partners; and 15% reported three or more partners for anal sex within the previous six months. The majority (94%) were taking antiretroviral therapy. Approximately three-quarters (72%) had a CD4 cell count above 350 cells/mm$^3$ and 90% had an undetectable viral load.

The majority of the patients (59%) had pre-cancerous anal lesions, including 30% with HGAIN. Three-quarters of individuals were infected with a high-risk HPV genotype. HPV16 was the most common individual genotype, present in 28% of patients.

“HPV16, which has been shown to cause an even greater proportion of anal cancers than cervical cancers, is seen as the dominant genotype in HGAIN disease categories,” write the authors. “Other HPV genotypes vary substantially in their prevalence and attribution estimates in our study.”

The prevalence of high-risk HPV genotypes increased significantly according to the severity of pre-cancerous anal lesions ($p < 0.05$). Patients with more severe disease were also significantly more likely to be infected with multiple high-risk HPV genotypes. Up to seven individual high-risk genotypes were identified in individual lesions.

Depending on the number of infecting HPV genotypes, the proportion of cases of HGAIN attributed to HPV16/18 and other individual genotypes covered by currently licensed vaccines ranged between 12 and 62%. The fraction of cases attributed to the individual genotypes targeted by investigational vaccines ranged between 39 and 89%.

Taken together, 95% of all high-grade lesions were attributed to high-risk genotypes. The licenced quadrivalent vaccine covered 71% of genotypes present in the highest-grade lesions, whereas the investigational nonavalent vaccine would have provided protection against 89% of HPV genotypes in high-grade lesions.

“The prevention of anal cancer in high-risk populations such as HIV-infected MSM [men who have sex with men] remains an urgent priority,” conclude the investigators. “The analytical framework presented in this study can be applied to larger and pooled efforts to improve estimations of the causative role of individual genotypes and expand our understanding of the natural history of and prevention approaches for anal neoplastic disease.”
AIDS Activist Spencer Cox Dies of AIDS-related Causes
Published on Thursday, 27 December 2012 00:00
Written by Liz Highleyman
Photo: Walter Kurtz

Spencer Cox, a leading AIDS activist who played a key role in the development of effective antiretroviral therapy, died of AIDS-related causes at Columbia Presbyterian Hospital in New York City last Tuesday, December 18. He was 44.

Committee and a co-founder of its offshoot, the Treatment Action Group (TAG), at a time when activists, doctors, health officials, and researchers alike were teaching themselves about HIV and its treatment.

"The significance of Spencer's contributions to HIV treatment research is immeasurable," said Tim Horn, TAG's new HIV Project Director. "Not only did he apply his genius and perseverance to ensure speedy access to desperately needed antiretrovirals, he made sure we had the sound, scientific data necessary to make informed treatment decisions—a 2-pronged research activism approach that remains with us to this day."

Patrick Spencer Cox was born March 10, 1968, near Atlanta. Escaping Georgia's homophobic climate, he studied theater and literature at Bennington College in Vermont. Throughout his life, he was an avid fan of theater and movies, often regaling friends with impressions of stage and screen divas.

Cox moved to New York as a teenager in the late 1980s and was diagnosed with HIV soon thereafter. He worked as an intern and later on the staff of amfAR (the Foundation for AIDS Research) and co-founded the Community Research Initiative on AIDS (now the AIDS Community Research Initiative of America).

As a member of ACT UP/NY and TAG, Cox helped push HIV protease inhibitors through the development pipeline, as portrayed in the award-winning documentary How to Survive a Plague.

"I'm still amazed how young he was during the ACT UP and TAG years, meeting with the likes of [National Institute of Allergy and Infectious Diseases head Anthony] Fauci and [former National Institute of Health director Harold] Varmus, and blowing their socks off," said fellow TAG co-founder Peter Staley. "We were all just kids, and he was seven years my junior. But mostly I'll remember his dark humor, which helped us all handle those years a little easier."

Cox developed a novel clinical trial protocol for testing HIV protease inhibitors, in which participants added a new medication or a placebo to a background combination of existing drugs.

The trial design was controversial, as some felt it was unethical not to give all participants the new drugs. An article by Cox in Barron's magazine defending the design made him "the most-hated AIDS activist in America," according to Plague director David France. But the first such trial was able to show a 50% reduction in deaths over 6 months, leading to protease inhibitor approval in late 1995 and early 1996.

"Spencer reminded us that faster answers to treatment questions are not always the best," said former ACT UP/Golden Gate member Virg Parks. "That pragmatism has a place even when making demands of a monolithic drug approval process."

"He wanted the facts and was always very meticulous about getting good data rather than just screaming for getting something approved," Fauci told the New York Times.

Today, ACT UP and TAG are credited with lasting changes in the way new drugs are developed, clinical trials are conducted, and healthcare providers relate to their patients, and the movement defined by Cox and his comrades has inspired a new generation of activists.

Life after TAG
Once protease inhibitors were approved and combination antiretroviral therapy was widely adopted, AIDS activism entered a lull as some people went into the medical field or AIDS service organizations, while others tried to put the epidemic behind them. But the burden of grief was not so easy to shrug off.

Reference
Cox's later life and death exemplify the fate of many activists and people with AIDS who recovered their health but found it difficult to resume normal lives after witnessing so much death, or to find equally meaningful work.

Cox left TAG in 1999, endured a period of serious illness and living on disability for several years. Over the years he had periodic bouts of methamphetamine use, went on and off antiretroviral treatment, developed resistant virus, and came down with AIDS-related illnesses attributed to inconsistent therapy.

Around 2005 Cox founded the Medius Institute for Gay Men's Health, a think tank focusing on gay men's emotional health including depression and substance use and their relation to HIV infection. The institute folded due to lack of financial support, but he continued to do freelance writing on topics such as post-traumatic stress and survivor guilt.

"I think those of us who were in the middle of it were deeply affected by what we experienced and that it affects the choices we make today," he wrote in the June 2006 issue of POZ. "[M]aybe once in a while, we need to stop and remember what happened to us. Maybe if we made some room for our sadness, we wouldn't be so depressed."

Cox returned to Georgia, but he found that the political climate remained hostile. In recent years he spent increasing amounts of time interacting on news and social media websites such as Gawker and Facebook, offering irascible argument, biting wit, and pictures of bulldog puppies.

In the months before his death Cox went back to New York, where he participated in events related to How to Survive a Plague. His death last week was attributed to AIDS-related causes, but many friends and fellow activists blamed a legacy of despair.

"Spencer died of despair, racism, homophobia, AIDS-phobia, and a host of other ills that afflict our country and our world," TAG co-founder and current director Mark Harrington wrote in a memorial statement. "He saved millions of lives, but could not save his own."

"His sharp wit often masked his thoughtful kindness, and his joyful and devilish spirit sometimes masked the inescapable wounds of the early years of the epidemic," added Brenda Lein, program manager for the Delaney AIDS Research Enterprise at UCSF. "History will remember Spencer as a hero of the AIDS activist movement and likely everyone who knew him will remember him also as a casualty—not just of AIDS, but of being present during the most difficult years of the epidemic."

But Mr. Cox emphasized the joy as well as the pain of the early AIDS years. In an October POZ blog entry commenting on the film—which brought the founding TAG members back into the spotlight and helped spur an ACT UP revival—he recalled "the sheer joy inherent in the whole thing."

"We laughed so very much...we sang, we made love...and we very consciously tried to make sure that, when the plague was over, there would be something left that would have been worth preserving," he continued. "If I have one piece of advice for young, aspiring activists, it is to always hold on to the joy, always make it fun. If you lose that, you have lost the whole battle."

"The loss and mourning of Spencer Cox calls upon activists to find sustainable and joyous ways to engage in political work," said Alan Gutierrez, a member of the new ACT UP/San Francisco. "Spencer is leaving us with an obligation to de-stigmatize drug use and enhance the life opportunities of people living with HIV."

Mr. Cox is survived by his mother and brother. A memorial service will take place at 3 p.m. on Sunday, January 20, at the Cutting Room, 44 East 32 Street in New York. Donations in his memory may be made to the Ali Forney Center, Broadway Cares/Equity Fights AIDS, or HeavenSent Bulldog Rescue. [Another version of this obituary appeared in the December 27, 2012, issue of the Bay Area Reporter.]

NYTimes

Alabama to End Isolation of Inmates With H.I.V.
Jamie Martin/Associated Press

By ROBBIE BROWN

Published: December 21, 2012

Alabama is one of two states, along with South Carolina, where H.I.V.-positive inmates are housed in separate prisons, away from other inmates, in an attempt to reduce medical costs and stop the spread of the virus, which causes AIDS.

Judge Myron H. Thompson of the Middle District of Alabama ruled in favor of a group of inmates who argued in a class-action lawsuit that they had been stigmatized and denied equal access to educational programs. The judge called the state's policy “an unnecessary tool for preventing the
transmission of H.I.V." but “an effective one for humiliating and isolating prisoners living with the disease.”

After the AIDS epidemic of the 1980s, many states, including New York, quarantined H.I.V.-positive prisoners to prevent the virus from spreading through sexual contact or through blood when inmates tattooed one another. But most states ended the practice voluntarily as powerful antiretroviral drugs reduced the risk of transmission.

In Alabama, inmates are tested for H.I.V. when they enter prison. About 250 of the state’s 26,400 inmates have tested positive. They are housed in special dormitories at two prisons: one for men and one for women. No inmates have developed AIDS, the state says.

H.I.V.-positive inmates are treated differently from those with other viruses like hepatitis B and C, which are far more infectious, according to the World Health Organization. Inmates with H.I.V. are barred from eating in the cafeteria, working around food, enrolling in certain educational programs or transferring to prisons near their families.

Prisoners have been trying to overturn the policy for more than two decades. In 1995, a federal court upheld Alabama’s policy. Inmates filed the latest lawsuit last year.

“Today’s decision is historic,” said Margaret Winter, the associate director of the National Prison Project of the American Civil Liberties Union, which represented the inmates. “It spells an end to a segregation policy that has inflicted needless misery on Alabama prisoners with H.I.V. and their families.”

Brian Corbett, a spokesman for the Alabama Department of Corrections, said the state is “not prejudiced against H.I.V.-positive inmates” and has “worked hard over the years to improve their health care, living conditions and their activities.”

“We will continue our review of the court’s opinion and determine our next course of action in a timely manner,” he wrote.

During a monthlong trial in September, lawyers for the department argued that the policy improved the treatment of H.I.V.-positive inmates. Fewer doctors are needed if specialists in H.I.V. focus on 2 of the 29 state’s prisons.

The state spends an average of $22,000 per year on treating individual H.I.V.-positive inmates. The total is more than the cost of medicine for all other inmates, said Bill Lunsford, a lawyer for the Corrections Department.

South Carolina has also faced legal scrutiny. In 2010, the Justice Department notified the state that it was investigating the policy and might sue to overturn it.

Higher Dose Flu Vaccine Works Better for People with HIV
Published on Thursday, 03 January 2013 00:00
Written by Liz Highleyman
Image: CDC
HIV positive people who received a quadruple dose of a trivalent seasonal influenza vaccine produced more protective antibodies without a significant increase in side effects, researchers reported in the January 1, 2013, Annals of Internal Medicine.

People with HIV may be more susceptible to and prone to complications from certain types of influenza, and are therefore advised to receive an annual flu vaccine each year. However, individuals with impaired immune function may have difficulty mounting an adequate antibody response after vaccination.

Noah McKittrick from the University of Pennsylvania Center for AIDS Research and colleagues compared the immunogenicity—or ability to stimulate an immune response—of a standard dose versus a high dose of a trivalent inactivated vaccine designed to protect against 3 strains: H1N1 influenza A, H3N2 influenza A, and influenza B.

This double-blind controlled trial enrolled 195 adult participants at the University of Pennsylvania hospital in Philadelphia between October 2010 and March 2011. Participants were randomly assigned (1:1) to receive single intramuscular injections of either a standard-dose formulation (15 mcg of antigen per flu strain) or a high-dose formulation (60 mcg per strain) of the Fluzone vaccine. The high-dose formulation was approved in 2009 for people over age 65, who also may have difficulty producing enough antibodies.
About 70% of participants were men and the median age was 45 years, with a good representation of white and black patients. Nearly 90% were on stable antiretroviral therapy (ART)—mostly with suppressed HIV viral load—while the rest were not yet on ART and not planning to start during the next month. The median current CD4 T-cell count was approximately 445 cells/mm³, but the nadir or lowest-ever level was about 170 cells/mm³, indicating considerable immune impairment. About half had protective H1N1 and influenza B titers at baseline, likely reflecting the high flu vaccination rate in 2009.

The primary efficacy endpoint was the proportion of people who achieved seroprotection, or sufficient antibody production 21-28 days after vaccination (defined as antibody titers of 1:40 or greater on a hemagglutination inhibition assay). The researchers also looked at the rate of seroconversion (> 4-fold increase in antibody concentrations) and average antibody titers. The primary safety endpoint was frequency and intensity of adverse events.

190 participants who completed the study (93 in the standard-dose group and 97 in the high-dose group) were included in the efficacy analysis, while all 195 were included in the safety analysis.

**Results**

- Seroprotection rates after vaccination were greater in the high-dose group compared with the standard-dose group for all 3 flu strains in the vaccine:
  - H1N1: 87% standard-dose vs 96% high-dose (P = 0.029);
  - H3N2: 92% vs 96%, respectively (P = 0.32);
  - Influenza B: 80% vs 91%, respectively (P = 0.030).
- Likewise, seroconversion rates were also higher in the high-dose compared with the standard-dose group:
  - H1N1: 59% standard-dose vs 75% high-dose (P= 0.018);
  - H3N2: 74% vs 78%, respectively;
  - Influenza B: 34% vs 56%, respectively.
- For both comparisons, the differences were significant for H1N1 and influenza B, but responses were statistically similar for H3N2.
- The high-dose vaccine also appeared more effective for participants with fewer than 200 cells/mm³, but the number of such patients was too small to determine significance.
- Both vaccine doses were described as "well-tolerated," with similar frequency of adverse events in both dose groups and no serious adverse events related to vaccine administration.
- The most common side effects were myalgia or muscle aches (18% standard-dose vs 19% high-dose), malaise (15% vs 13%, respectively), and localized tenderness at the injection site (11% vs 10%); localized pain was more frequent in the high-dose group, however (4% vs 15%, respectively).
- Based on these findings, the study authors wrote, "HIV-infected persons reach higher levels of influenza seroprotection if vaccinated with the high-dose trivalent vaccine than with the standard-dose."

"The results from this randomized, controlled study suggest that 1 way to increase the protective antibody titers for influenza in HIV-infected persons is to administer a higher dose (60 mcg/antigen—4 times the standard dose of 15 mcg/antigen) of the trivalent seasonal influenza vaccine," they elaborated in their discussion. "For every antigen studied, the high-dose formulation resulted in an increased average antibody titer and higher seroconversion and seroprotective rates compared with the standard-dose influenza vaccine."

They cautioned that the study did not evaluate whether participants were protected against clinical influenza. Also, the number of people with CD4 counts below 200 cells/mm³ was small, and this group might have a lower vaccine response rate due to extensive immune system impairment.

"This study suggests that a substantial number of HIV-infected patients may not be obtaining sufficient protection with the standard influenza vaccine," they concluded. "A strategy with a single high-dose immunization is much easier to implement than a multiple-dose schedule. Although a higher dose is 1 route to the protection of this vulnerable population, other strategies may also be explored in the future, such as alternative vaccines, the use of adjuvants, or new schedule strategies."

**Reference**

Inactivated Virus Shows Promise Against HIV

Science News, (01.03.2013) Nathan Seppa

A new study shows that injecting heat-inactivated HIV can arouse the immune system in some patients, allowing them temporary freedom from drugs. Ultimately, this approach could lead to a long-term treatment of HIV.

Researchers extracted HIV and a sampling of immune system cells (dendritic cells) from 36 patients. The researchers used heat to inactivate the HIV of 22 randomly selected patients, and then administered the patients a vaccine comprised of their own dendritic cells and their inactivated HIV. In 12 of the 22 patients, virus levels dropped 90 percent over 12 weeks.

According to study co-author Felipe Garcia, an infectious disease physician at the University of Barcelona, the combination of dendritic cells and inactivated HIV stir the immune system to attack the live virus circulating in patients' bodies. In the treated patients, the immunity to HIV diminished and virus levels increased eventually. After 48 weeks only three participants who received the experimental vaccine maintained the 90-percent drop in virus levels. The patients in the control group who received their own unchanged HIV and dendritic cells showed little benefit. Prior to the study, all participants were being treated with standard antiretroviral therapy.

Garcia suggests that a therapeutic vaccine would still be beneficial, even if it offered only long-lasting temporary effects rather than completely eradicating HIV from the body. He stated that dropping the virus down to extremely low levels may mean patients would not need drugs, would not show symptoms, and would not be likely to transmit the disease to others. He noted that people with these low levels of virus (elite controllers) already exist, in the less than 1 percent of people who have been infected with HIV for years, but whose immune systems suppress the virus.

The study, "A Dendritic Cell–Based Vaccine Elicits T Cell Responses Associated with Control of HIV-1 Replication," was published in the journal Science Translational Medicine (2013; 5 (166): 166ra2).

Yearlong Moratorium On H5N1 Research Soon Lifted, New Rules Implemented,

Science Reports

"U.S. government officials say they expect to put the finishing touches this month on new rules designed to help funding agencies identify and regulate especially problematic H5N1 studies before they begin," which would allow influenza researchers "to lift a year-old, self-imposed moratorium on certain kinds of potentially dangerous experiments," Science reports. "The two developments would essentially end a long and bruising controversy over the risks and benefits of H5N1 research," the magazine notes, adding the debate was initiated by two research teams that lab-engineered H5N1 strains to be transmissible among mammals. "The issue has been especially sensitive for the U.S. government, because its National Institutes of Health (NIH) funded the two studies and is one of the world’s biggest funders of H5N1 research," Science writes. The magazine discusses the moratorium’s impact on research worldwide and summarizes differing views about its effects (Malakoff, 1/4).

Experts At December WHO Meeting Agree Upon Sleeping Sickness Elimination Plan

Experts at a December 2012 WHO meeting agreed on a plan to eliminate sleeping sickness (human African trypanosomiasis), the Lancet reports. Highlighting the difference between eradication—"incidence is permanently reduced to zero cases worldwide and no further action is needed"—and elimination—"incidence is reduced to zero cases worldwide or in a defined geographical area but action might be needed to keep it that way"—the journal writes the goal is to bring the number of cases to zero, as eradication would mean ridding the world of the tsetse fly, which is responsible for transmission.

"Achieving the zero-cases-zero-transmission target, the WHO meeting participants agreed, will not be easy," the Lancet notes and discusses a number of challenges, such as "a lack of field-friendly diagnostic tests" and the hunt for cases "in the remote jungle villages where most patients—and most tsetse flies—live." However, "despite these difficulties, the meeting participants expressed few doubts about their ability to reach the zero-case target, at least for the west African form of the disease," the journal notes, adding, "One reason for optimism is that the target was almost reached in the past" (Maurice, 1/5).

Editorial, Opinion Pieces Address Effects Of Health Worker Murders In Pakistan On Polio Eradication

Several news outlets published opinion pieces regarding the recent murders of polio vaccination and other aid workers in Pakistan. The following summarizes two opinion pieces and one editorial on the issue.
Japanese team creates cancer-specific killer T cells from induced pluripotent stem cells

Researchers from the RIKEN Research Centre for Allergy and Immunology in Japan report today that they have succeeded for the first time in creating cancer-specific, immune system cells called killer T lymphocytes, from induced pluripotent stem cells (iPS cells). To create these killer cells, the team first had to reprogram T lymphocytes specialized in killing a certain type of cancer, into iPS cells. The iPS cells then generated fully active, cancer-specific T lymphocytes. These lymphocytes regenerated from iPS cells could potentially serve as cancer therapy in the future.

Previous research has shown that killer T lymphocytes produced in the lab using conventional methods are inefficient in killing cancer cells mainly because they have a very short life-span, which limits their use as treatment for cancer. To overcome these problems, the Japanese researchers led by Hiroshi Kawamoto and presenting their results in the journal Cell Stem Cell online today, reprogrammed mature human killer T lymphocytes into iPS cells and investigated how these cells differentiate.

The team induced killer T lymphocytes specific for a certain type of skin cancer to reprogram into iPS cells by exposing the lymphocytes to the 'Yamanaka factors'. The 'Yamanaka factors' is a group of compounds that induce cells to revert back to a non-specialized, pluripotent stage. The iPS cells obtained were then grown in the lab and induced to differentiate into killer T lymphocytes again. This new batch of T lymphocytes was shown to be specific for the same type of skin cancer as the original lymphocytes: they maintained the genetic reorganization enabling them to express the cancer-specific receptor on their surface. The new T lymphocytes were also shown to be active and to produce the anti-tumor compound interferon γ.

"We have succeeded in the expansion of antigen-specific T cells by making iPS cells and differentiating them back into functional T cells. The next step will be to test whether these T cells can selectively kill tumor cells but not other cells in the body. If they do, these cells might be directly injected into patients for therapy. This could be realized in the not-so-distant future." explains Dr Kawamoto.
Rethinking bacterial persistence

Optofluidics allow for a new understanding of resistance to antibiotics

It's often difficult to completely eliminate a bacterial infection with antibiotics; part of the population usually manages to survive. We've known about this phenomenon for quite some time, dating back nearly to the discovery of penicillin. For more than 50 years, scientists have believed that the resistant bacteria were individuals that had stopped growing and dividing.

Up to now, in fact, it hasn't been possible to track the growth of cells before and after their exposure to antibiotics, which makes any analysis of the phenomenon quite imprecise. "Using microfluidics, we can now observe every bacterium individually, instead of having to count a population," says John McKinney, director of EPFL's Microbiology and Microsystems Laboratory (LMIC).

Active survivors

This new tool has revealed quite a few surprises. "We thought that surviving bacteria made up a fixed population that stopped dividing, but instead we found that some of them continued to divide and others died. The persistent population is thus very dynamic, and the cells that constitute it are constantly changing – even though the total number of cells remains the same. Because they're dividing, the bacteria can mutate and thus develop resistance in the presence of the antibiotic," explains LMIC scientist Neeraj Dhar.

This point is extremely important. "We were able to eliminate a purely genetic explanation of the phenomenon," continues Dhar. In other words, "a population of genetically identical bacteria consists of individuals with widely varying behavior. Some of them can adapt to stressors that they have not previously encountered, thanks to the selection of persistent individuals. This could lead to a revision of the entire theory of adaptation," says McKinney.

Intermittent efficiency

The EPFL scientists were particularly interested in a relative of the tuberculosis bacterium. Their observations enabled them to formally challenge the argument that persistent bacteria are those that have stopped growing and dividing. "We were able to reveal the role of an enzyme whose presence is necessary in order for the antibiotic to work, and show that the bacilli produced this enzyme in a pulsatile and random manner," explains Dhar. "Our measurements showed that bacterial death correlated more closely with the expression of this enzyme than with their growth factor." The research is being published this week in Science magazine.

These conclusions could mark the beginning of a new theory of bacterial resistance, or perhaps even introduce a new view of how such resistance evolves. Further research is being done using other microorganisms, such as tuberculosis and E. coli bacteria. The persistence of some cancer cells to treatment could also be studied in a different manner. "It's a new approach for trying to figure out why some infections are so difficult to eliminate. The techniques we've developed for this study are now also being used to develop new antibiotics, in collaboration with pharmaceutical companies," says McKinney, adding that "it is the microengineering expertise at EPFL that has enabled us to create these innovative tools and open up new avenues for investigation."

Breast milk contains more than 700 bacteria ***

Microbes taken from breast milk by the infant are identified

Spanish researchers have traced the bacterial microbiota map in breast milk, which is the main source of nourishment for newborns. The study has revealed a larger microbial diversity than originally thought: more than 700 species.

The breast milk received from the mother is one of the factors determining how the bacterial flora will develop in the newborn baby. However, the composition and the biological role of these bacteria in infants remain unknown.

A group of Spanish scientists have now used a technique based on massive DNA sequencing to identify the set of bacteria contained within breast milk called microbiome. Thanks to their study, pre- and postnatal variables influencing the microbial richness of milk can now be determined.

Colostrum is the first secretion of the mammary glands after giving birth. In some of the samples taken of this liquid, more than 700 species of these microorganisms were found, which is more than originally expected by experts. The results have been published in the 'American Journal of Clinical Nutrition'.

"This is one of the first studies to document such diversity using the pyrosequencing technique (a large scale DNA sequencing determination technique) on colostrum samples on the one hand, and breast
milk on the other, the latter being collected after one and six months of breastfeeding," explain the coauthors, María Carmen Collado, researcher at the Institute of Agrochemistry and Food Technology (IATA-CSIC) and Alex Mira, researcher at the Higher Public Health Research Centre (CSISP-GVA).

The most common bacterial genera in the colostrum samples were *Weissella*, *Leuconostoc*, *Staphylococcus*, *Streptococcus* and *Lactococcus*. In the fluid developed between the first and sixth month of breastfeeding, bacteria typical of the oral cavity were observed, such as *Veillonella*, *Leptotrichia* and *Prevotella*.

"We are not yet able to determine if these bacteria colonise the mouth of the baby or whether oral bacteria of the breast-fed baby enter the breast milk and thus change its composition," outline the authors.

**The heavier the mother, the fewer the bacteria**

The study also reveals that the milk of overweight mothers or those who put on more weight than recommended during pregnancy contains a lesser diversity of species.

The type of labour also affects the microbiome within the breast milk: that of mothers who underwent a planned caesarean is different and not as rich in microorganisms as that of mothers who had a vaginal birth. However, when the caesarean is unplanned (intrapartum), milk composition is very similar to that of mothers who have a vaginal birth.

These results suggest that the hormonal state of the mother at the time of labour also plays a role: "The lack of signals of physiological stress, as well as hormonal signals specific to labour, could influence the microbial composition and diversity of breast milk," state the authors.

**Help for the food industry**

Given that the bacteria present in breast milk constitute one of initial instances of contact with microorganisms that colonise the infant’s digestive system, the researchers are now working to determine if their role is metabolic (it helps the breast-fed baby to digest the milk) or immune (it helps to distinguish beneficial or foreign organisms).

For the authors, the results have opened up new doors for the design of child nutrition strategies that improve health. "If the breast milk bacteria discovered in this study were important for the development of the immune system, its addition to infant formula could decrease the risk of allergies, asthma and autoimmune diseases," conclude the authors.

**Reference:**


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**Rainfall, brain infection linked in sub-Saharan Africa**

UNIVERSITY PARK, Pa.—The amount of rainfall affects the number of infant infections leading to hydrocephalus in Uganda, according to a team of researchers who are the first to demonstrate that these brain infections are linked to climate.

Hydrocephalus—literally "water on the brain"—is characterized by the build-up of the fluid that is normally within and surrounding the brain, leading to brain swelling. The swelling will cause brain damage or death if not treated. Even if treated, there is only a one-third chance of a child maintaining a normal life after post-infectious hydrocephalus develops, and that chance is dependent on whether the child has received the best treatment possible.

"The most common need for a child to require neurosurgery around the world is hydrocephalus," said Steven J. Schiff, the Brush Chair Professor of Engineering, director of the Penn State Center for Neural Engineering and a team member.

In sub-Saharan Africa, upward of 100,000 cases of post-infectious hydrocephalus a year are estimated to occur. The majority of these cases occur after a newborn has suffered from neonatal sepsis, a blood infection that occurs within the first four weeks of life, the researchers reported in a recent issue of the *Journal of Neurosurgery: Pediatrics*.

Benjamin C. Warf, associate professor of neurosurgery, Harvard Medical School, Boston Children's Hospital, noticed that about three or four months after an infant in East Africa had an infection like
neonatal sepsis, the child would often return to the clinic with a rapidly growing head—hydrocephalus. Schiff joined Warf to help figure out what caused this disease so frequently.

Schiff and colleagues tracked 696 hydrocephalus cases in Ugandan infants between the years 2000 and 2005. The researchers obtained localized rainfall data for the same time frame through NOAA (National Oceanic and Atmospheric Administration) weather satellites using the African Rainfall Estimation Algorithm developed at the U.S. NOAA Climate Prediction Center. Uganda has two peak rainfall seasons, in spring and fall. By comparing the data from NOAA and the hydrocephalus cases, the researchers found that instances of the disorder rose significantly at four different times throughout the year—before and after the peak of each rainy season, when the amount of rainfall was at intermediate levels. In Uganda an intermediate rainfall is about 6 inches of rain per month.

Schiff and colleagues previously noted that different bacteria appear associated with post-infectious hydrocephalus at different seasons of the year. While the researchers have not yet characterized the full spectrum of bacteria causing hydrocephalus in so many infants, they note that environmental conditions affect conditions supporting bacterial growth, and that the amount of rain can quench bacterial infections. The moisture level clearly affects the number of cases of hydrocephalus in this region of East Africa.

"Hydrocephalus is the first major neurosurgical condition linked to climate," said Schiff, who is also professor of neurosurgery, engineering science and mechanics, and physics, and a faculty member of the Huck Institutes of the Life Sciences. "This means that a substantial component of these cases are almost certainly driven from the environmental conditions, and that means they are potentially preventable if we understand the routes and mechanisms of infection better."

Biologists Unlock 'Black Box' to Underground World: How Tiny Microbes Make Life Easier for Humans

Jan. 2, 2013 — A BYU biologist is part of a team of researchers that has unlocked the "black box" to the underground world home to billions of microscopic creatures.

That first peek inside, recently published in the Proceedings of the National Academy of Sciences, may well explain how the number of species in an ecosystem changes the way it functions.

"The organisms that live in soil do all kinds of important things for us—they decompose and decontaminate our waste and toxic chemicals, purify our water, prevent erosion, renew fertility," said BYU biology professor Byron Adams, a study coauthor. "But we know very little about how they do this. What species need to be present? What are the different jobs that we need them to do?"

For their analysis, Adams and his colleagues took 16 soil samples from all reaches of the globe, from Antarctica to tropical forest locations, extracted the DNA out of all the organisms in each sample, and sequenced it.

With information about the genome (the complete set of its DNA and all of its genes) of each microbe in the soil, the researchers were able to see which organisms do what, and whether or not their functional roles are redundant or unique.

"People think you're going to pick up a handful of dirt anywhere in the world and you'll pretty much have the same bunch of microbes doing pretty much the same things," Adams said. "That's simply not true. They function very differently based on their environment. And when you have more species, you get more, and different functions."

Having several different species that do the same job might mean that if one species goes extinct then the others can pick up the slack. On the other hand, in ecosystems like deserts, where there are few species and even fewer jobs, removing some species could result in collapse, or failure of the ecosystem to provide the services we need.

Understanding the relationship between biodiversity and the different jobs that soil microbes do is a first step towards understanding how to better harness these organisms in order to prevent the collapse of the very systems that provide critical ecosystem services, such as fertile soil and clean water.

"The most obvious applications of this understanding will probably be in agricultural ecosystems," Adams said.

A better understanding of below-ground ecosystems can help humans predict how those systems will respond to things such as climate change or perturbations to the soil from mining, drilling or waste. And, hopefully, that understanding can help prevent agricultural or environmental catastrophes.

"We've been walking around on soil since the beginning of time and never really knew what was going on underneath us," Adams said. "Now we will be able to make predictions of how ecosystems function,
what causes them to collapse, and perhaps even predict, where collapses will take place and how we can prevent them."

The lead author on the study was Noah Fierer, an associate professor of Ecology and Evolutionary Biology at the University of Colorado, Boulder.

The researchers' data also may have something to say about how new species form. For centuries it was thought that geographic barriers (like mountains, peninsulas, rivers and deserts) were the primary engines of speciation. However, it could be that interactions with other species are just as important.

The authors believe this study will open up significant additional research addressing speciation and the evolution of microbial communities.

**Journal Reference:**

**Previous Studies On Toxic Effects of BPA Couldn't Be Reproduced**

Jan. 2, 2013 — Following a three-year study using more than 2,800 mice, a University of Missouri researcher was not able to replicate a series of previous studies by another research group investigating the controversial chemical BPA. The MU study is not claiming that BPA is safe, but that the previous series of studies are not reproducible. The MU study, published in the *Proceedings of the National Academy of Sciences*, also investigated an estrogenic compound found in plants, genistein, in the same three-year study.

"Our findings don't say anything about the positive or negative effects of BPA or genistein," said Cheryl Rosenfeld, associate professor of biomedical sciences in MU's Bond Life Science Center. "Rather, our series of experiments did not detect the same findings as reported by another group on the potential developmental effects of BPA and genistein when exposure of young occurs in the womb."

Creating reliable data on the effects of the chemicals on mice is important to human health since people are frequently exposed to BPA and genistein and humans share similar biological functions with mice. BPA is a chemical used in certain plastic bottles and may be found in the lining of some canned goods and receipt paper. Genistein occurs naturally in soy beans and is sold as a dietary supplement.

Research by Fredrick vomSaal, professor of biological science at MU, and others suggests the chemicals may have other adverse effects on many animals, including humans.

Researcher who conducted the original series of experiments claimed that exposure to BPA and genistein resulted in yellow coat color, or agouti, offspring that were more susceptible to obesity and type 2 diabetes compared to their brown coat color, healthy siblings. However, Rosenfeld and her team did not obtain the same results when repeating the study over a three-year period.

After failing to repeat the original experiments findings with similar numbers of animals, Rosenfeld's group extended the studies to include animal numbers that surpassed the prior studies to verify that their findings were not a fluke and to provide sufficient number of animals to ensure that significant differences would be detected if they existed. However, even these additional numbers of animals and extended experiments failed to reproduce the earlier findings. However, the current studies demonstrate that a maternal diet enriched in estrogenic compounds leads to a greater number of offspring that express an agouti gene compared to those that do not, even though equal ratios should have been born.

"This finding suggests that certain uterine environments may favor animals with a 'thrifty genotype' meaning that the agouti gene of mice may help them survive in unfavorable uterine environments over those mice devoid of this gene, Yet, the downside of this expression of the agouti during early development is that the animals may be at risk for later metabolic disorders, such as obesity and diabetes" Rosenfeld said. "In this aspect, humans also have an agouti gene that encodes for the agouti signaling protein (ASIP) that is expressed in fat tissue and pancreas, and there is some correlation that obese individuals exhibit greater expression of this gene compared to leaner individuals. Therefore, the agouti gene may have evolved to permit humans the ability to survive famine, but its enhanced expression may also potentiate metabolic diseases under bountiful food conditions."

While the research casts doubt on the previous study, Rosenfeld said that by understanding the genetic profile of the mice in the first series of studies, scientists could learn more about the correlation between certain genes and obesity. This could eventually influence prevention and treatment programs for patients with diabetes and other obesity-related diseases in humans.
Epidemics of Community-Associated Methicillin-Resistant *Staphylococcus aureus* in the United States: A Meta-Analysis
Vanja M. Dukic, Diane S. Lauderdale, Jocelyn Wilder, Robert S. Daum, Michael Z. David

Abstract
*Staphylococcus aureus* is the most frequent cause of skin and soft tissue infections in humans. Methicillin-resistant strains of *S. aureus* (MRSA) that emerged in the 1960s presented a relatively limited public health threat until the 1990s, when novel community-associated (CA-) MRSA strains began circulating. CA-MRSA infections are now common, resulting in serious and sometimes fatal infections in otherwise healthy people. Although some have suggested that there is an epidemic of CA-MRSA in the U.S., the origins, extent, and geographic variability of CA-MRSA infections are not known. We present a meta-analysis of published studies that included trend data from a single site or region, and derive summary epidemic curves of CA-MRSA spread over time. Our analysis reveals a dramatic increase in infections over the past two decades, with CA-MRSA strains now endemic at unprecedented levels in many US regions. This increase has not been geographically homogeneous, and appears to have occurred earlier in children than adults.

Conclusions
Many single-center studies have demonstrated an increase in MRSA infections outside of the health care setting in the past two decades. Using all available published data in our models, we confirmed this dramatic increase across the U.S. in CA-MRSA infections, and for the first time, we documented a plateau in this trend that differs by age group. CA-MRSA infections now appear to be endemic and at unprecedented levels in many regions. This is true whether we measure CA-MRSA infections as a proportion of all *S. aureus* infections, as a proportion of all MRSA infections, or as population incidence. This increase has not been geographically homogeneous, and we found that the dissemination of CA-MRSA strains appears to have occurred earlier in children than among adults.

Our models suggest that CA-MRSA infections began to appear in the U.S. in the early or middle 1980s, earlier than most published studies would suggest, and increased slowly through the 1990s. Beginning around 2000, there was a rapid rise that started to plateau in the late 2000s – with the exception of pediatric cases which appeared and plateaued earlier. Cases among military populations also appeared and plateaued earlier than other adult populations. The rapid rise coincided with the recognition of USA300, now the predominant strain of CA-MRSA in the U.S. [5]. Overall, our models, largely based on urban populations, support the findings of previous studies that have shown that, with the emergence of CA-MRSA strains, there was a rapid, consistent, nation-wide shift in the genetic backgrounds of *S. aureus* strains causing human infections in the U.S. in a relatively short period of time. Our study does not address why this shift occurred; this remains a conundrum for further study.

Our findings contrast with those from the CDC’s ABC, which recorded only invasive MRSA infections, a clinically severe subset of MRSA infections diagnosed most often among hospitalized patients [7], [26]. The CDC’s ABC data demonstrate that the incidence of health care-associated invasive MRSA infections decreased steadily in 2004–2008 [26]; this may reflect interventions by infection control programs in the health care setting, or the changing genetic backgrounds of MRSA clones circulating in that setting. In the present study we found that the incidence of CA-MRSA infections rose dramatically among adults in the same period. This apparent inconsistency is plausible because CA-MRSA infections are predominantly non-invasive and tend to have their onset outside of the health care setting.

There are several limitations to our study. First, to perform the meta-analyses, we grouped together studies that were similar but not identical in case definition and denominator definition. While it was previously demonstrated that there is overlap in identifying CA-MRSA cases defined by various criteria (the CDC definition, 48-hour criterion, non MDR criterion, etc.) [27], differences among the three studies of CA-MRSA infections as a proportion of all *S. aureus* infections (Figure 3) may relate, in part, to differences in patient populations and case definitions. The case series in Morristown, NJ [15] and Springfield, MA [13] only included children while the study from Denver, CO [14] included both children and adults. Similarly, the New Jersey study was restricted to patients in the emergency department (ED) and the denominator was all SSTI ED patients; this was deemed appropriate as the vast majority of SSTIs in an ED are in fact caused by *S. aureus*. The three studies also use slightly different criteria to distinguish
CA-MRSA and HA-MRSA. However, despite these differences, the curves have similar shape and time course.

Second, the studies in our meta-analyses are predominantly from cities, and they may not reflect the epidemiology of CA-MRSA in rural areas of the U.S., where a slower trajectory in the CA-MRSA epidemic has been reported [28]–[29]. However, it is worth noting that a surveillance study of ten microbiology laboratories in both rural and urban Minnesota in 1996–1998 [30] was consistent with the modeled curve shown for the Como-Sabetti et al. study [21] in Figure 4. Third, the earlier rise of CA-MRSA as a proportion of all MRSA in children compared with adults (see Figure 4) may reflect a true contrast with adults in the rate of CA-MRSA dissemination, or it may in part reflect the relative infrequency of HA-MRSA infections in children compared to adults. Fourth, our projection of the model into years beyond the published data in studies included in the meta-analyses does not account for the possibility that there may be subsequent changes in the molecular epidemiology of S. aureus that could affect the incidence of CA-MRSA infections. Any such change would require additional modeling features, and revised predictions. Fifth, for studies that used a non MDR bacterial phenotype as the criterion for CA-MRSA infections, it is possible that an increase over time in the number of resistant classes of antibiotics for USA300 MRSA would lead to a progressive rise in the underestimation of the percent of MRSA infections that were CA-MRSA. If this is a bias in the included studies, our curves would underestimate the increase in CA-MRSA infections relative to all MRSA infections. Our data nevertheless demonstrated an increasing incidence of CA-MRSA infections among all MRSA infections, suggesting that this trend likely reflects a true increase.

Sixth, there are several methodological limitations. It is important to point out that the model employed in this analysis, based on the logistic curve, is only an approximation of reality. While it was able to describe the changes in the epidemiology of CA-MRSA, we cannot be sure about its performance in the future. In particular, the leveling-off that we are seeing might not be permanent, and the future might in fact hold a decline in the CA-MRSA rates. In addition, we have described the course of CA-MRSA spread in several geographic regions and have noted the differences in that spread in different locations. Our model is not however a spatial model: it does not account for distance between different study centers, and cannot be used to estimate rates of CA-MRSA spread in locations outside of those analyzed in this paper. Finally, the fixed-effects approach we take in this paper corresponds to the limit of the random effects approach, obtained as the variances of the random effects approach infinity. While a fully random effect approach could be used instead, the number of studies available for this meta-analysis would make our results sensitive to any choice of the random effect variances. Due to a lack of any information about these variances, we only present the fixed effect results in this paper. Our meta-analysis in the second and third group of studies should thus be viewed only as an average CA-MRSA spread in individual subpopulations, and not as a “true epidemic curve” corresponding to the spread in the underlying meta-population.

There were several studies of incident CA-MRSA infections that did not meet the inclusion criteria for our meta-analysis, in particular the requirement that they include data from more than one year to estimate a site-specific trend. A few studies were excluded because they were the only study to use a particular type of denominator and therefore could not be grouped with any other studies for meta-analysis. In other cases we could not include a study because we were unable to obtain the data represented in published graphs. There were also several studies with only case counts and no denominator. The data from all these studies, however, were consistent with our meta-curves. For example, CA-MRSA incidence reported in two single-year population-based studies in California [31]–[32] are both quite similar to the rates of CA-MRSA infections in Chicago, IL [9] estimated from the fitted meta-curve in the corresponding years (the only city population incidence data represented in the meta-analyses). In addition, data from two studies in veterans’ populations [33]–[34] are consistent with the meta-curves in Figure 3, although shifted slightly to the right. Four pediatric studies that did not meet our inclusion criteria also support the trends shown in our meta-curves [35]–[38].

In summary, our analysis shows that in the U.S., CA-MRSA infections, including both invasive and noninvasive disease, likely first appeared in the 1980s, rose dramatically between the mid-1990s and 2005, and have recently leveled off. We found evidence of considerable geographic variation, with the timing of the first reported cases varying by more than ten years between locales. We also provide evidence that CA-MRSA infections reached a steady endemic level earlier as a proportion of all MRSA infections among children, then later, among adults. CA-MRSA infections appear to have reached a plateau around 60 to 70% of all MRSA infections among children as early as the middle 1990s, but this proportion was likely still rising among adults in 2010. Additional population-based studies of CA-MRSA
infection incidence in large population groups are needed to confirm the stability of the plateau values estimated by our models for more recent years.

**Which Came First: Burden of Infectious Disease or Poverty?**
Jonathan Chase
A few years ago, I was at an event where the CEO of a coal company was giving the keynote extolling the virtues of "green coal". The crux of his argument was that restrictions on carbon emissions from fossil fuels to generate electricity would in fact be quite detrimental, particularly to the world's poorest people. He backed this up by showing positive correlations between the per capita electricity use in a given country and several indices of the quality of the human condition, which he interpreted to mean that electricity usage causes economic prosperity. Although it was clear that he was twisting cause and effect, my statistical rancor didn't reach its limit until he showed that people from countries with lower per capita electricity use were also more likely to suffer from some of the world's worst infectious diseases and had lowered life expectancies. His concluding slide stated "coal-generated electricity is not only good for the economy, but also good for your health".

Clearly, economics plays a strong role in the burden of infectious diseases. Wealthier countries can invest more in immunizations, control of disease vectors, and treatment following infection, allowing people to live longer, healthier lives, while those in poorer countries are relegated to an often shortened lifetime filled with malady. However, our collective anthropocentric perspective often forgets that we are embedded within a complex ecological web. Nearly two-thirds of the pathogens and parasites that infect humans involve interactions with animals as vectors or alternative hosts. These include some of the worst chronic and emerging diseases we face, including malaria, cholera, and plague. While it's well known that populations with high infectious disease burden are less prosperous, the cause and effect relationships between infectious diseases and prosperity are so intimately intertwined that we have not been able to disentangle whether pathogens drive economies or economies tame pathogens. Said another way, are poor people more likely to get sick, or are sick people more likely to be poor?

A paper published in this issue of *PLOS Biology* by an interdisciplinary team of ecologists and economists led by Matthew Bonds, who has PhDs in both ecology and economics, makes a substantial advance in understanding the interplay between infectious diseases and economic prosperity. It does so by applying a form of structural equation modeling, which allows several different pathways of causality to be examined simultaneously, to disentangle the relative importance of each. The team jointly examined World Bank data on the per capita income of people from 139 countries and the burden of some of the most globally important parasitic and vector-borne diseases, measured as the per capita years of life lost due to mortality and the weighted equivalent of years lost due to morbidity. They also included several other variables known to influence income and infectious disease in a systematic way. For example, economies are known to be strongly influenced by several indicators of governance, including political stability and corruption, while the ecological burden of infectious disease is strongly influenced by latitude (tropical countries have higher burdens than temperate countries).

With the caveat that disentangling cause and effect is always a bit tricky with comparative data, the beauty of the statistical approach employed is that it allowed the investigators to evaluate the relative importance of a potential causal link in the system of equations while controlling for other confounding variables. It also allowed them to evaluate the success of alternative scenarios by which ecology and economics interact. For example, on the economic side, there is a well-known positive relationship between per capita income and latitude; wealthier countries tend to be at higher latitudes, whereas tropical countries tend to be poorer. Economists have typically assumed this to be a historical artifact of colonial expansion from Europe and erroneously discounted the role of pathogens. The current study showed that the latitudinal income gradient most likely results because infectious diseases are more burdensome in the tropics, and that per capita income in many impoverished tropical countries could be doubled simply by reducing the burden of disease to the level found in temperate areas.

On the ecological side, the authors examined an important, but controversial, link between biodiversity and infectious disease burden on an unprecedented scale. On the one hand, biodiversity and infectious disease burden are positively related because increases in infectious disease correlate with increases in biodiversity towards the tropics. On the other hand, there is often a negative relationship between biodiversity and the burden of several important infectious diseases, including Lyme disease, schistosomiasis, West Nile virus, and sin nombre virus. The current study showed that after controlling for the positive covariation between biodiversity and infectious diseases with latitude, a strong negative
relationship between biodiversity and disease burden emerged, with direct consequences for per capita income.

While biologists have often borrowed ideas from economics (e.g., game theory), the study by Bonds and colleagues turns the table and shows the utility of ecological ideas for understanding economic systems. Even if the effect of coal-generated electricity on human health remains equivocal, this study provides a compelling case for both the role of infectious diseases in driving economies, and the health benefits of biodiversity conservation, both are of direct relevance to national and global economic prosperity.


Natural Killer Cell Dependent Within-Host Competition Arises during Multiple MCMV Infection: Consequences for Viral Transmission and Evolution
Andrea R. McWhorter, Lee M. Smith, Laura L. Masters, Baca Chan, Geoffrey R. Shellam, Alec J. Redwood

Author Summary
Infection of the host with multiple strains of a pathogen is common and occurs with the herpesvirus, human cytomegalovirus (HCMV). However the effects of multi-strain infection on the host and the pathogen remain poorly studied. Here we show, in a mouse model, that infection of C57BL/6 mice with multiple strains of murine CMV (MCMV) results in profound within-host competition. Competition between the strains of MCMV is dependent on Ly49H+ natural killer (NK) cells. The NK cell activation receptor Ly49H receptor targets certain genotypes of the viral protein, m157. During multi-strain infection, strains of MCMV encoding an m157 capable of binding Ly49H are excluded from the salivary gland and the saliva of C57BL/6 mice, allowing for the shedding of only non-Ly49H binding strains of MCMV in the saliva. This within-host competition could therefore have significant impacts on the circulation of MCMV strains, as only the most virulent MCMV strains were present in the saliva.

The Roles of Competition and Mutation in Shaping Antigenic and Genetic Diversity in Influenza
Daniel Zinder, Trevor Bedford, Sunetra Gupta, Mercedes Pascual

Author Summary
Influenza A (H3N2) has circulated in the human population since 1968 causing considerable annual morbidity and mortality worldwide. Despite the rapid evolution of the hemagglutinin (HA) protein and strong diversifying selection, the global virus population is characterized by a low standing diversity, evident in the serial replacement of antigenic types and in the ‘cactus-like’ structure of its genealogical tree. Elucidating the mechanisms behind these puzzling patterns is key to understanding the evolution of seasonal (H3N2) influenza. One recent epidemiological model proposes a restricted set of antigenic types whose waves of dominance result from frequency-dependent immune selection. Here we develop a model of limited antigenic diversity that explicitly incorporates mutational processes, and use it to address, first, whether this type of antigenic space is capable of generating the characteristic phylogeny of HA sequences, and second, whether the dynamics of (H3N2) influenza are primarily limited by the arrival of mutations or by the opening of antigenic niches. We conclude that a limited antigenic space can explain the observed phylogenetic patterns and that a limited mutation rate is a key property underlying the dynamics of (H3N2) influenza. Our study provides a general framework for assessing the relative roles of selection and mutation in a variety of infectious disease systems.

Candida and Host Determinants of Susceptibility to Invasive Candidiasis
Michail S. Lionakis, Mihai G. Netea

Introduction
Candida is the most common human fungal pathogen and the cause of invasive candidiasis, the fourth leading cause of nosocomial bloodstream infection in the United States with an estimated annual cost of ~US$2 billion and mortality that exceeds 40% despite administration of antifungal therapy in modern intensive care unit facilities [1]. Hence, invasive candidiasis is an unmet medical condition for which better understanding of its pathogenesis at the host–pathogen interface is essential to improve patient outcomes. To that end, a mouse model of the infection, which introduces Candida yeast cells intravenously and mimics skin-derived bloodstream human candidiasis, has been successfully employed to study fungal and host factors that regulate susceptibility to the infection [2].
Perspective

*Candida* is a commensal organism that colonizes 50% of individuals of a population at any given time, but in conditions leading to weakening of host defense mechanisms it can convert to an opportunistic pathogen causing localized mucosal disease or life-threatening invasive infections with high mortality rate despite antifungal therapy. In recent years we have witnessed a surge of studies of *Candida* pathogenesis at the host–pathogen interface. Dissecting the fungal virulence factors that foster the transition of *Candida* from a commensal to an opportunistic pathogen, and deepening our understanding of the molecular and cellular basis of effective antifungal immunity should lead to novel risk stratification, prognostication, vaccination, and therapeutic strategies in patients.

Disease Eradication

Donald R. Hopkins, M.D., M.P.H.

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Since the last case of naturally occurring smallpox, in 1977, there have been three major international conferences devoted to the concept of disease eradication.1-3 Several other diseases have been considered as potential candidates for eradication,4 but the World Health Organization (WHO) has targeted only two other diseases for global eradication after smallpox. In 1986, WHO’s policymaking body, the World Health Assembly, adopted the elimination of dracunculiasis (guinea worm disease) as a global goal,5 and it declared the eradication of poliomyelitis a global goal in 1988.6 Although both diseases now appear to be close to eradication, the fact that neither goal has been achieved after more than two decades, and several years beyond the initial target dates for their eradication, underscores the daunting challenge of such efforts, as does the failure of previous attempts to eradicate malaria, hookworm, yaws, and other diseases.1

The word “eradicate” is defined as “to pull or tear up by the roots” and “to remove entirely, extirpate, get rid of.”7 Definitions of eradication and elimination have also been suggested by various international bodies (and are used herein), and the International Task Force for Disease Eradication uses certain scientific and social criteria when evaluating candidate diseases (see Definitions).1,2,4 Eradication of a disease means worldwide interruption of transmission, whereas elimination means interruption of transmission in a limited geographic area. The term “elimination” is often used imprecisely.8 For example, the World Health Assembly resolutions in 1986 and 1989 referred to the “elimination” of dracunculiasis but changed the term to “eradication” for the same global goal in a 1991 resolution.

A brief review of five diseases selected for eradication or elimination will illustrate the potential benefits of such efforts and some of the challenges they pose (see the interactive graphic, available with the full text of this article at NEJM.org). Although dracunculiasis and poliomyelitis are now the only officially sanctioned targeted diseases of eradication campaigns, the WHO has designated the campaign against lymphatic filariasis as the Global Program to Eliminate Lymphatic Filariasis. These three programs represent different levels of international commitment to disease eradication. The program to eliminate onchocerciasis (river blindness) from the Americas is an example of a highly successful regional initiative, whereas the effort to eliminate malaria and lymphatic filariasis from Hispaniola is an example of a compelling, binational initiative that might suggest the feasibility of a global eradication effort.

Several key principles are inherent in an eradication or elimination campaign: the need to intervene everywhere the disease occurs, no matter how remotely located or difficult to access occurrences of disease are or how minor the perceived problem is in an individual country or area; the importance of monitoring the target disease and the extent of interventions closely; the need for flexibility and urgency in response to ongoing monitoring and operational research; and the need for an intense focus on the goal of stopping transmission of the targeted disease, even when the costs per case rise sharply as the number of cases declines. Common difficulties faced by such campaigns include sporadic or widespread political insecurity in areas where the disease is endemic, inadequate or delayed funding, and the challenges of motivating officials, health workers, and affected populations.

**Dracunculiasis**

The global campaign to eradicate dracunculiasis began in 1980 at the Centers for Disease Control and Prevention (CDC)9 and since 1986 has been led by the Carter Center in close cooperation with the WHO, the CDC, and the United Nations Children’s Fund (UNICEF).10 The life cycle of the parasite *Dracunculus medinensis* is shown in Figure 1A.
Pathogen Life Cycles and Points of Intervention (in Red) for Five Diseases That Can Be Eradicated or Eliminated. When exposed to water, the adult worms discharge thousands of larvae, which are ingested by tiny crustaceans (cyclops). About a year after a person has drunk water from ponds or open wells contaminated with these crustaceans, adult worms measuring about 1 m in length slowly begin to emerge through the infected person’s skin.

Dracunculiasis met the scientific criteria for eradication (see Criteria for Assessing the Eradicability of a Disease), although the campaign was handicapped by the 1-year incubation period of the parasite and the lack of a vaccine or curative treatment. The true extent and burden of the disease among neglected populations were unknown because cases of dracunculiasis were greatly underreported. The adverse effects of this disease on health, agriculture, and school attendance were easy to imagine, however, since the pain and secondary infections associated with the emergence of the worms incapacitated many affected persons for several weeks during the agricultural season. The main interventions included health education focused on teaching villagers how to filter their drinking water and avoid contaminating the water, application of a mild larvicide to water sources, voluntary isolation of patients (case containment), and provision of safe water sources when possible. Synergistic benefits of this campaign have included the development of village-based active case surveillance and health education and improved supplies of drinking water.

Down from an estimated 3.5 million cases in 20 African and Asian countries in 1986, the number of cases reported in 2011 was only 1058, most of which were in the new Republic of South Sudan, with a few in Mali (12 cases) and Ethiopia (8 cases), as well as Chad (10 cases), in which a new outbreak was discovered in 2010 (Figure 2). The eradication strategy evolved from an emphasis on the provision of safe water supplies to a focus on health education and the use of cloth filters and, later, to case containment. The active leadership of former U.S. President Jimmy Carter, the focus on village-based reporting and interventions, and major funding provided by the Bill and Melinda Gates Foundation all facilitated this program’s achievements. Political instability in some affected areas of South Sudan and Mali are the main challenges to eradicating dracunculiasis. The estimated cost for this program (1986–2015) and for certification of eradication, not including provision of a water supply, is approximately $350 million.

**Poliomyelitis**

The Global Polio Eradication Initiative, which began in 1988, was inspired by the successful elimination of this disease in the Americas. An enteroviral infection characterized by influenza-like symptoms, poliomyelitis causes muscle paralysis in one or more limbs or the chest, or both, in less than 1% of infected persons. People are infected by ingesting virus shed in feces or by inhaling viral particles exhaled by those already infected (Fig 1B). Patients may exhale virus for a week and shed virus in feces for a month, beginning just before symptoms develop, 7 to 14 days after they are infected. Persons who recover are then immune to the viral type that infected them (poliovirus 1, 2, or 3). Vaccination to prevent infection requires three or more doses of live attenuated virus administered orally or of killed virus administered by injection. Before polio vaccination was introduced, in the 1950s, the disease killed or paralyzed an estimated 600,000 persons each year worldwide.

The Global Polio Eradication Initiative engendered massive global immunization and surveillance efforts with the support of the WHO, UNICEF, the CDC, Rotary International, the Bill and Melinda Gates Foundation, and others. These efforts have helped strengthen routine immunization in some instances (e.g., measles immunization in the Americas) and the delivery of vitamin A supplements in others. Surveillance for polioviruses, which is performed in health facilities and laboratories, involves the use of sophisticated methods for characterizing polioviruses detected in specimens from sewage or from patients with suspected infection. Type 2 wild poliovirus was eradicated worldwide by 1999. By 2006,
transmission of indigenous wild virus had been halted in all but four countries. In India, suboptimal seroconversion due to poor sanitation and high population density required immunization with many more doses than expected; parts of Afghanistan and Pakistan became inaccessible after 2002, owing to political conflict; and rumors of side effects from vaccination compromised the acceptance of immunization in Nigeria. Additional problems included the discoveries that immunosuppressed persons could excrete virus indefinitely and that the virus in the live-virus vaccine could, in rare cases, regain virulence and spread to others, just as the virus in the attenuated vaccine did, although spread of the attenuated virus was beneficial, augmenting herd immunity.18

By 2011, after setbacks that resulted in cases being exported to other countries, 650 confirmed cases of poliomyelitis were reported provisionally from 16 polio-affected countries: 4 countries where the disease was endemic and 12 countries with reestablished transmission (lasting ≥12 months) or outbreaks (lasting <12 months) after importations (Figure 3). Global coverage of infants with three doses of oral trivalent vaccine was about 85% in 2010 but is uneven at the national and subnational levels.15 In January 2012, India celebrated a full year with no cases of poliomyelitis, leaving Nigeria, Afghanistan, and Pakistan as countries with endemic disease where eradication was problematic because of political instability or fear of immunization.20-22 Among countries with reestablished transmission, Chad and the Democratic Republic of Congo reported the most cases (132 and 93, respectively) in 2011.19 The goal is to interrupt transmission of poliovirus types 1 and 3 by December 2012. The main challenges to poliomyelitis eradication are donor fatigue; political instability in parts of Afghanistan, Pakistan, and some other affected countries; public fatigue with repeated immunizations against poliomyelitis alone; and weak routine immunization systems. This program is estimated to cost $9.5 billion for the period from 1988 through 2013.23

Lymphatic Filariasis
In 1997, after the International Task Force for Disease Eradication had first suggested the potential eradicability of lymphatic filariasis, the World Health Assembly formally targeted the disease for global elimination.24 Characterized by painful adenolymphangitis, damage to kidneys and other organs, and grotesque swelling of limbs and genital organs, lymphatic filariasis is caused by the filarial parasites Wuchereria bancrofti, Brugia malayi, and B. timori and is transmitted to humans by repeated bites of mosquitoes that previously ingested microfilariae from the blood of an infected person (Figure 1C). In Africa, lymphatic filariasis is transmitted by the same anopheles species of mosquitoes that transmit malaria (Figure 1D). Annual oral mass drug administration with ivermectin and albendazole or with diethylcarbamazine and albendazole suppresses microfilaremia and interrupts transmission. About 6 years of treatment are required before the adult worms die. Mass drug administration with ivermectin is contraindicated in African areas where the parasite Loa loa occurs (because treatment of persons with heavy L. loa infections may have fatal side effects), but bed nets to thwart nocturnal, indoor-biting mosquitoes such as anopheles also prevent the transmission of lymphatic filariasis.25 In 2010, about 120 million people were infected and almost 1.4 billion were at risk for lymphatic filariasis in 72 countries of Asia, Africa, and Latin America (Figure 4). In 2000, generous donations of drugs helped launch the Global Program to Eliminate Lymphatic Filariasis, which aims to eliminate lymphatic filariasis “as a public health problem” by 2020. In 2010, a total of 466 million (34%) of the persons at risk for lymphatic filariasis received treatment, and mapping was complete in 59 countries.26 India, Indonesia, and Nigeria have the most cases. Scaling up mass drug administration for lymphatic filariasis has been slowest in Africa, where the expanding use of long-lasting impregnated nets provides synergy between efforts to eliminate lymphatic filariasis and efforts to control malaria. Mass drug administration for lymphatic filariasis also treats onchocerciasis and several soil-transmitted helminths.27 There is evidence that mass drug administration has interrupted the
transmission of lymphatic filariasis in some parts of Nigeria where the disease is heavily endemic,28 in Egypt29 and in Togo30 and has reduced microfilariae levels to less than 1% in 12 Asian and Pacific Island countries.26 There is also evidence from Nigeria that widespread use of long-lasting impregnated nets can halt transmission of the disease (Richards F: personal communication). The main challenges to a full-scale campaign for lymphatic filariasis eradication are inadequate political and financial support for scaling up mass drug administration, constraints on such treatment because of the presence of L. loa in certain areas (although the use of impregnated nets may eliminate this constraint), and political insecurity in certain countries. The overall costs of this program have not been estimated, although limited studies have suggested that interventions against lymphatic filariasis are very beneficial in relation to their cost.31,32

**Onchocerciasis in the Americas**

The Americas was the first WHO region to eliminate smallpox, poliomyelitis, and measles. Since 1992, the region has pursued a program to eliminate onchocerciasis from 13 foci in six countries of Central and South America with the use of mass administration of ivermectin twice a year.33,34 The parasite *Onchocerca volvulus* is spread to humans by the bites of tiny black flies, after which the adult worms cluster in nodules and release millions of microfilariae that migrate to the skin, causing intense itching, and to the eyes, where they may impair sight and, after many years, cause blindness (Figure 1E). By the end of 2011, onchocerciasis transmission had been halted or suppressed in all but 2 of the 13 foci and in four of the six affected countries (Table 1).35-36 Accessing indigenous populations in remote adjacent areas of Venezuela and Brazil is still a challenge. Progress in the effort to eliminate onchocerciasis in the Americas has inspired a reappraisal of ongoing programs to control the disease in Africa, where most cases occur.37,38 Over the past two decades, the Onchocerciasis Elimination Program for the Americas has cost approximately $124 million, with $46 million of that amount paid for by the countries themselves, $51 million paid by Merck in the form of donated drugs, and most of the remainder raised by the Carter Center.

**Malaria and Lymphatic Filariasis in Hispaniola**

A special opportunity also exists in the Americas to apply the principles of disease elimination in Hispaniola, comprising the Dominican Republic and Haiti. These two countries are the only remaining foci of endemic malaria among the Caribbean islands and account for more than 90% of all cases of lymphatic filariasis in the Western Hemisphere. The International Task Force for Disease Eradication highlighted this compelling opportunity in 2006, concluding that eliminating both diseases from Hispaniola “is technically feasible, [is] medically desirable and [would be] economically beneficial.”39 The Dominican Republic has almost eliminated lymphatic filariasis already. Despite the earthquake in 2010, Haiti extended mass drug administration for lymphatic filariasis to all affected districts for the first time in 2011 and estimates that $49 million will be needed to eliminate the disease by 2020. In 2009, the two countries also announced a binational plan to eliminate malaria by 2020 by combining active case detection and treatment with vector control at an estimated cost of $194 million over the decade.40 An outbreak of malaria in 2004 cost the Dominican Republic an estimated $200 million in lost revenue from tourism alone.39

**Some Lessons and Conclusions**

Past and current experience confirms that disease eradication is difficult and risky and will probably require more effort, time, and money than initially expected, even when it is successful. It is advisable to start early in the most heavily affected areas, since they will present the most difficult challenges and require the longest effort and because the specific challenges cannot be anticipated on the basis of work in areas that are less heavily affected. The inherent risks of failure to achieve eradication are offset by the benefits that accrue indefinitely from a successful eradication campaign. The unique power of eradication campaigns derives from their supreme clarity of purpose, their unparalleled ability to inspire dedication and sacrifice among health workers, and their attractiveness to donors, all of which are needed to overcome the barriers to successful eradication. Evidence that disease incidence and intervention coverage are being monitored closely and that progress is being made toward eradication can help secure the resources needed for these demanding campaigns.
Political instability and insecurity, which are usually outside the realm of public health professionals and can be avoided in a program designed to control disease, are inescapable challenges in an eradication program. Smallpox eradication succeeded despite civil wars in Nigeria, Pakistan, and Sudan, and the programs to eradicate dracunculiasis and poliomyelitis face similar challenges. Unlike the dracunculiasis eradication program, the programs to eradicate smallpox and poliomyelitis must address the risk of waning immunity levels, should the virus be reintroduced by bioterrorists after eradication, when routine immunizations have ceased.

In the medical realm, each eradication or elimination program is different and will require its own strategies and tactics. No program will have all the answers from the outset, so ongoing innovation and research are important. The smallpox eradication program switched from mass vaccination to the successful surveillance-containment strategy after it was under way, and the guinea worm and poliomyelitis eradication programs also developed new strategies after they had begun.41 All eradication programs, however, require an intensive focus. Opportunities for integrating interventions of eradication programs with those of control programs will be scarce, but such opportunities should be seized when it makes sense to do so. Measles immunization was combined with smallpox eradication efforts in West Africa, despite the additional logistic and financial burdens imposed by the need to refrigerate the measles vaccine (but not the smallpox vaccine), because the African governments requested it.42 Meeting this request added public health value and political virtue to the campaign. Similar opportunities for mutually beneficial, combined interventions against lymphatic filariasis, onchocerciasis, malaria, and soil-transmitted helminths in Africa are also evident.27

The successful eradication of dracunculiasis with interventions other than a vaccine will soon validate and expand the concept of disease eradication as we have known it, such as in the use of vaccination to eradicate smallpox (and in the impending eradication of poliomyelitis). That imminent success, generous drug donations for combating lymphatic filariasis, and ongoing elimination efforts in the Americas and elsewhere against other diseases augur well for the future, although the eradication of lymphatic filariasis is not yet an official goal of the WHO. However, the fact that neither dracunculiasis nor poliomyelitis was eradicated by December 2012, as planned, underscores the inherent difficulties of disease eradication. I believe this powerful public health tool will be used to eradicate other carefully selected diseases in the future, provided that inflated promises and failure to deliver on them do not tarnish the concept. In the meantime, lessons from eradication programs could be adapted to improve control of many other diseases.

**Definitions**

**Eradication**
Zero disease globally as a result of deliberate efforts
Control measures no longer needed

**Elimination**
Zero disease in a defined geographic area as a result of deliberate efforts
Control measures needed to prevent reestablishment of transmission

**Criteria for Assessing the Eradicability of a Disease**

**Scientific feasibility**
Epidemiologic susceptibility (e.g., no nonhuman reservoir, ease of spread, naturally induced immunity, ease of diagnosis)
Effective, practical intervention available (e.g., vaccine, curative treatment)
Demonstrated feasibility of elimination (e.g., documented elimination from island or other geographic unit)

**Political will and popular support**
Perceived burden of the disease (e.g., extent, deaths, other effects; relevance to rich and poor countries)
Expected cost of eradication
Synergy of eradication efforts with other interventions (e.g., potential for added benefits or savings)
Need for eradication rather than control

**Doctors See Rise in HPV-related Cancers**
*USA Today* [Blog](https://wwwusatoday.com), (01.07.2013) Liz Szabo

Increased screening has resulted in lower rates of cervical cancer in the United States, but the incidence of other cancers related to the human papillomavirus (HPV) went up from 2000 to 2009. The National Cancer Institute reported that “changes in sexual practice” are the most likely reason for higher rates of HPV-related oral, anal, vulvar, and penile cancers.
The rate of oral cancer went up by almost 5 percent for Native American men and 3.9 percent for white men from 2000 to 2009. During the same time frame, anal cancer rates increased for every population group, especially black men, white women, white men, and Asian men. HPV caused only 16 percent of oral cancers from 1984 to 1989; from 2000 to 2009, over 70 percent of oral cancers are due to HPV. The Journal of the American Medical Association estimates that 10 percent of men and 3.6 percent of women have active oral HPV infections. No screening tests exist for cancers of the throat, tonsils, and base of the tongue, according to Otis Brawley, MD, chief medical officer of the American Cancer Society.

HPV vaccines are effective in preventing cervical, vaginal, and vulvar cancers. CDC recommends the HPV vaccines for boys and girls at age 11 or 12. The vaccine targets HPV 16, which also causes most of the HPV-associated oral cancers. Richard Schlegel, chair of Pathology at Georgetown Lombardi Comprehensive Cancer Center, stated that the HPV vaccine would probably block oral cancers, too. HPV-related oral cancers occur in 7,100 Americans each year.


**Hepatitis B Kills 29 People in West Nile**
*Daily Monitor (Kampala)*, (01.05.2013) Martin Okudi
Health officials in West Nile, Uganda, reported that cases of hepatitis B virus infection continued to increase in Moyo and Adjumani Districts because the health facilities in the area do not have the vaccines to prevent the virus. In private clinics a dose of hepatitis B vaccine costs about 80,000 Uganda shillings (US $29.44), which was too expensive for most patients. District disease surveillance teams report that between 2010 and 2012, there were at least 21 deaths from hepatitis B recorded in Moyo and eight in the Adjumani District. Health workers state that many more people may have died from hepatitis B infection, but it was not recorded as most of them were treated at private clinics.

Dr. Dominic Drametu, medical superintendent of Adjumani District, stated that in the last three years, the hospital had treated about 90 cases of hepatitis B and approximately 8 of the patients had died. He noted that the hospital treats at least two cases of hepatitis B virus infection every month, but that the facility lacked the necessary drugs to treat them.

**New Pills Show Promise for Hepatitis C***
*HealthDay News* (01.02.2013) Serena Gordon

Pills may soon replace injections with interferon as the preferred treatment for hepatitis C, according to studies conducted in Texas and New Zealand. The University of Texas Health Science Center study reported a 95 percent success rate in suppressing blood levels of genotype 1 hepatitis C, the most common form of the virus. The pill regimen included a combination of the drugs ABT-450/r and ABT-333. The New Zealand study tested the new drug sofosbuvir in combination with existing therapies on groups of people infected with hepatitis C genotypes 1, 2, or 3. Researchers stated a combination of sofosbuvir and ribavirin achieved 100 percent success in suppressing genotypes 2 and 3, and 84 percent success with genotype 1.

The current treatment for hepatitis C requires patients to take ribavirin and three weekly injections of interferon for 48 weeks. Interferon suppresses the entire immune system and can cause flu-like side effects for the entire course of treatment. Both of the new drugs target only the hepatitis C virus and require 12 weeks of treatment. Side effects of the new treatments were not severe enough to cause patients to stop treatment.

Over three million people in the United States have hepatitis C, which is spread through contact with the blood of a hepatitis C-infected person. Chronic hepatitis C can lead to cirrhosis of the liver and liver failure.


**Post-Disaster Disease Myth Diverted Attention From Cholera Outbreak Following Haiti Earthquake**

"Few post-disaster myths have a stronger hold on our imaginations than the specter of a follow-on epidemic ... But we can all take a deep, healthy breath: It's not true," Jonathan Katz, a journalist stationed in Haiti, writes in a PopSci opinion piece. "But myths have their price. And nowhere has the price of this
particular myth been higher than in Haiti," he continues. Noting the third anniversary of the 2010 earthquake that struck the nation, Katz writes, "No less a luminary than Bill Clinton, the U.N. Special Envoy for Haiti, warned in early 2010 that diarrheal disease sparked by squalid conditions could prove a 'second round of death.'" He continues, "In fact, there was a second catastrophic round of death in Haiti that year: an epidemic, no less. But that epidemic—a virulent outbreak of El Tor cholera—had nothing to do with the earthquake at all.

"Rather, cholera was almost definitely introduced into Haiti by U.N. peacekeepers in October 2010," Katz says, noting "there had never been a confirmed case of cholera in Haiti before that outbreak, ever." And "[t]hat's where the epidemic myth came in," he writes, adding, "The attitude made epidemiologists and aid workers less likely to seek out the source of what was in fact a particular infection not only new to Haiti, but the entire hemisphere. And it has since continued to provide cover for the United Nations as advocates press for reparations, and public health experts try to reform the peacekeeping system to prevent such a catastrophic error from happening again." He concludes, "In Haiti, where cholera has claimed 7,800 lives and counting, becoming a permanent feature of the landscape, the diversion has proven particularly ironic. Conditioned to look for a problem that wasn't there, responders ignored the greatest public health threat of all: themselves" (1/7).

**Nobel laureate James Watson publishes novel hypothesis on curing late-stage cancers**

Cold Spring Harbor, NY – "Although mortality from many cancers has been steadily falling, particularly those of the blood [i.e., leukemias], the more important statistic may be that so many epithelial cancers (carcinomas) and effectively all mesenchymal cancers (sarcomas) remain largely incurable." With these words as preface, Nobel laureate James D. Watson, Ph.D., in a newly published paper that he regards "among my most important work since the double helix," sets forth a novel hypothesis regarding the role of oxidants and antioxidants in cancers that are currently incurable, notably in late-stage metastatic cancers.

At the heart of his thesis are the group of molecules that scientists call reactive oxygen species, or ROS. Noting their fundamental two-sidedness, Watson calls ROS "a positive force for life" because of their role in apoptosis—an internal program that highly stressed cells use to commit suicide. It's one of the key mechanisms that have arisen through eons of evolution to weed out biological dysfunction that poses a threat to the survival of organisms. On the other hand, ROS are also well understood—indeed are notorious—"for their ability to irreversibly damage key proteins and nucleic acid molecules [e.g., DNA and RNA]."

When they're not needed to curb wayward or out of control cells, which is to say under normal circumstances, ROS are constantly being neutralized by anti-oxidative proteins. We are often urged to eat foods rich in antioxidants such as blueberries; but, if Watson is correct about the role of ROS and antioxidants in late-stage cancer, as he writes in his new paper, "blueberries best be eaten because they taste good, not because their consumption will lead to less cancer."

Understanding why this might be so—why antioxidants can in late-stage cancers actually promote cancer progression—is central to Watson's paper, which appears online January 9 in Open Biology, a journal of Great Britain's Royal Society.

He proposes that the cell-killing ability of currently used anti-cancer therapies—toxic chemotherapeutic agents such as Taxol as well as radiation treatment—is mainly due to the action of ROS to induce apoptosis, or programmed cell death. This would explain "why cancers that become resistant to chemotherapeutic control become equally resistant to radiotherapy." The common feature would be their common dependence upon a ROS-mediated cell-killing mechanism.

Watson, who is Chancellor Emeritus of Cold Spring Harbor Laboratory, then takes up the case of cancer cells largely driven by mutant proteins such as Ras and Myc. These, he notes, are often hardest to get to respond to treatment. He suggests this could be due to their high levels of ROS-destroying antioxidants. He cites recent research showing up-regulation of a gene transcription factor called Nrf2 when cells proliferate as well as when oncogenes such as Ras, Myc and Raf are active. Nrf2 controls the synthesis of antioxidants, and "this makes sense because we want antioxidants present when DNA functions to make more of itself," Watson writes.

In calling for "a much faster timetable for developing anti-metastatic drugs," the Nobel laureate wants those reading his new paper to consider a proposition he considers grossly underexplored: "Unless we can
find ways of reducing antioxidant levels, late-stage cancer 10 years from now will be as incurable as it is today."

Lamarck and the Missing Lnc

Epigenetic changes accrued over an organism’s lifetime may leave a permanent heritable mark on the genome, through the help of long noncoding RNAs.

By Kevin V. Morris | October 1, 2012

Rudyard Kipling’s Just So Stories tell tales not so much of evolution, but of the magic and wonder of the animal world. He describes the wizard who gave the camel a hump for its laziness, and the alligator who snapped and stretched the nose of a naïve young elephant to its current lengthy proportion. Those delightful fables, published some 70 years after Jean-Baptiste Lamarck’s death, provide entertaining explanations for such evolved traits, and were clearly inspired by Lamarck’s description of adaptive change, not Charles Darwin’s. In his 1809 publication Philosophie Zoologique, Lamarck wrote of the giraffe, from whose habit of reaching for the green leaves of tall trees “it has resulted . . . that the animal’s forelegs have become longer than its hind legs, and that its neck is lengthened to such a degree that the giraffe, without rearing up on its hind legs . . . attains a height of six meters.”

Although biologists have generally considered Lamarck’s ideas to contain as much truth as Kipling’s fables, the burgeoning field of epigenetics has made some of us reconsider our ridicule. While no biologist believes that organisms can willfully change their physiology in response to their environment and pass those changes on to their offspring, some evidence suggests that the environment can make lasting changes to the genome via epigenetic mechanisms—changes that may be passed on to future generations.

Epigenetics: genome gatekeeper

Epigenetic changes can range from chemical modifications of histone proteins—such as acetylation and methylation—to modifications made to the DNA itself. Such changes usually cause chromatin compaction, which limits the ability of the RNA polymerase II transcription complex to access DNA, ultimately resulting in reduced messenger RNA (mRNA) and protein output. Many view epigenetics as an annotation or editing of the genome that defines which genes will be silenced in order to streamline protein production or squelch unnecessary redundancy. That annotation, they say, does not and cannot permanently change the original manuscript (i.e., DNA), but merely access to the manuscript.

Infographic: The Epigenetic Lnc, Credit: Precision Graphics

A fascinating 2008 study that looked at people born during the Dutch Hunger Winter in 1944–1945 hints at the possibility that transgenerational epigenetic inheritance also occurs in humans. Adults who were conceived during the famine had distinct epigenetic marks that their siblings born before or after the famine did not. These marks reduced the production of insulin-like growth factor 2 (IGF2) and affected the growth of the famine-gestated children. Notably, these marks were retained for several decades in the afflicted individuals. While these observations suggest the possibility of transgenerational epigenetic inheritance, the modifications could also have occurred in utero as a result of famine conditions rather than being inherited in the germline. Therefore, whether such a distinct phenomenon occurs in humans remains to be definitively determined.
Epigenetic modifications to the genome are well studied, far less is known about how particular epigenetic marks are directed to their target loci. Clearly, something is guiding the modifications, which appear to be differentially distributed based on particular stresses induced on the cell or organism. Recent studies suggest that epigenetic changes, and possibly transgenerational epigenetic inheritance, could be explained by a somewhat unexpected molecular player: long noncoding RNA.

Long noncoding RNAs (lncRNAs) are transcripts generally expressed from regions of "junk" DNA that are not thought to code for proteins. Estimates of lncRNA abundance range from 70 to 98 percent of transcripts present in the cell, and some are several thousand bases long.[6. T.R. Mercer et al., “Long non-coding RNAs: insights into functions,” Nat Rev Genet, 10: 155–59, 2009.] Unlike short noncoding RNAs, such as short interfering RNA, which silence genes by cutting mRNAs in the cytoplasm, lncRNAs appear to bind to transcripts in the nucleus as they emerge from the replication fork of the DNA, and recruit enzyme complexes to induce epigenetic changes at these loci.[7. K.V. Morris, “Long antisense non-coding RNAs function to direct epigenetic complexes that regulate transcription in human cells,” Epigenetics, 4:296–301, 2009.]


DNA methylation itself can be passed down from a cell to its daughter cells.[11. M.S. Weinberg et al., “The antisense strand of small interfering RNAs directs histone methylation and transcriptional gene silencing in human cells,” RNA, 12:256–62, 2006.] In addition, it has been known for some time that such modifications can also lead to permanent changes in the genetic code. Methylation of a cytosine (C), for example, can cause that nucleic acid to change to a thymine (T) through deamination, or the removal of an amine group. Nearly 80 percent of methylation sites in the human genome occur on a cytosine that is followed by a guanine, in a CpG sequence. Deamination occurs when the methylated C undergoes a hydrolysis reaction resulting in the production of ammonia, followed by the conversion of the cytosine to a thymine at that spot in the DNA sequence. While this C-to-T conversion is considered random, the spontaneous deamination of methylated CpGs has been found to be about 2-fold faster than C-to-T conversions in nonmethylated CpG sequences.[12. J.C. Shen et al., “The rate of hydrolytic deamination of 5-methylcytosine in double-stranded DNA,” Nucleic Acids Res, 22:972–76, 1994.] suggesting a bias toward CpG regions in the deamination process.

Although these ideas have yet to be substantiated by complete experimental evidence, one can envision this as a model for how the system might work—a mechanism by which epigenetic changes, guided by lncRNAs, could make permanent and heritable changes to the genome. Indeed, such a lncRNA-based DNA editing system could be driving some aspects of genetic variation and could explain the
common appearance of single nucleotide polymorphisms within a species. If this is true, one has to wonder what role lncRNA-directed DNA methylation has been playing in the evolution of the genome. 

Driving diversity

DIRECTING EVOLUTION: Epigenetic modification most often occurs on cytosines (C) that are followed by a guanine (G) (top). These methylated cytosines are more likely to undergo a chemical reaction that converts the C into a thymine (T), permanently changing the genetic sequence. When that altered sequence is replicated during cell division, the newly generated matching strand will copy this altered sequence (bottom), giving the next generation a slightly altered genomic manuscript. This new manuscript could alter the structure of the encoded protein, or change the mRNA homology sequence for lncRNA binding, rendering the lncRNA unable to bind and suppress that gene, thus allowing the altered sequence to be transcribed again.

Intriguingly, a greater frequency of targeted C-to-T changes could also result in an overall loss of complementarity between the sequence and the lncRNA that targets it. As a result, rather than initiating suppression of the target gene, the change could result in renewed transcription in subsequent generations. At the same time, this process could permit the target transcript to fold into a different conformation, thereby allowing other subsets of lncRNA interactions to occur at slightly different loci.

Alternatively, changes to the lncRNAs themselves might lead to a loss of lncRNA-protein associations, resulting in different cellular machinery being localized to the particular target loci. Thus, the over-activity of one lncRNA could doom that lncRNA to a loss of function, but simultaneously result in the evolution of a new regulatory lncRNA network with potentially different downstream effects.

Furthermore, a site frequently targeted by lncRNAs would likely contain a larger proportion of T:A bonding between the DNA strands, due to deamination events. Such permanent and heritable changes in the genetic code could change the shape of the encoded protein, its function, or its ability to be transcribed altogether.

One can begin to envision how environmental variation, by instigating epigenetic changes, could increase organismal complexity, thus giving populations a greater chance at surviving new and perhaps permanent environmental threats. In other words, epigenetics, rather than random genetic point mutations, could provide the missing link between environmental pressure and the resulting genetic variability that generates robustness of a species.

Most certainly, if such a pathway were to exist in human cells, one would expect it to be elusive purely due to the sheer complexity of the process—involving lncRNAs, epigenetic changes, DNA methylation, and deamination. Thus, it is not out of the realm of possibility that such a mechanism exists, but has yet to be elucidated by science.

The inner molecular workings of the cell are vastly complex, and the emerging realization that lncRNAs are active modulators of gene transcription and epigenetic states only complicates the picture.
Clearly, as more data emerges in this exciting area of research, additional layers of regulation will need to be added to the central dogma of molecular biology. Although an organism cannot pass down specific information about its own experiences—the giraffe will not be able to help its offspring reach taller trees just by stretching its own neck—it may give succeeding generations a fighting chance in a difficult environment by offering them a slightly altered arsenal of genetic tools.

**Kevin V. Morris is an associate professor at The Scripps Research Institute in La Jolla, California, and the University of New South Wales in Sydney, Australia.**

**Comments**

**jvkohl**, October 1, 2012

In an article published earlier this year, I detailed how an environmental drive evolved from that of nutrient chemical ingestion in unicellular organisms to that of socialization in insects. Using the honeybee model organism as an example, the article also makes it clear that food odors and pheromones cause changes in hormones, which also have developmental affects on behavior in nutrient-dependent, reproductively fit individuals across species of vertebrates.

It is the epigenetic effects of nutrient chemicals and pheromones on intracellular signaling, on stochastic gene expression, and on genetically predisposed behavior that enable transgenerational epigenetic inheritance in species from microbes to man. There are now hints in the literature that transgenerational epigenetic effects on behavior are receiving the consideration that is due. But the idea that there are transgenerational epigenetic effects on behavior has already been substantiated by complete experimental evidence from every species that requires nutrient chemicals for individual survival and pheromones to control reproduction.

I wrote: "The concept that is extended is the epigenetic tweaking of immense gene networks in â€œsuperorganismsâ€”(Lockett, Kucharski, & Maleszka, 2012) that â€œsolve problems through the exchange and the selective cancellation and modification of signals (Bear, 2004, p. 330)â€”Those immense gene networks enable epigenetic effects of nutrient chemicals and pheromones on stochastic gene expression that lead to species-specific changes in behavior via transgenerational epigenetic inheritance. Don't they? (That was a rhetorical question.) Can random mutations cause adaptive evolution? (That was a foolish question.)


corrigible, October 2, 2012

While there are, no doubt, epigenetic epiphenomena from nuances of differences in food and pheromone variations upon species over time, there also are other epigenetic consequences of other ecological parameters.

Selective pressures come in many varieties—not merely in olfactory influences.

To survive over numerous generations, during local environmental changes, niche changes, a species must not merely hang on. It must, as a species, change morphologically. Else it would persist in applying anticipated solutions to no-longer-extant challenges.

Until the current century, there were—in regard to biological theorizations—many lay thinkers and many astute biology-specialized thinkers who presumed that changes in a species over time are a result of fortuitous (or not-so-fortuitous) mutational happenstances. More and more, however, we realize that the odds against any new mutation's being beneficial, rather than carcinogenic or mal-adaptive are diminuitive to so great an extent that the presumption that fortuitous mutational accidents will come along by pure chance and produce a few individuals who have superior adaptive DNA-scripted morphologies to pass on to future generations.

The more we learn about mutations generally, and breakdowns in "corrective" processes, the more clear it becomes that such "MAINTENANCE" work does NOT bring about supra-generational adaptations to environmental change.

What is NECESSARY for supra-generational adaptation is mechanisms of adaptation that are "solution-appropriate"—that is, RESPONSIVE adaptation of an epigenetic kind.

A random, drunken sailor kind of random mutation would take far too long to luck up to the extent necessary. Some mechanisms MUST bring about appropriate changes in morphology for APPROPRIATE SOLUTIONAL supra-generational changes to occur. Were it not for such necessarily appropriate changes, there would be such INAPPROPRIATE changes in a species over time as would cause mal-adaptive changes to be "tested," which would merely result in population loss and, ultimately, population extinction.

To demonstrate one single route of epigenetic signalling pathway alternatives is not to establish it is the sole such set of alternatives.

It is inconceivable in any rigorous analysis of supra-generational changes in a species over thousands of generations, that just one set of epigenetic influences upon morphologies being posed for selection to act upon, would explain all variations of all morphological adaptations. And to rule in one pathway is not to rule out the likelihood of others.

**jvkohl**, October 2, 2012

"To demonstrate one single route of epigenetic signalling pathway alternatives is not to establish it is the sole such set of alternatives."

In the context of adaptive evolution via ecological, social, neurogenic, and socio-cognitive niche construction, I demonstrated the only known route: gene, cell, tissue, organ, organ system, and concluded that "Olfaction and odor receptors provide a clear evolutionary trail that can be followed from unicellular organisms to insects to humans."

What other pathway would you like to rule in? Suggesting there may be one is not like detailing the fact that there is not, and exemplifying that fact via the common molecular biology in species from microbes to man.

Did you have trouble understanding what I detailed in my published work, or have you simply commented without reading it?

October 2, 2012


**EllenHunt**, October 2, 2012

There was a paper some years back about environmental stress causing genes to be expressed, relieving suppression. This was proposed as a mechanism for apparent evolutionary leaps of phenotype. Now, where is that article?

**jvkohl**, October 2, 2012

If you find the paper, please let us know.
The environmental stressors are primarily linked to nutrient chemical acquisition that is required for maintenance of an ecological niche by conspecifics that establish themselves in an ecotypically evolved social niche. Nutrient chemical stressors, when there is a lack of food, and social stressors, which are linked to control of nutrient-dependent reproduction, drive adaptive evolution because the chemical ecology of the environment must be balanced between how many conspecifics or heterospecifics can be supported in a given ecological niche.

That’s life in or outside the microbiology department and the variable always is nutrient chemical-dependent and pheromone-controlled epigenetic effects on intracellular signaling and stochastic gene expression, which leads to de novo odor receptor gene expression and the transgenerational epigenetic inheritance of receptor-mediated behavior that helped ancestral species survive.

Some people think that stochastic means random. In the context of adaptive evolution, however, stochastic gene expression for de novo odor receptor proteins is driven by the epigenetic effects of nutrient chemicals (e.g., food odors) and social odors (e.g., pheromones). It’s a simple concept that’s been bastardized by those who would rather have a random event, like a mutation, cause adaptive evolution via some unknown but somehow beneficial intracellular/intermolecular change, but even endocrine disruptors alter the same evolved pathway as nutrient chemicals and pheromones in vertebrates.

Besides, most of us know that mutations are not adaptive. But if you look at the data and comments from the ENCODE project research groups, you find that most of the 442 researchers seem to want to continue to hang on to the idea that randomness might still be useful to explain something about adaptive evolution that is obviously nutrient chemical-dependent and pheromone dependent. I never expected geneticists to hold on so tightly to what can only be called the “Just-So” stories of evolutionary theorists, which is why I am interested in where this article takes us.

Vincent Maldia, October 3, 2012
Someone is bound to use research like these to jump to conclusions that "darwin’s theory of evolution has been discredited". AFAIK the epigenetic effects are quite small compared to the effect of the usual genes and this in no way disproves evolution

Ed M., October 6, 2012
This is going to leave a La Marck on the strict Darwinists.

When scientists mock one another’s ideas they should remember how many once proud theories have fallen into the ether.

And how many others have been proven correct after decades of scorn.

Get my continental drift?

ufsapog, October 7, 2012
You might be interested to look at the book Escape of the Ufsapog which is free at www.ufsapog.com which puts forward in the later chapters a speculative suggestion as to how change in the genome might have occurred.

Paul Héroux, October 9, 2012
Cancer cells can readily expand or contract their chromosome numbers from environmental cues, using endoreduplication (http://www.springerlink.com/content/p2701r7668763t0/fulltext.pdf). This genetic plasticity capability, that goes much beyond point or random mutations and epigenetics, is part of the capabilities of all cells, in our opinion.

James V. Kohl, Replied to a comment from Paul Héroux made on October 9, 2012, October 28, 2012
Thanks, Paul. Do you know if anyone has attributed the extent of the plasticity directly to microRNA / messenger RNA homeostasis and/or perturbed intracellular signaling changes that drive intermolecular changes in DNA?

Roy Niles, December 23, 2012
"While no biologist believes that organisms can willfully change their physiology in response to their environment and pass those changes on to their offspring, some evidence suggests that the environment can make lasting changes to the genome via epigenetic mechanisms"

How does an unintelligent environment make a change in an intelligent entity without any input from that entity’s intelligence? And there are of course biologists that do believe that epigenetic mechanisms are intelligently constructed. Intelligence after all can reside in our cells and in our strategic mechanisms as well as in our more modern brains.

Curculio, December 24, 2012
What strikes me as odd is the fact that the germ line is impacted by all of these somatic changes. How is it that certain epigenetic changes get passed along but not the rest of the possibilities? I can see non-Weissmanian organisms, like plants, fungi; well all others except animals exhibiting this phenomenon but germ-line sequestering creatures. Perhaps, the sequestration is only partial and there are aspects of the filter that need exploring. If in the future we (as in the royal we), find that other parts of the body contribute factors to these germ line changes, we will need to extend our belated apologies to Darwin for accepting Pangenesis and being ahead of his time. As Forrest Gump said, "Again".

HIV Evolves Vulnerability
In mutating to evade immune detection, HIV becomes susceptible to detection by different antibodies, suggesting new strategies for vaccination.
By Sabrina Richards | October 22, 2012
In response to the initial flood of antibodies the immune system releases upon infection with HIV, the virus shifts the location of sugar groups on its envelope protein to evade detection. But in doing so, the virus creates new glycosylation patterns that can be recognized by different antibodies, which appear to target a much broader range of viruses.

The research, published Sunday (October 21) in Nature Medicine, suggests that focusing on eliciting antibodies with a wide range of different specificities, to both acute and chronic viruses, may be a promising strategy for vaccination.

“We had always assumed the first virus would be special,” eliciting the most broadly neutralizing antibodies, but the new work challenges this assumption, explained Hanneke Schuitemaker, an immunologist at the University of Amsterdam who did not participate in the research.

HIV is an especially tricky virus for vaccine developers. Many important viral proteins that could be targeted by antibodies, regions known as epitopes, are often hidden—and thereby protected from immune detection—until HIV binds to CD4-expressing target cells, including T lymphocytes and macrophages. Furthermore, HIV’s rapidly mutating genome allows it to evade immune attack by changing its appearance, preventing recognition by initially effective antibodies.

But sometimes the immune system is successful in generating antibodies that block HIV binding and infection of CD4-expressing cells. Understanding what epitopes the immune system targets to generate such broadly cross-neutralizing responses is a promising area of inquiry by researchers hoping to develop a vaccine against the virus. The most potent class of known broadly cross-neutralizing antibodies recognizes a particular glycan sugar, found at position 332 on the gp120 envelope glycoprotein that facilitates viral entry into cells by binding CD4.

To investigate the evolution of HIV and the antibody responses against it, Penny Moore and Lynn Morris at South Africa’s National Institute for Communicable Diseases of the National Health Laboratory Service tracked the antibody titers of HIV-1-C-infected women. The scientists noticed that as time passed, more patients began expressing broadly cross-neutralizing antibody responses.

Two women, who had high levels of viral replication, produced antibodies that neutralized viruses glycosylated at 332. But the viruses that had first infected the women had no sugar group at 332.

“We were astonished,” said Moore. The infecting viruses were not glycosylated at position 332, but the immune system began making antibodies to target that epitope. The answer, it turned out, had to do with viruses that arose later in infection, which did express this sugar group. About a year into infection, all viruses were glycosylated at 332, at which point the broadly neutralizing antibodies were found at high levels in the blood.

The timing of this switch suggests that viral escape from the first wave of antibodies, which target epitopes found on the initially infecting viruses, had led HIV to carry the glycan group that is susceptible to the broadly cross-neutralizing antibodies. To test this hypothesis, Moore and colleagues combined antibodies generated during acute infection with viruses expressing the 332 glycan epitope. Sure enough, the antibodies were unable to block cell entry, supporting the idea that evolving this epitope enables HIV to avoid the initial wave of antibodies generated in response to infection.

Widening her scope to almost 70 patients, Moore found the pattern—the appearance of glycosylation at 332 only later in infection—repeated in nearly a third of infections. Though rare in viruses establishing infections, glycosylation at this residue is common in viruses from chronically infected individuals, helping to explain how antibodies that target this epitope often neutralize viruses from many different patients.

“This is the first time we’ve really understood that viral evolution itself shapes the antibodies that come out,” said Moore. “Being able to work out the pattern of viral evolution will help us think about designing vaccines,” she added. One strategy that may prove successful could be to provide sequential immunizations with vaccines containing different epitopes, “mimicking what happens naturally” as the viruses evolve, she speculated.

It’s unclear, however, why viruses that initially establish infections tend to not to be glycosylated at this position, but vaccine developers may still have success using this epitope in combination with others, said David Montefiori, a viral immunologist at Duke University who did not participate in the study.

Another lingering question is how new epitopes generate different antibodies, said Schuitemaker—specifically, whether the broadly neutralizing antibodies are produced by the same B lymphocytes that responded to the initial infection, or by different B cells only called into action after the viruses have switched epitopes. “If they’re different B cells, maybe a vaccine could trigger them immediately,” rather than waiting for the virus to evolve, said Schuitemaker.
Of course, it won’t be easy to find the perfect vaccine strategy amongst the constantly shifting interplay between B cells and viruses for vaccine development. “It really blew my mind—how incredibly dynamic the whole system is,” said Moore.


**Alternative Medicines (long)**

*As nonconventional medical treatments become increasingly mainstream, we take a look at the science behind some of the most popular.*

By The Scientist Staff | July 1, 2012

While traveling in China in 1971, two-time Pulitzer Prize-winning journalist James Reston underwent an emergency appendectomy, after which Chinese medical personnel treated his pain with acupuncture. His description of the experience in the pages of the *New York Times* brought the practice of traditional Chinese medicine front and center.

Two years later, Lewis Thomas, then president of Memorial Sloan-Kettering Cancer Center, delivered an address in which he said, “These are bad times for reason, all around. Suddenly, all of the major ills are being coped with by acupuncture. If not acupuncture, it is apricot pits.” Thomas was referring to laetrile, a compound extracted from the pits of apricots and bitter almonds, one of the most sought-after alternative treatments for cancer at the time, but one whose effectiveness had been the topic of bitter controversy for years. Banned since 1963 in the U.S., laetrile is reported to still be readily available in the Bahamas and Mexico and is sold online.

And the examples don’t end there. Lots of ballyhoo, head-scratching, and accusations of quackery attended growing patient demand for alternative treatments, hyped in the popular press as cures that were “natural” and based on millennia-old medical traditions practiced in places such as China and India.

In 1999, in response to a growing outcry for some kind of evidence-based scientific analysis of the safety and efficacy of this blizzard of nonconventional treatments, the National Institutes of Health, then under the direction of Harold Varmus, established the National Center for Complementary and Alternative Medicine (NCCAM). Since its founding, NCCAM has funded basic and clinical research at institutions around the world on plant and animal products such as acai, black cohosh, gingko biloba, and shark cartilage, as well as on the therapeutic value of treatments including acupuncture, yoga, massage, reiki, and meditation.

Almost 40 percent of US adults and 12 percent of US children have used complementary or alternative therapies, according to a 2007 survey by NCCAM, and much of what was once considered “alternative,” including acupuncture, is now part of more-holistic regimens offered at 40 percent of US hospitals, including Memorial Sloan-Kettering Cancer Center. According to a 2010 survey by the American Hospital Association and the Samuei Institute, a nonprofit center for the study of wellness and healing, this trend is driven by patients demanding alternative or complementary treatment options for conditions that are difficult to manage or cure, such as diabetes, chronic pain, and cancer. Most physicians have lukewarmly embraced such therapies, often because they feel that patients will desert conventional therapy out of desperation if they are not offered a wider range of treatment options.

Researchers who study the scientific validity of nonconventional treatments rarely see them as stand-alone remedies, preferring to call the union of conventional and nonconventional “integrated therapy.”

*The Scientist* staff asked experts about the scientific evidence for a number of treatments that may be on the verge of becoming incorporated into integrated therapies, from acupuncture and probiotics to marijuana and psychedelics. We sought to highlight the data that either supports or contravenes the effectiveness of these alternative therapies. As with most health interventions, we uncovered both positive and negative aspects of these treatments for which patients are clamoring and physicians are demanding evidence. —**Mary Beth Aberlin**

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**Probiotics: Poised for Prime Time**

*Though research is deepening our understanding of the role of microbes in our health, good clinical trials are still needed before consumers can be sure they will enjoy any benefits.*

Microbes, mostly bacteria and yeast, teem throughout our bodies, setting up their own ecosystems on our skin and in our mouths and guts. As it becomes ever clearer that microbial ecosystems are intimately connected to our health, consumers look to probiotics—strains of bacteria or yeast that may have health...
benefits if ingested or applied externally—as gentler alternatives to current therapies. Beyond the obvious interest in developing probiotic treatments for gastrointestinal disorders, researchers hope to understand how probiotics may influence obesity, skin health, vaginal health, and even our moods. With probiotics showing up in everything from yogurt to face cream, it’s difficult to know whether these products have credible benefits. Clinical studies are beginning to support the early promise of some probiotic treatments, and scientists are rapidly expanding their knowledge of how microbes interact with our bodies and how probiotics might be rationally employed both to treat and to prevent disease.

“It’s a very exciting time to be a microbiologist,” says Maria Marco of the University of California, Davis, who studies how lactic acid bacteria, which include strains used in milk fermentation, interact with our intestines to improve health. She points to a confluence of genetic data from the Human Microbiome Project and experimental data, which together are beginning to illuminate the role of microbes in health.

About 200 clinical trials have investigated the use of probiotics to treat gastrointestinal disorders, and the science is finally catching up to the hype, says Marco. A March 2011 Cochrane Review recommended the use of probiotics in premature babies to help prevent necrotizing enterocolitis, in which sections of bowel tissue die. In November 2011 another Cochrane Review of 16 studies reported efficacy in treating children with probiotics to prevent antibiotic-associated diarrhea. But the evidence is not overwhelmingly positive, notes Matthew Ciorba, a gastroenterologist at Washington University in St. Louis. “If there were super-strong results, all physicians would be prescribing [them],” Ciorba says. The Cochrane study showed that probiotic treatment reduced antibiotic-associated diarrhea from more than 220 cases per 1,000 children to fewer than 90. But the review’s lead author, Bradley Johnston at the University of Toronto’s Hospital for Sick Children, explains that due to a lack of high-quality data, he and his coauthors are not extremely confident about those numbers. About 25 percent of patients did not complete the studies, and even though they collected data from 3,000 children, there were relatively few cases of diarrhea, making it difficult to draw strong conclusions.

Another antibiotic-associated infection that is on the rise, the occasionally life-threatening Clostridium difficile, may be amenable to probiotic treatment, but again, rock-solid results are lacking. One reason for the dearth of convincing clinical trials, Johnston notes, is that it’s more difficult to conduct trials for a rare disease like C. diff, because they require larger numbers of base participants to catch the rare cases needed to power the study. A 2008 meta-analysis examining probiotic treatment of C. diff infection did not recommend the therapy, but Johnston says that an updated analysis is expected to be completed this summer. Fecal transplants of healthy—donor gut microbes—also considered a probiotic treatment—have shown promise in case studies of C. diff, but clinical trials are needed. Investigations of the probiotic potential of Saccharomyces boulardii, closely related to brewer’s yeast, and Lactobacillus rhamnosus GG have produced mixed results, but suggest that both may aid in treating recurrent C. diff infections. Johnston expects to see more strain-specific trials for this hospital-acquired infection in the future. (See “Wrestling with Recurrent Infections,” The Scientist, May 2011.)

Treatments investigating probiotic treatment of chronic inflammatory bowel diseases, such as Crohn’s disease and ulcerative colitis, have so far failed to demonstrate a strong effect. A 2011 Cochrane Review of four clinical trials surveying probiotic treatment of ulcerative colitis couldn’t recommend the therapy due to a lack of large, well-designed, randomized trials. The pooled studies covered only 587 participants; two trials were not completely blinded; and one had a dropout rate of nearly 50 percent.

It’s clear that larger and better-designed studies are necessary, but researchers are also contending with microbial ecosystems that aren’t easily altered. “Our microbes are fairly established,” says Mary Ellen Sanders, of Dairy and Food Culture Technologies in Colorado. “They can be perturbed [with new probiotics or pathogenic strains] but they tend to bounce back,” so eating yogurt won’t permanently colonize the gut with beneficial bacteria. Thus, chronic problems stemming from a specific spectrum of microbes—unlike antibiotic-associated diarrhea—will be unlikely to respond to a quick dose of probiotics.

Lackluster trial results may also stem from using the wrong probiotic to treat an illness. Specific probiotic strains may have drastically different effects, even if the microbes are from the same species, explains Marco. Her own work on the immunomodulatory effects of Lactobacillus plantarum on human immune cells showed that production of the pro-inflammatory cytokine IL-12 differed up to 16-fold based on the strain, and the amount of the anti-inflammatory cytokine IL-10 differed 14-fold. Immunomodulation is one key mechanism thought to underlie probiotic effects. Cell-wall components of probiotics, such as peptidoglycans and teichoic acids, can spur pro- or anti-inflammatory reactions from mucosal and immune cells, depending on modifications like glycosylation and acetylation. A strain of L. plantarum that promotes more IL-10 production has been shown to protect against colitis in a mouse model.
Although controlling inflammation is thought to be one mechanism, how, exactly, probiotics work against conditions such as antibiotic-induced diarrhea is unclear, says Gregor Reid, a microbiologist at the University of Western Ontario who helped write the World Health Organization’s definition of probiotics 10 years ago. It’s known that commensal (nonpathogenic) microbes can stimulate mucus or antimicrobial peptide production by gut epithelial cells, Reid explains, and probiotics might also compete with pathogenic bacteria for an ecological niche.

One future challenge will be translating promising animal studies into effective human trials, says Sanders. For example, she notes, probiotics “give really nice results” in mouse models of Crohn’s disease, but so far attempts to replicate this in humans have fallen short.

Researchers are also beginning to tackle the question of how probiotics may help in conditions seemingly unrelated to our guts, such as periodontal disease, allergic disorders, and even mental health. It’s known that our microbial ecosystems are in flux for several months after birth, and if certain strains are linked to later disease, like asthma, early manipulation of our microbiota might be a wise prophylactic strategy, says Reid. Sanders, in turn, postulates that the Human Microbiome Project may provide us with information that will help us identify the right microbes to help infants and children develop appropriately. Research linking obesity or stress responses to the gut microbiome is in tantalizing early stages. Marco points to one study in which probiotic treatment influenced mouse stress behaviors, and several which suggest that gut microbes may influence energy expenditure and abdominal fat.

In the meantime, says Ciorba, it remains difficult for the consumer to benefit from successful probiotics studies. Even if a yogurt contains a probiotic strain that is backed by scientific research, it’s difficult to know how the viability of the commercial strain compares to the doses tested in the lab or how long it should be taken for optimal effect. Touching again on the notion that our intestinal health may influence our mental health, Ciorba points to irritable bowel syndrome—a constellation of generally mild symptoms that may be difficult to measure clinically. Though probiotic treatment may not change the amount of diarrhea or timing of bowel movements, patients still report improvements in pain symptoms. When taking probiotics, Ciorba says, “they just feel better.”

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**Acupuncture: The Real Needle**

*Acupuncture may not work any better than its placebo, but even the placebo often improves patient outcomes.*

In 1997, the National Institutes of Health convened a conference to evaluate acupuncture—the insertion of needles into the skin at points that run along so-called meridian lines outlined by Chinese traditional medicine—with the goal of determining whether the technique had a place in Western medicine. The practice is used to treat a wide range of conditions, from pain to infertility, epilepsy and schizophrenia, and the NIH consensus conference was tasked with determining if the claims were valid. “A consensus conference is more like a court of law than a scientific meeting,” explains Richard Hammerschlag, Emeritus Dean of Research at Oregon College of Oriental Medicine, who presented at the meeting. “At that point, there was relatively little good research. Most of the studies were underpowered, low-sample studies.”

Twelve professionals from fields including anthropology, psychiatry, public health, osteopathic medicine, and substance abuse evaluated the presentations, and at the end of the conference drafted a report summarizing their collective opinion.

Despite the limited data available, and the panel’s rather hedged wording, the conference report found that there was enough evidence to support the use of acupuncture for post-operative dental pain and for nausea after chemotherapy, and evidence for several other applications that seemed promising. The conference report, which was published in the *Journal of the American Medical Association*, lent an air of validity to the use of acupuncture. “I think it was considered a milestone in accepting acupuncture in medical practice,” says Eric Manheimer, an administrator of the Cochrane Collaboration’s Complementary Medicine Field.

5 years and some 4,000 clinical trials later, researchers are still not convinced that acupuncture is any better than the often-used placebo of sham acupuncture, which employs only superficial needle insertion into random points on the skin. The confounding issue, and the one which most researchers seem to agree on, is that both acupuncture and sham treatment appear to have benefits over the standard of care, creating what researchers call the “efficacy paradox.” It suggests that either acupuncture exerts a powerful but reproducible placebo effect in patients, or that inserting needles randomly has the same effect as
Researchers studying placebo effects have demonstrated that acupuncture can go a long way towards helping patients feel better. One recent study by placebo researcher Ted Kaptchuk at Beth Israel Deaconess Medical Center compared albuterol, an asthma medication, with sham acupuncture, no intervention, or a placebo inhaler (NEJM, 365:119-26, 2011). Patients reported feeling better after albuterol treatment, as well as after sham acupuncture and the placebo inhaler, but not if they received no treatment at all. However, when researchers took an objective measure of their asthma—the maximum forced expiratory volume in one second—it was clear that only those treated with albuterol actually improved.

In another study, participants were asked to rate their belief that acupuncture would work prior to acupuncture treatment for pain. Those with high expectations showed greater pain relief than those with lower expectations, regardless of whether they received real or sham acupuncture (Pain, 128:264-71, 2007). While the research suggests that there is a strong placebo component to acupuncture, that may not be a bad thing, says acupuncture practitioner and placebo researcher Tao Liu, a visiting scholar at the University of Maryland School of Medicine. “Placebo effects can be clinically relevant and can be harnessed to improve patient care. Acupuncture is a good example,” Liu says in an e-mail.

Another possible explanation for the efficacy paradox touches on the fact that researchers still don’t have a good idea what acupuncture’s mechanism of action might be, which makes it extremely difficult to create an appropriate control. “That was the problem [in 1997] and is still the problem today,” says Hammerschlag. When drug trials are performed to test efficacy, “you know what the real drug’s mechanism is—how it’s absorbed, how it’s metabolized, and how it’s degraded,” he says. That knowledge allows researchers to design a placebo that doesn’t do any of those things, but that mimics the treatment enough to deceive the patient. Some sham acupuncture trials use methods such as poking a person with the blunt end of the needle or using placebo needles which retract into the handle of the needle, but these can be too easy for a patient to spot, rendering the placebo ineffective. Real needles superficially inserted into the skin at nonmeridian points are harder for patients to differentiate from “true” acupuncture, but some researchers think that even apart from patients’ belief that they are getting the real thing, this placebo could still activate the same mechanism of action as needles inserted into the traditional meridian points.

While there is no agreement on how acupuncture might work, a number of physiological changes do occur as a result of acupuncture needling, both in animal models and in humans, along meridian lines or not, which may or may not be related to acupuncture’s proposed medicinal effects. For example, studies in mice suggest that acupuncture’s reported effect of relieving pain may be mediated by the localized release of adenosine, which has analgesic effects (Nat Neurosci, 13:883-88, 2010). Other studies show that connective tissue in mice sticks to acupuncture needles and measurably wraps around the needle, which stretches the tissue. As a result of this stretching, nearby fibroblasts become enlarged and, over the course of 30 minutes, cause the connective tissue to relax. Simple mechanical stretching of the connective tissue appears to have the same effect on fibroblasts, but acupuncture provides a way of creating a local and sustained stretch, says Helene Langevin, a neuroscientist who studies connective tissue and mechanotransduction at the University of Vermont. But, she says, “we don’t know how that translates to changes in pain [perception]. We haven’t tested that yet.”

Although the question of whether acupuncture helps patients due to a placebo effect or an actual physiological change remains open, a number of insurance companies both in the United States and in the United Kingdom have begun to cover the practice, at least for a few conditions, such as lower back pain. Whether it works for the right reasons or the wrong ones, the treatment does appear to work for some people, says Hammerschlag. “We certainly don’t know enough yet to throw it out.” —Edyta Zielinska

Facts about the benefits of medical marijuana are sparse, hampered by the politics and regulatory difficulties of doing such research.
Marijuana (Cannabis sp.) has been used as a medicine for more than 4,000 years. But in the eyes of the US federal government, cannabis is an illegal drug that has no place in the clinic. Biomedical researchers who would like to study cannabis in a medical setting are frustrated by the challenges of obtaining government clearance and funding. But some data pointing to medical benefits of smoking marijuana do exist.
In 1970, the US Congress voted to classify cannabis under Schedule I of the Controlled Substances Act. Marijuana joined heroin, LSD, and peyote on Schedule I, and according to the Act, it—which along with all other Schedule I drugs—has a high potential for abuse, lacks safety, and has “no currently accepted medical use in treatment in the United States.”

Since then, 16 US states and the District of Columbia have legalized the use of medicinal cannabis for a variety of indications, from chronic pain to cancer- and HIV-related appetite and weight loss, nausea, and vomiting. But despite the recent wave of state-level legalization, and the enactment of similar laws in Canada and elsewhere around the globe, the US federal government still classifies marijuana as a Schedule I drug, a designation that makes studying the medical effects of the drug in the U.S. extremely difficult (requiring approval from the Drug Enforcement Administration in addition to the Department of Health and Human Services (HHS)). Therefore, it has been far more common (and easier) to get funding and clearance to study the negative impacts of marijuana as a substance of abuse than to investigate its positive effects as a therapeutic agent.

 Nonetheless, some researchers have braved the bureaucratic obstacles to conduct a handful of randomized, placebo-controlled trials that point to benefits of smoking cannabis, though they acknowledge that smoking the plant comes with its own risks and drawbacks. A more extensive body of literature involves molecular components, extracts, or synthetic forms of marijuana, simply because studying these non-Schedule I substances is less fraught with regulatory obstacles than is studying the whole plant.

 The strongest evidence of smoked marijuana’s benefit exists in patients who experience chronic pain. With funding from the University of California Center for Medicinal Cannabis Research (CMCR), researchers published studies in 2007, 2008, and 2009 that all suggested smoked cannabis possessed analgesic properties. A study published in 2007, for example, noted that HIV patients experiencing neurological pain, or neuropathy—a general name for burning pain, hypersensitivity to light touch, and other uncomfortable symptoms—experienced a dulling of that pain when they smoked a cannabis cigarette three times a day for 5 days.

 Psychiatrist Igor Grant, director of the center and an HIV/AIDS researcher at the University of California, San Diego, says that patients suffering from neuropathy in particular seem to find relief in cannabis. “We don’t have terrific agents to treat it. There are agents [such as antiepileptics and antidepressants] and they are modestly effective in many people,” Grant says. “The bottom line is that [cannabis] seems to work, and the effects are comparable in strength to traditional agents.”

 Other studies from the CMCR have probed new conditions the plant might be used to treat. For example, UC San Diego researchers reported in 2008 that smoked marijuana has the potential to reduce muscle spasticity in multiple sclerosis (MS) patients. That finding was bolstered by a randomized, double-blind, placebo-controlled study published last year on the liquid marijuana extract Sativex, which is approved for use in some European countries, Canada, and New Zealand. The results of that trial, conducted by European researchers, indicated that a 4-week course of Sativex, an oral spray that contains the cannabinoids cannabidiol (CBD) and delta-9 tetrahydrocannabinol (THC), was safe and effective at reducing spasticity in many MS patients.

 US researchers are completing Phase III trials of Sativex for the treatment of pain associated with cancer, and Otsuka Pharmaceutical, the US licensing partner of UK drugmaker GW Pharmaceuticals, hopes to gain FDA approval soon.

 Aside from the relative logistical ease of studying constituents, extracts, or synthetics due to the fact that they do not run afoul of the Controlled Substances Act, these compounds stimulate the endocannabinoid system, the body’s homegrown constellation of receptors that interact with the active components of cannabis in a more tractable way than does smoked cannabis. “Harnessing that system with medications is a potentially new avenue for therapeutics,” says Mark Ware, McGill University neurologist and pain physician.

 For example, Marinol is a synthetic THC drug that is used by chemotherapy patients experiencing nausea and vomiting or AIDS patients who are rapidly losing weight. It is the only FDA-approved synthetic cannabinoid, and offers an alternative to conventional therapies for these patients, though results have been mixed when comparing its effects to those of smoked cannabis, with the herbal version usually outperforming the synthetic.

 This highlights one problem with going the synthetic route in the eyes of some cannabis researchers. “We shouldn’t forget that the herbal product contains multiple other constituents which may add to the effects of any one single agent,” says Ware. Also problematic are isolated cannabinoids’ tendency to be rapidly broken down in the liver and the difficulty in determining optimal doses.
As the political and social storm around medical cannabis continues to brew, most researchers who have seriously tested the drug’s therapeutic properties lament their inability to freely study it in a medical context. “The [cannabis] laws date to a time when what we knew about marijuana was voodoo,” says Mayo Clinic psychiatrist Michael Bostwick. “[The drug] can’t be applied to humans and to therapeutics because the laws don’t permit it to be done. The whole attitude towards medical marijuana is just irrational.”

For its part, the NIH claims that studying smoked marijuana is fair game. “Research projects seeking to determine the therapeutic potential of smoked marijuana are considered under the same criteria as any other project submitted for NIH funding,” the agency wrote in an e-mail to The Scientist. “Investigator-initiated applications for NIH funding are evaluated by peer-review groups composed of scientists from outside the NIH. The peer-review group evaluates the scientific and technical merit of the proposed research.” That said, the NIH’s Research Portfolio online Reporting Tools (RePORT) database lists many more active projects focusing on molecular components of cannabis or marijuana as a harmful drug than it does projects seeking to probe the potential medical benefits of smoking cannabis. Still, officials at the HHS also claim that the US government is game to fund studies of medical marijuana. “We’re very open to people submitting applications and trying to make [evaluating medical marijuana study proposals] a transparent and efficient process,” says Sarah Wattenberg, senior advisor for substance abuse policy at HHS. “In order for us to move this forward at all, we have to take the politics and stigma away, deal with it as a therapeutic class, and give people what science there is,” says Ware.

Particularly vexing to Ware is that so many people all over the world are using marijuana either recreationally or for the treatment of some ailment, legally or more often illegally, while science is forced to sit idly by and miss out on all that potential data. “We have so many people who are already doing the drug in one form or another in some sort of legal framework, but they’re not being involved in any type of research,” he says. “There’s kind of a huge natural experiment going on right now, and we’re not learning from it.” —Bob Grant

**Psychedelic Fervor**

While research on LSD and other hallucinogenic drugs slowed dramatically after their illegalization in the 1960s, the little research that continued has touted their promise in treating a wide range of disorders.

In the late 1940s, researchers began experimenting with the controlled use of psychedelic drugs, such as lysergic acid diethylamide (LSD), as possible therapeutics to supplement psychotherapy. The drugs’ psycholytic or “mind-loosening” effects, they realized, made it easier for patients to explore repressed memories. Over the next few decades, research on psychedelics expanded to include their potential application to anxiety disorders, obsessive-compulsive tendencies, depression, drug and alcohol dependence, pain, bereavement reactions, sexual dysfunction, and more. By 1965, more than 2,000 published articles—most of them, admittedly, anecdotal case reports—touted the effectiveness of psychedelic drugs in helping to safely treat some 40,000 patients, with few negative side effects reported.

But rampant, uncontrolled recreational use and reports of adverse reactions during the 1960s led to the illegalization of LSD and other such drugs in the United States—cutting off the supply to research labs around the country and slowing psychedelics research to a trickle. Like marijuana, the drugs are now listed as Schedule I drugs, and researchers hoping to study their medical benefits must get approval from several different agencies and boards. In the last 10 years or so, however, new research on their therapeutic benefits has warranted the drugs’ entry into clinical studies, and today, a handful of trials are bringing psychedelics closer to use in the clinic.

“Psychedelic drugs, from a scientific viewpoint, shouldn’t even be a controversial subject,” says Ben Sessa, a child and adolescent psychiatrist working in South West England. “They are effective and safe treatments for mental illness, and there’s very good evidence for that.”

Psychedelics act on various neuro-transmitter and hormone systems in the brain. LSD and psilocybin, the psychedelic component of “magic” mushrooms, for example, affect serotonin and dopamine signaling, while MDMA, or “ecstasy,” increases output of oxytocin, among other changes. Although these neural pathways are known to regulate mood, learning and memory, bonding, and more, and their dysregulation is implicated in psychosis, exactly how the drugs’ actions in the brain translate into a therapeutic effect (or a bad trip) is still unclear. “We know what receptors they’re targeting, we know basically what kind of second messenger signals inside the cells they get started, but beyond that we don’t know how they work,” says Emmanuelle Schindler, a physician scientist and neurology resident at Yale School of Medicine. Of
course, “that is not known for any psychiatric drug,” adds South Carolina–based psychiatrist and researcher Michael Mithoefer.

Uncertainties aside, several psychedelic drugs have started to show real promise in recent clinical trials. In 2010, a phase II trial of MDMA conducted by Mithoefer and colleagues successfully “cured” 10 of 12 posttraumatic stress disorder (PTSD) patients—who no longer exhibited symptoms typical of the disorder after participating in just two 8-hour psychotherapy sessions while on MDMA. The three subjects who had had to leave their jobs as a result of their PTSD were all able to return to work.

Another treatment advancing through clinical trials is the use of LSD and psilocybin to manage anxiety in patients with terminal illness. Just last year, advanced-stage cancer patients participating in a Phase II study of psilocybin responded positively after a single treatment. “We found fairly strong and consistent evidence that it did reduce anxiety and also improve mood, not simply for the hours and day of that experience but even in the weeks and months that followed,” says Charles Grob, a professor of psychiatry at the University of California, Los Angeles.

Because therapy with psychedelics involves only one or a handful of treatments over several weeks or months, there is little risk of side effects or dependence. “You just have to take them once or twice, and they can cause long-lasting changes that we don’t really see with other types of medication,” says Schindler.

However, the fact that so few doses are necessary makes it hard to find funding, notes Mithoefer. “That’s not a very profitable business model,” he says, particularly for pharmaceutical companies looking to cash in on future drug sales. Currently, researchers rely heavily on foundations such as the Multidisciplinary Association for Psychedelic Studies (MAPS) and the Heffter Research Institute, as well as a hodgepodge of other sources, to fund their work.

The illicit drugs’ unsavory history and continued recreational use also complicate the funding and clearance processes. “We have to jump through a lot of hoops . . . [to ensure that] our studies are fully sanctioned and approved,” says Grob.

Despite the hurdles, psychedelics researchers are hopeful that the next decade will see some of these therapies gain FDA approval—at least for use in patients who are not responding to traditional therapies. “What I’m seeing in the last couple of years is a real shift away from prejudice to actual interest and healthy skepticism,” says Mithoefer. “Certainly there are some detractors still out there, but for the most part it’s turned into more of a real scientific discussion.” —Jef Akst

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**Costs: Herbal Hazards**

_Natural doesn’t always mean safe: the scary consequences of taking understudied herbal supplements._

In the early 1990s, dozens of women, most under the age of 50, were being admitted to hospitals in Belgium with renal failure. About half of the women who had surgery to remove their nonfunctioning kidneys also had tumors in the upper urinary tract. The cases clustered around a medical clinic that had been prescribing Chinese herbs, which for more than 15 years had appeared to safely help women lose weight.

It turned out that aristolochic acid, a nephrotoxic chemical derived from _Aristolochia_ vines, had mistakenly made it into in the slimming pill’s mix of ingredients. And while the Belgian tragedy was considered an accident, people around the world have taken the herb intentionally to aid wound healing, soothe arthritis, expel the placenta after childbirth, and repel snakes. “Every culture in the world has used _Aristolochia_ in their traditional medicines,” says Arthur Grollman, a professor at Stony Brook University School of Medicine. “Don’t they know this is one of the most potent carcinogens that’s ever been recorded, and it’s renotoxic?”

In Taiwan, for example, one study found that one out of three people had received a prescription that included _Aristolochia_ before the country banned the herb, and that prescriptions continued even after the ban. Interestingly, Taiwan also has one of the highest rates of upper urinary tract cancers in the world. Grollman and colleagues recently decided to test whether this coincidence has any backing in biology, and found that of 151 Taiwanese patients with upper urinary tract cancer, 83 percent had taken _Aristolochia_ (PNAS, 109: 8241-46, 2012). The evidence was right there in the tissue: aristolochic acid metabolites actually bound to DNA in the kidneys, and were associated with specific mutations in the p53 tumor suppressor gene.

Despite the dangers uncovered by Grollman and others, such complementary and alternative therapies, referred to now as integrative medicine, aren’t regulated as drugs in the United States. “There
are thousands and thousands of products being sold through all different kinds of channels,” says Stephen Bent, a professor at the University of California, San Francisco. "And there isn’t the safety framework to capture and monitor how often people are having side effects or problems.”

In August of last year, Ranit Mishori, a family physician at Georgetown University School of Medicine, published case reports of two patients who ended up hospitalized after a seemingly innocuous colon cleanse (Journal of Family Practice, 60: 454-57, 2011). Sometimes taken orally, sometimes given enema-style, colon cleanses are intended to flush the system, but they can also cause a "tremendous amount of harm," Mishori says. In one case, a patient was left severely dehydrated and with pancreatitis and an inflamed colon. In another case, a woman’s Crohn’s disease flared up shortly after a cleanse, causing days of cramping, diarrhea, and dehydration. “Since the publication of this article, I’ve heard about a lot more cases that haven’t made it into the medical literature,” Mishori adds.

Other herbal medicines that have been implicated in causing health problems include St. John’s wort, whose leaves and yellow flowers are used to treat depression, but can interfere with HIV medications; the roots of the kava-kava plant, the improper preparation of which has been linked with liver damage; and ephedra, a short evergreen bush that goes by the name *ma huang*, and has been tied to high blood pressure and heart attacks.

The Dietary Supplement Health and Education Act requires that manufacturers follow quality-assurance guidelines and report adverse events. But Grollman says it does not protect consumers as well as the US Food and Drug Administration’s regulations for drugs. “If herb A is such a potent carcinogen and nephrotoxin, how do you know that herbs B, C, and D are not? They’ve never been tested. . . .

Natural is definitely not safe,” says Grollman. At least, as his work shows, not always. —Kerry Grens

**Costs: Threat to Wildlife**

As demand for traditional medicines booms, conservationists worry about the toll it takes on the animals and plants that serve as ingredients.

Traditional folk remedies and the modern alternative medicines that harken back to such treatments rake in annual revenues of $80 billion to $200 billion worldwide. The market for such products is expected to grow exponentially in the coming years, and this has conservationists worried about unsustainable hunting and gathering of the world’s fauna and flora for medicinal uses.

The past decade has witnessed the extinction of several high-profile species hunted, in part, for their use in traditional medicines. Late last year, the International Union for Conservation of Nature (IUCN) officially declared the western black rhinoceros (*Diceros bicornis longipes*) of central-west Africa to be extinct due to widespread poaching and listed the northern white rhinoceros (*Ceratotherium simum cottoni*) as “possibly extinct in the wild.” Both species were hunted mercilessly for their horns, which have been highly valued in East Asian medicine for more than a millennium, and can sometimes approach the price of gold.

The use of wild fauna and flora in traditional Chinese medicine (TCM), in particular, is a concern for worldwide wildlife conservation efforts. TCM is practiced by more than a quarter of the world’s population and represents a $60 billion global market. More than 10,000 plants and animals, including endangered species such as rhinos, saiga antelopes, musk deer, Asiatic Black bears, Yangtze River dolphins, pangolins, turtles, and certain species of monkeys, orchids, and sea horses, are used in TCM.

Despite the implementation of policies banning the international trade of endangered wildlife species such as tigers and rhinos in the 1980s and ‘90s, poaching and illegal trafficking of both species has seen a dramatic rise in the last decade, largely due to increasing demand from the burgeoning economies of Southeast and East Asia.

But the problem extends beyond Asia. “When rural communities were harvesting medicinal animals for their own uses, overexploitation was seldom a problem,” explains Rômulo R.N. Alves, an expert in animal-based Latin American remedies at the Universidade Estadual da Paraíba in Brazil. “However, the growing market demands and the promise of quick returns have encouraged hunters to concentrate on species with higher economic value.”

The problem is compounded by the fact that ingredients for traditional medicines are almost always collected from the wild and seldom farmed. “The medicinal fauna in Latin America is largely based on wild animals, including many endangered species,” Alves says. And it’s not just animals. In the United States, overharvesting of American ginseng (*Panax quinquefolius*), which has been found to lower blood-sugar levels, boost the immune system, and have anticancer properties, have rendered it endangered in the wild.
Monitoring illegally traded natural products destined for the traditional medicine market is also notoriously hard due to lack of regulation, poor quality control, and often-nonexistent labeling. Yet there is hope that by employing sophisticated technologies, such as next-generation sequencing and genetic barcoding, customs agents will be better able to confiscate traditional medicines that incorporate illegal ingredients, says Mike Bunce, a geneticist at Murdoch University in Australia who helped sequence mitochondrial and chloroplast DNA in 15 TCM products confiscated by Australian border protection officials earlier this year.

A major focus for the IUCN, the World Wildlife Fund, and other such organizations, however, has been to raise awareness among traditional medicine practitioners and patients in China about the origin of the products they use. “It’s important that users of these products take responsibility for the use and help the [bordering] countries concerned to effectively conserve these species,” says David Morgan, Chief of Scientific Support in the secretariat of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). —Cristina Luiggi

Comments
bsardi, July 5, 2012
Are small molecules like curcumin and resveratrol considered alternative medicine? They activate more genes than any conventional medicines and exhibit safer and more effective biological action compared to many drugs. A Resveratrol inhibits cancer at all three stages of development: initiation, growth and spread (metastasis), something no cancer drug has demonstrated. A Resveratrol is an antidepressant, anti-cholesterol, anti-bacterial, anti-viral, anti-fungal, anti-brain plaque, anti-inflammatory molecule. A Why isn’t resveratrol primary and the drugs secondary medicine?
stress124, July 5, 2012
Why is no mention made of electromedical approaches that are much safer and in many cases more effective than drugs, particularly for certain types of cancer. Similarly, cranial electrotherapy stimulation is FDA cleared for treating insomnia, depression and other stress related complaints and has a 30 year record of safety and efficacy supported by numerous articles in peer-reviewed journals.
gmilarkin, July 5, 2012
Although I am not a huge proponent of herbal dietary supplements/medications, I find the above story to be exceedingly biased and unbalanced. While it is true that there are sometimes dangerous consequences to using these therapies, how do they differ from the litany of side effects that accompany the use of pharmaceuticals (approved by FDA)? Also what about the long history of botanicals that have been exploited into single compound drugs? For example Salix spp. that provided aspirin, valerian that yielded valium, foxglove that gave us digitalis? The list goes on. I suggest that fair reporting would be of great benefit to your reputation and to your readership. Oh I forgot your bills are paid by BIG PHARMA.
gabrik56, July 5, 2012
Surprisingly this very interesting article does not mention at all homeopathy: Is this medicine alternative or official? In the first case it should have been thoroughly discussed, in the second case what I’m deeply afraid anyone can understand the huge financial and maybe political interests that revolve around “this fine invention”. Personally I trust much more in the laying on of hands –pranotherapy- (which should have been mentioned and discussed too) than in homeopathy
E Elaine Connelly, July 5, 2012
I have been told by my family physician that I have high Cholesterol. The very 1st testing I underwent showed my good cholesterol to be @ 71, after taking a regimen of statins (all of which gave me severe muscle pain) my next test showed extremely lowered HDL. I cannot take statins, I refuse to. I am not obese, so I am taking red yeast rice (2000 mg) a day, my next test is July 9. I am anxious to find out if that is doing the trick. I also take cinnamon to lower blood sugar levels as they also found out that I was pre-diabetic. Again, I believe both of these conditions are genetically related. I try to eat well, to not pig out on sugar loaded foods, and as little processed food as I can manage. I have done research on my own about a little gland called parathyroid. When this gland is no longer functioning properly, I have discovered that it can mimic both conditions to which I am pre-disposed (supposedly). Clinical trials do not apply in my case. Guess I’ll find out in 4 days whether or not I am doing okay. I am on Actos (which has been proved to cause bladder cancer). I really don’t want to remain on more chemical drugs which cause some of the very problems I am supposed to have. Scientists do not know everything and they are not Gods, even though they seem to think so.
steinp2, July 5, 2012
Scientists don’t believe they are gods. They are much too humble and altruistic. They are the ones who did all the research on the parathyroid you are looking at and came up with all of the drugs which may or may not work on you. They are also the ones who are working on weekends and into the night in confined laboratories at fairly low pay to try to figure out just what the hell to come up with next to help you and everyone else out there. The Greek and Roman gods were the ones who would toy with and just as easily dismiss man at their whim. Who, in the readily visible healthcare system of today does that really look like?
Paul M. Stein
StanYoung, July 5, 2012
Many alternative treatments have been rigorously tested. Virtually all of them failed in randomized clinical trials.
Jim English, July 5, 2012
When your writers do a piece on modern pharmaceuticals I hope they will be fair and take the same approach as in your section on herbs: 1. Choose to focus your article only on drugs with significant side effects; 2. Point out that FDA approved drugs are implicated in over 100,000 deaths per year in the U.S., according to the NIH; 3) Fail to include a single example of a drug that “actually” improves health and quality of life, and 4) End with a quote from an “expert” stating that the side effects and risks from approved pharmaceuticals are too risky to consider taking at this time.
Mark Maier, July 5, 2012
Many of the best drugs were discovered in plants...aspirin, digitalis, docetaxel... the list is long. It is not an hypothesis that non-traditional therapies work. They do. We need consistent dose, response and quality control so at least practitioners can reach anecdotal conclusions that can become testable hypotheses. FDA and EMEA are doing pretty well, but could put more focus on alternative therapies. It is Draconian to regulate marijuana as a controlled substance.
In all of the article, and the comments, not a solitary mention of essential oils and specific bioactive plant fractions from essential oils! More and more health care institutions are introducing essential oil treatment systems into their treatment regimes, whereby patients are obtaining measurable benefits in perceived pain reduction, nausea, anxiety, etc. Use of simple, cheap devices such as passive inhalers allows self-administration by patients of tiny controlled amounts, thereby freeing nurses for other tasks, freeing patients from the frustration of button-pushing, and presenting a cost-effective alternative to administrators: an all-round win/win/win. Â There is plenty of evidence to support the use of essential oils; just make sure the rigorous testing in randomized trials uses protocols established for evaluation of essential oils, not hydrophilic drugs.

Robert Slovak, July 5, 2012

The article was patently incompetent. Naïve even. The authors (the Scientist Staff), if I may quote Shakespeare, are "full of sound and fury signifying nothing". Judging by the comments, your readers possess far more scientific knowledge and wisdom. Move along to other topics for which you may be qualified..."For many are called but few are chosen".

Ted Howard NZ, July 5, 2012

A little over 2 years ago I was told that there was nothing known to medical science that could alter the probability of my survival. I had metastasised melanoma, with inoperable tumours on my liver.

As a biochemist by training I decided to do my own investigation, and to try anything that seemed to have some evidence for its usefulness, and didn't cost much.

I radically altered my diet—went strict Vegan (RAVE Vegan) with supplements of Vitamin C (about 20g per day) and Mineral/Multivitamin—one capsule per day.

It took about 4 months for the tumours on my liver to shrink below resolution by ultrasound or CAT.

I have twice reduced vitamin C, and each time had new tumours show up, which I had surgically removed and identified by histology. I haven't missed a day on Vitamin C for 16 months, and my scans before Christmas were all clear.

I seem to have beaten it, with the regime I am on.

My full details are on my blogsite: www.tedhowardnz.wordpress.com/... if anyone is interested (indluding all medical reports, and histology).

While there are many great people in the medical establishment, the profit motive seems to be a major impediment to health.

healthforyou, July 5, 2012

Has anyone checked out the Science of Glycobiology? It looks like when a person takes these plant sacharrides that the body can pretty much look after itself.

Paul Walker, July 5, 2012

Whatever happened to science based pharmacology? In the early 90's the The US Congress mandated the NIH to fund a dozen or, so alternative medicines and treatment therapies. If I remember they were all a bust. No value what so ever when blind and statistical testing were done.

Hominid, July 6, 2012

You claim to be a biochemist and you present your uncontrolled, under-sampled, anecdotal, personal experience as evidence in favor of an unrationlized, wholly empirical therapeutic regime? Puh-leez!

ryman123, July 6, 2012

Based on the flawed perception that herbsals and naturals are free of side effects appears to be common hope with its users. Taking both herbs and prescription medications points to real and consistent risks of serious life threatening events. Let's not forget the situation with Seldane and Grapefruit inhibiting the enzymatic conversion of a Seldane metabolite that caused cardiac arrhythmias and several deaths. The information regarding serotonin enhancements with St. Johns wort if combine with SSRI's. we must remember that so many of the modern pharmaceuticals had their genesis from natural products' Aspirin, Ace inhibitors, Cardiac , Oncology drugs. As a society we are led to believe that potenecy comes from the pharmaceutical manufacturer.

John Hanes, July 6, 2012

What a poorly informed article! At least in Australia, our therapeutic herbal and nutritional remedies are controlled somewhat by the Therapeutic Goods Administration so we have some quality control in our professional products. But woe betide the consumer who goes for the bargain medicines available via the internet from US. The article only mentioned the far-out alternatives which, except for acupuncture, are not used by qualified natural therapists. Herbal and nutritional medicines have been studied in depth and have been shown to work. I am a naturopath and I get good results, even with the medical failures—Crohn's, colitis, IBS, chronic respiratory infections, etc. The naturopath does not apply the natural medicines using the same health model as conventional medicine does, i.e. use the herb in the same way as a drug and expect a result. The naturopath treatrs the person with diet (a major factor) and lifestyle modifications supported by herbal and nutritional medicine where appropriate. Probiotics are included where necessary as a support, but not expecting drug-like responses as the trials in the article did.

Perhaps the medical model of health needs changing.

John Hanes, BSc, ND

David_Colquhoun, July 6, 2012

I see the quacks are piling in already. These articles are, by and large, far too lenient on disproven and unproven "remedies".

The way in which US universities have lined up to take cash from NCCAM and Bravewell is utterly disgraceful. In most countries these activities are limited to a handful of univerities at the bottom of the pecking order. In the USA, Yale, Harvard, Mayo, all have departments filled with quackademics.Â See some of the nonsense they spout here http://www.youtube.com/watch?v=... I just cancelled by sub to the Scientist.

steinp2, July 6, 2012

Did that, got a doctorate, read a lot in the discipline every week, and attend the annual Experimental Biology meeting. I have yet to hear a scientific explanation for the term "boost". Perhaps your immunology course and background is better than mine, so what cells, receptors, cytokines, etc. are "boosted" by the chemicals in question? What is significantly upregulated and what is downregulated? What specific targets are affected? Please enlighten us.

edwardwhite65, July 6, 2012

Â Good response, Jim. And I'll add that there is an arrogance about 'rationally designed' drugs that pervades even so-called unbiased, scientific approaches and investigations into alternative medicines (ie. the article above). It's a tacit 'I know better, but I'll give you a few minutes of my professional opinion. I recently heard a renowned colleague scorn at the idea of natural products actually working—how could they, he said, when we don't know the mechanism? He forgot that the most successful drugs in history—analgesics and anesthetics—had for many years told us little of how they actually worked.

John Hanes, BSc, ND
Here is the danger of alternative treatments: "Patients reported feeling better after albuterol treatment, as well as after sham acupuncture and the placebo inhaler, but not if they received no treatment at all. However, when researchers took an objective measure of their asthma, the maximum forced expiratory volume in one second, it was clear that only those treated with albuterol actually improved."

**Don Margolis**, July 7, 2012

First—kudos for a fine balanced series of articles. I disagree with a few items but I learned more than I thought I would. Second are the many many critical "comments," which I find especially humorous. You have been accused of being biased both for and against alternatives and also for and against alternatives. Third— I wish to advise serious readers of something none of your writers dared mention, and that it the super-strong control Big Business has on the FDA, on most doctors, and on ALL major media. There simply is NO available data from any source accurately portraying the corruption in all major drug companies, lying about results, denying side effects, adding unapproved diseases, and hiding deaths by the thousands. Â

Last week I pointed out a few samples of such tactics on a major blog and was soundly attacked on Sunday and Monday by two commenters saying "How dare you. Our drug companies are doing a wonderfully honest job of saving lives." Then, Tuesday came the news that Glaxo had just been fined 3 BILLION dollars for breaking more laws than I could count. On Wednesday I received, unsolicited, an analysis of six other glaxo-like frauds over the past 12 moths.

Never mentioned is the fact that Big Pharma paid Congress in the 1930s and bribed their way over the AMA's recommendations and made one of the finest cancer cures illegal. Today it is legal as a pain reliever in some states. But Pharma has such a noose around the public mindset that the one big state, California, voted 59% to make that use of marijuana illegal, even for dying cancer patients. Laetrile falls into that category as do dozens of others. You can bet that whenever a working natural cure gains popularity, Pharma will pay a group of crooked scientists to "prove" otherwise, and that "proof" will make it into most major publications, from newspapers, to magazines, and to now-controlled major websites. So whenever you see the word 'quack' or 'quackwatch,' know that like every national disease society, they are controlled and funded by Pharma to keep you buying useless, toxic pills in a medical system which forbids the cure of ANY chronic disease.

**Blake**, July 12, 2012

A more balanced journalistic piece on 'alternative' medicine would contain some mention that fish oil is currently a FDA drug (Lovaza) approved to treat high triglyceride levels. Vitamin B3 is also an FDA approved drug marketed as Niaspan.

Nearly every day, randomized, placebo-controlled clinical trials are published on non-drug nutritional and natural products. Most are indexed in Pubmed.

It is also worth noting that out of all the hysteria on drug-herb interactions, finding any original research on the 'harmful' effects of herbs is difficult. With ~70% of people taking dietary supplements, one might think the journals would be filled to the brim with case studies documenting the scourge. Lastly, it is interesting to view FDA budget allocation in terms of their main objective: risk management. 2012 budget for Drug Safety, Premarket Review and Generics totals about $2,900 million. Food Safety is $1,100 million. Dietary Supplements? $19 million. Source: page 548, [http://www.fda.gov/downloads/…](http://www.fda.gov/downloads/…)

**Can Epigenetics Explain Homosexuality?**

Scientists propose a new model for how homosexuality develops, but observers say it will be difficult to test.

By Sabrina Richards | January 1, 2013

Researchers looking for a genetic signature of homosexuality have been barking up the wrong tree, according to a trio of researchers in the United States and Sweden. Instead, the scientists posit, epigenetic influences acting on androgen signaling in the brain may underlie sexual orientation. In a paper published last week (December 11) in *The Quarterly Review of Biology*, they propose a model describing how epigenetic markers that steer sexual development in males could promote homosexual orientation in females, and vice versa. The scientists offer their model to explain both the tendency of homosexuality to run in families, and the fact that so far no “homosexual gene” has been identified.

“It’s a very provocative, very interesting new twist that is plausible,” said Margaret McCarthy, a neuroscientist at the University of Maryland who studies how hormones influence brain development and was not involved in producing the model. But, she cautioned, so far the theory “is not supported by any data.”

Indeed, Andrea Ciani, an evolutionary psychologist at the University of Padova, thinks that a variety of factors, including genes and epigenetics, influence sexual orientation. “It’s a little bit vain to think we’ll find the answer to homosexuality as a whole.”

The model was developed by William Rice, an evolutionary geneticist at the University of California, Santa Barbara; Sergey Gavrilets, a mathematician at the University of Tennessee; and Urban Friberg, an evolutionary biologist at the University of Uppsala. The notion that epigenetics, rather than genetics, is the primary force promoting homosexuality sprang from several observations, explained Rice.

First, evidence shows that homosexuality can run in families. Still, only 20 percent of identical twins are both gay, said Rice. Furthermore, linkage studies looking for a genetic underpinning to sexual orientation have not turned up any “major” homosexual genes, Rice noted. “This made us suspicious that something besides genes produces heritability that isn’t genetic.” Epigenetics fits the bill.

The model focuses on the role of epigenetics in shaping how cells respond to androgen signaling, an important determinant of gonad development. The researchers suggest that androgens are also important
factors in molding sexual orientation, and that various genes involved in mediating androgen signaling are regulated by epigenetic modifications. These epigenetic marks, they argue, can be passed on between generations.

As an example of how androgens shape sexuality, the researchers point to girls with congenital adrenal hyperplasia (CAH), who produce very high levels of testosterone and often display masculinized genitalia and higher rates of same-sex attraction. But testosterone levels are sometimes the same in normally developing male and female fetuses—without masculinizing the females—suggesting that something else must be playing a role.

The answer, they hypothesized, has to do with sensitivity to androgens. There are a variety of proteins that can modify androgen signaling, and the researchers hypothesize that differences in sensitivity to these signals between male and female fetuses help mediate their sexual differentiation. Rice and his colleagues suggest that such sensitivity may be regulated by the acquisition of epigenetic marks that make girls less sensitive to masculinizing androgens, or make boys more sensitive.

Such epi-marks are typically accrued early in development, as cells are programmed to become specific adult cell types. But, the researchers speculate, perhaps they could be inherited from a parent. Most epigenetic modifications are erased during development of germ cells and soon after fertilization so that cell lineages can be programmed with new epigenetic modifications. But if epi-marks that direct sexual development are not erased correctly, a mother could pass down epi-marks that direct female development to her son, resulting in an attraction to men, and vice versa for a father and his daughters, the researchers theorize.

They also expect that specific epi-marks will regulate sensitivity differently in the brain versus gonads, resulting in same-sex attraction even when normal genital development occurs, said Gavrilets.

Eric Vilain, a neuroscientist at the University of California, Los Angeles, worries that the model, which “might be true,” makes a few simplistic generalizations. “It assumes the same mechanism [for development of sexual orientation] in both sexes . . . and that androgen levels play an important role in the development of sexual orientation”—neither of which has been demonstrated, he said.

Though girls with CAH do show higher rates of homosexual orientation, their exposure to testosterone “is so high it actually masculinizes their genitalia,” said Vilain, who researches mammalian sexual development. “It remains to be seen whether smaller variants of testosterone that do not result [in masculinized genitalia] also lead to attraction of same sex partners.”

In addition, the model’s predictions may be difficult to examine. Determining whether epi-marks have not been erased will be difficult to test, said Vilain, because the marks relevant to sexual orientation will probably be in the brain. But Rice proposes that because homosexuality can run in families, surveying the epigenomes of sperm from men with or without lesbian daughters could reveal key differences.

Fascinating as it may be to understand the biological basis of sexual orientation, however, not everyone is convinced it’s a necessary line of investigation. “Should we test this? Is it important for us to know?” asked McCarthy. “Homosexuality is not a disease, it’s part of natural human variation. I’m not sure there’s a good reason to delve this deeply into it. I think we’ve reached the point that we have enough evidence that there’s a biological basis for sexual orientation.” It would be more helpful to people to get a better handle on the epigenetics of cancer or mental illness, she added.


Comments
Salticidologist, January 2, 2013

Genetics (or epigenetics) is one of the most popular ‘devil made me do it so it’s OK’ theories in recent years. What is most interesting is just why this theory, but not the testing of this theory, is so popular. What has happened is that it has become ‘politically correct.’ This is cultural change. The body has basic mechanisms that provide biochemical rewards for sexual conduct, and there are a lot of methods that can be used to evoke these mechanisms and secure those rewards. This is separate from social mechanisms related to empathy and manipulation in human groups, most of which have always been same-sex since most human interactions in ‘primitive’ societies appear to be same-sex and related to manipulation of status and social alliances. Sex could be used into the context of these social interactions. For example, in ancient Greece, sex between males was often an important part of male culture, and I’m sure that a genetic change was not behind this.

Monnibell, January 2, 2013

Although suggesting that epigenetics is causal does bring a needed change of focus from the deterministic “gene” perspective, it cannot of itself resolve the mystery. The source of change is likely wrapped deeply in subtle variations of development at, perhaps, multiple junctures.

Of course epigenetic change will be found and duly tallied, but the question is Which of such changes indicate causality (or precursory early indicators of change) and which result from the convoluted cascade(s) of minutely skewed developmental events? Good luck in parsing that data.
A more productive research program might be to follow interactions between the predisposed immune system of mother and that of the developing prenate, as earlier studies suggest. Still, one might expect that only an integrated spectrum of data types from serum taken over the course of gestation will offer suggestive signals.

Perhaps while you’re at it you might work up some autism (ASD) data as well.

James V. Kohl, January 2, 2013

On page 210 of his book: Gay Straight and the Reasons why, LeVay discusses my model for the development of heterosexual and homosexual preferences: “This model is attractive in that it solves the “binding problem” of sexual attraction. By that I mean the problem of why all the different features of men or women (visual appearance and feel of face, body, and genitals; voice quality, smell; personality and behavior, etc.) attract people as a more or less coherent package representing one sex, rather than as an arbitrary collage of male and female characteristics. If all these characteristics come to be attractive because they were experienced in association with a male- or female-specific pheromone, then they will naturally go together even in the absence of complex genetically coded instructions.”

We now know considerable more about the complexity of genetically coded instructions — enough to say that what is known is insufficient in attempts to explain anything about the adaptive evolution of sexual preferences.

LeVay adds that “Still, even in fruit flies, other sensory input besides pheromones — acoustic, tactile, and visual stimuli — play a role in sexual attraction, and sex specific responses to these stimuli appear to be innate rather than learned by association [26].” We simply don’t know where the boundary between prespecified attraction and learned association lie in our own species, nor do we have compelling evidence for the primacy of one sense over another.

Neuroscientists have known for many years precisely where the boundary lies between genetically predisposed attraction and learned associations in species from microbes to man. The most compelling evidence available shows that the epigenetic effects of olfactory/pheromonal input clearly establish olfaction as the primary sense and that it is responsible for adaptive evolution via ecological, social, neurogenic, and socio-cognitive niche construction across the evolutionary continuum that includes differences in sexual orientation.


As an alternative read the 57-page journal article concurrently published as a book chapter (that LeVay discussed in the context of my model): The Mind’s Eyes: Human pheromones, neuroscience, and male sexual preferences

Howard A. Doughty, January 2, 2013

I am not a trained biologist, so I remain agnostic on the question of the “causes” of homosexuality.

I am, however, concerned by the criticisms of Rice et al., offered by McCarthy and Vilain. If correctly reported, they seem to discount the new model because it lacks empirical verification. On the other hand, the last time I looked, scientists tended to generate hypotheses and then subject them to rigorous testing. The contribution if Rice et al. seems to qualify as a hypothetical model awaiting testing (however difficult that might be). So, surely the criticism is at best premature.

More unsettling is Ciani’s comment that Rice et al. are “a little bit vain” because their model purports to explain so much with so little. Apart from any possible connection to the “Gordian knot,” I wonder about the idea that scientists might be vain. What a shock! But what does this have to do with whether or not these arrogant creatures have actually figured something out?

James V. Kohl, January 2, 2013

Rice et al (2012) with my emphasis: “All of the steps in Figure 2 could also be influenced by sex-specific regulation of miRNA levels that are known to influence sexually dimorphism of mRNA concentrations in the brains of mice, and to be influenced by epigenetic control that is heritable across at least one generation (Morgan and Bale 2011).”

Others may hear more about the miRNA / mRNA balance, which I included in the notes that detail the diagram of my model linked below (click twice or cut and paste if it does not lead to the FI0000 poster).

Kohl (2012) This model of systems biology represents the conservation of bottom-up organization and top-down activation via:

1. Nutrient-dependent stress-induced and social stress-induced intracellular changes in the homeostatic balance of microRNA(miRNA) and messenger RNA (mRNA);
2. Intermolecular changes in DNA (genes);
3. Non-random experience-dependent stochastic variations in de novo gene expression for odor receptors;
4. The required gene-cell-tissue-organ-organ system pathway that links sensory input directly to gene activation in neurosecretory cells of the brain;
5. The required reciprocity that links gene expression to behavior that alters gene expression (i.e., from genes to behavior and back).

ironjustice, January 3, 2013

“Homosexuality is not a disease, it’s part of natural human variation.”

It is caused by man , as an obligate herbivorefrugivore , eating meat. This leads to increased iron which leads to increased oxidation of the DNA and increased reproduction of epigenetic markers (increasing the number of cells with faults) and the result , homosexuality as well as all other genetic diseases. Iron causing the increase in faults is evidenced in this study , iron leads to bowel cancer by increasing the number of cells with faults.

"Iron could be raising the risk of bowel cancer by increasing the number of cells in the bowel with APC faults."

GerryS, January 4, 2013

I am convinced that with the current evidence showing trans-sexualizing of certain fish species from run-off of birth control chemicals that these substances have much to do with the etiology of homosexual tendency from residual effects in those who have used them and from the environmental pollution they have caused. Since evidence shows that estrogen plays a role in masculinization during certain stages of gestation, it would be no surprise that these chemicals, most properly called Zeno-estrogens could influence the masculinization of especially the male fetus and possibly have an effect on the female’s fetus also. Since these compounds can be horrifically stable and can essentially wipe out the sites to which they are attached causing potential re-cycling of them in the organism, the possibility of these altering the sexual development of the fetus is a quite plausible possibility. Since the number of these sites is quite variable inter-individually, presumably affected by genetic variation, it could explain at least in part the high coincidence of homosexuality among identical twins and in families. The same thing can explain why auto-immune disorders have quasi-genetic incidence. Suppose, for instance that exposure to a common cold pathogen produces an antibody that is direct for the antigen but mildly cross-reacts with a particular variant of a protein in some individuals. The possibility of an auto-
immune disorder developing increases. The same line of reasoning can be used to explain apparently genetic, or, quasi-genetic origins of homosexual tendency.

Such a theory needs to be well thought out and investigated, but I do not think it will be as it cuts into the holy grail of birth control, which although it was specifically developed for the eugenic purpose of mass murder (the inventor if “the pill” was on the Nazi commission responsible for mass-eugenic murder) and was employed with the full intent of exterminating many peoples such as was attempted in Puerto Rico, and in spite of the fact that it is directly causal of behaviors that have put women at an extremely high lifetime exposure risk for HPV, chlamydia, HPV and a host of other venereal diseases and treatment resistant variants. Also, the possibility of a huge class-action suit against the holy grail of Planned Parenthood and drug companies for their role in negligently exposing for profit so many to the difficulties associated with homosexual tendency would be economically crippling.

**DNA Jumps Between Vertebrates**

Scientists show that horizontal transfer of a particular DNA sequence among a diverse range of vertebrates is more widespread than previously believed.

By Dan Cossins | January 3, 2013

The lateral transfer of genetic information across species is common in bacteria, but rare among vertebrates—or so scientists believed. Now, researchers have demonstrated that a particular DNA sequence has likely jumped several times between the genomes of reptiles, marsupials, and mammals.

The study was published this week (31 December) in the *Proceedings of the National Academy of Sciences*.

BovB is a retrotransposon, a piece of DNA that can copy and paste itself around the genome to create large swathes of repetitive sequences. It is abundant in the cow genome. Researchers have also found it in the DNA of many other animals, including elephants, horses, platypuses, pythons, sea snakes, geckos, sea urchins, and zebrafish.

To better understand how BovB found its way into such a diverse range of creatures, researchers at the University of Adelaide used sequences from these animals to construct a phylogenetic tree. If BovB had been passed down from a common ancestor and remained in their genomes as they diversified, then the more closely related species would have more similar versions of the DNA sequence. But that was not the case.

Instead, the team found that BovB sequences from cows were more closely related to snakes than elephants, for example. The researchers suggest that the only explanation for such unexpected evolutionary relationships is that BovB has jumped between genomes, and they figured that it must have done so at least 9 times.

Finally, the researchers identified a potential vector. BovB sequences were found in two tick species that suck the blood of lizards and snakes, indicating that parasitic arthropods could be responsible for passing the jumping genes between species.

**Disappearing bacterium may protect against stroke**

*H. pylori isn’t a major cause of death and may protect against stroke and some cancers*

New York (January 9, 2013)—A new study by NYU School of Medicine researchers reveals that an especially virulent strain of the gut bacterium *Helicobacter pylori (H. pylori)* isn’t implicated in the overall death rate of the U.S. population, and may even protect against stroke and some cancers. The findings, based a nationwide health survey of nearly 10,000 individuals over a period of some 12 years, are published online, January 9, in the journal *Gut*.

Those individuals carrying the most virulent strain of *H. pylori*, the study found, had a 55 percent reduced risk of deaths from stroke compared with their counterparts who were not infected with *H. pylori*. Participants with the most virulent strain also had a 45 percent reduced risk of death from lung cancer.

These surprising findings emerged from an analysis by Yu Chen, PhD, MPH, associate professor of population health and environmental medicine, and Martin J. Blaser, MD, professor of internal medicine and professor of microbiology, of individuals who participated in a national survey designed to assess the health and nutritional status of adults and children in the United States. Previous studies by Dr. Blaser have confirmed the bacterium’s link to gastric diseases ranging from gastritis to stomach cancer. He and Dr. Chen have more recently shown that *H. pylori* may protect against childhood asthma. The most virulent *H. pylori* strains have a gene called cagA.

"The significance of this study is that this is a prospective cohort of participants representative of the U.S. population with a long follow-up," says Dr. Chen. "We studied both the overall *H. pylori* as well as cagA strain of *H. pylori*, which is more interactive with the human body. We found that *H. pylori* is not
related to the risk of death from all causes, despite it being related to increased risk of death from gastric
cancer."

"This finding confirms earlier work, however, that gastric cancers are now uncommon in the United
States," says Dr. Chen. "We also found that H. pylori was related to a reduced risk of stroke and lung
cancer, and these effects were stronger for the cagA strain, suggesting its mixed role in human health," she
says.

H. pylori, an ancient bacterium, lives in the mucous layer lining the stomach where, until recently, it
survived for decades. More than half of the world’s population harbor H. pylori in their upper
gastrointestinal tract. Mainly transmitted in families, the bacterium is usually acquired before age 10. In
developing countries H. pylori is still prevalent, but is vanishing in the developed world thanks to better
sanitation and widespread use of antibiotics.

To better understand the relationship between H. pylori and the overall death rate, or all-cause
mortality, the researchers analyzed data from 9,895 participants in the National Health and Nutrition
Surveys (NHANES III), enrolled from 1988 to 1994. Test results for H. pylori and cagA were available on
7,384 subjects at the time of enrollment, and participants were followed until 2000.

There was no association of either H. pylori-positivity or cagA-positivity with all-cause mortality in
the population, the researchers found. Participants with and without H. pylori experienced a similar risk
of death from all causes. Consistent with past reports, a strong association was observed between H.
pylori and gastric cancer mortality, according to the study. Individuals who were H. pylori positive were
40 times more likely to die from gastric cancer. The study also found that participants with cagA-positivity
had a 55 percent reduced risk of deaths from stroke compared with their counterparts who were H. pylori
negative/cagA-negative. Participants with cagA-positivity also had a 45 percent reduced risk of deaths
from lung cancer.

"The most interesting finding was that there is a strong inverse association with stroke which could be
protective," says Dr. Blaser. "There is some precedent for this and it is possible that the same cells (T reg
cells) that H. pylori induces that protect against childhood asthma could be the protective agents,
however, the findings need to be confirmed."

Americans Have Worse Health than People in Other High-Income Countries, Says New Report
Modern Medicine ©, (01.11.2013)
According to a report by the National Research Council and Institute of Medicine, the United States
spends more per capita on healthcare than any other nation, but its people—including those with health
insurance, college educations, high income or healthful habits—contract diseases, are injured, or die
earlier than the inhabitants of other high-income countries. The report notes that the health disadvantage
exists at all ages from birth to age 75, and even advantaged Americans appear to be less healthy than their
peers in other rich nations.

The report compared the United States with 16 peer nations, including Australia, Canada, Japan, and
many western European countries. The United States was at or near the bottom in nine key areas of
health: infant mortality and low birth weight; injuries and homicides; teenage pregnancies and sexually
transmitted infections; prevalence of HIV and AIDS; drug-related deaths; obesity and diabetes; heart
disease; chronic lung disease; and disability. Many of the health conditions disproportionately affect
children and adolescents. The United States has had the highest infant mortality rate of any high-income
country for decades, and it ranks low on premature birth and the proportion of children who live to age 5.
Also, US adolescents have higher death rates from traffic accidents and homicide, the highest rates of
teenage pregnancy, and higher likelihood of contracting STDs. Approximately two-thirds of the difference
in life expectancy between males in the United States and the other countries are because of deaths before
age 50.

The United States ranked higher than the other countries in some areas: Americans older than 75
years live longer; and Americans have lower death rates from stroke and cancer, better control of blood
pressure and cholesterol levels, and lower rates of smoking.

The report examines the role of social values and public policy in determining why the United States
is outdone by its peers on both health outcomes and conditions that affect health, but the results suggest
that the health disadvantage is more than a reflection of the serious health disadvantages among poor or
uninsured people or ethnic and racial minorities. When the analysis was limited to non-Hispanic whites
and people with high incomes and health insurance, nonsmokers or people who are not obese, Americans
still rated lower.
The report provides recommendations. It suggests an intensified effort to pursue established national health objectives, a comprehensive outreach campaign to share the findings with the public and stimulate national discussion about its implications, and data collection and research to better understand the factors responsible for the US disadvantage and potential solutions, including lessons learned from other countries.


**Nosocomial Transmission Responsible for XDR-TB Outbreak in South Africa**

*Healio, (01.10.2013)*

A report in The Journal of Infectious Diseases states that an epidemic of extensively drug-resistant tuberculosis (XDR TB) in Tugela Ferry, South Africa, is the result of interconnectedness that has allowed several generations of nosocomial transmission. Neel Gandhi, MD, associate professor of epidemiology at the Rollins School of Public Health at Emory University in Atlanta, Ga., explains that “rather than an isolated outbreak that can be traced back to a single index case, conditions in South African hospitals are allowing for multiple generations of transmission, which in turn allows for the propagation and expansion of the epidemic.” He goes on to note that without a comprehensive plan for infection control within the hospitals, it will be a challenge to control the current epidemic.

From 2005 to 2009, Tugela Ferry recorded 516 diagnosed cases of XDR TB, with most of the patients being infected with HIV as well. Due to the similarities between this outbreak and outbreaks of multidrug-resistant TB in the 1990s, researchers decided to examine the role of nosocomial transmission in the current epidemic.

Researchers conducted an observational study of patients diagnosed with XDR-TB from 2005 to 2006, reviewing medical records, identifying epidemiological links between patients, genotyping the TB isolates, and determining the method of transmission. Their findings revealed that 98 percent of the 148 study participants were co-infected with XDR TB and HIV, and 93 percent were hospitalized while infectious. Before their XDR TB diagnosis, 113 of the patients were hospitalized at least once, and 80 of the 113 were exposed to at least one patient infected with XDR TB. Genetic analysis demonstrated that one predominant cluster, ST60, accounted for 92 percent of the isolates and the KZN strain made up 96 percent of the ST60 cluster isolates. The researchers were able to establish an epidemiologic link for 42 out of 51 patients in the ST60/KZN cluster. These patients demonstrated a high degree of interconnectedness, with as many as three generations of transmission among men and five generations of transmission among women.

Gandhi notes that, in addition to examining transmission of XDR TB within hospitals, the researchers have expanded their investigation to include community settings such as schools, bars, and churches to better understand whether genetic alterations are occurring that may allow XDR TB to become more transmissible.


**McGill Launches Study on Seaweed-Based Gel That Prevents HPV**

*Montreal Gazette, (01.08.2013) Marian Scott*

Eduardo Franco, director of McGill University’s cancer epidemiology division, and colleagues will conduct a study of sea-algae extract to determine whether it can be used in a topical gel to prevent human papillomavirus (HPV) transmission. The seaweed extract, carrageenan, is used commercially as a thickener and has been found to inhibit transmission of HPV, the virus that causes cervical cancer.

Throughout the next year, 465 sexually active university-age women will participate in a clinical trial of the seaweed extract. They will be asked to apply a gel before sex. One-half of them will receive the gel with the active ingredient and the other half will receive a placebo. Participants will be continually monitored to determine if the gel prevents transmission. If a participant already has HPV, the researchers will monitor whether the gel prevents the virus from spreading to a wider area and whether it prevents the individual from contracting new strains.

In 2010, a McGill study noted that 56 percent of young adults in a new sexual relationship were infected with HPV and 44 percent of them were infected with a type of HPV that causes cancer. Although there are vaccines to prevent HPV, Franco noted that they are only effective against four of the more than 40 types of the virus. Also, the vaccines are very expensive in developing countries, which have the highest rates of cancer. If the trial is successful, the extract will provide a cheap solution, Franco added.
Franco said that if the trial is successful, the researchers will conduct larger trials with subjects in different age groups. Other considerations include the use of the extract as condom lubricant and mixed with gargle solution to prevent transmission during oral sex.

The Canadian Institutes of Health Research is funding this trial. Women interested in participating are asked to contact Allita Rodrigues at catch.study@mcgill.ca. For more information, visit www.mcgill.ca/catch/.

**Vaccinating 46% Of Haiti’s Population Could Control Cholera Epidemic, Study Concludes**

"Vaccinating fewer than half of Haiti’s population of 10 million should brake a cholera epidemic that has claimed nearly 8,000 lives and made more than 635,000 people ill, scientists said Thursday," Agence France-Presse reports. "Using a mathematical model, scientists in the United States determined that vaccination coverage of 46 percent of the population would 'suppress transmission,'" the news agency writes (1/10). "In the current debate on the use of cholera vaccines ... our results suggest that moderate cholera vaccine coverage would be an important element of disease control in Haiti," the research team wrote in the journal *Scientific Reports* (Mukandavire et al., 1/10). Study author J. Glenn Morris, director of the University of Florida’s Emerging Pathogens Institute, "points to the 'herd immunity' concept—which proposes that immunizing a significant portion of a population breaks a chain of infection—in support of the efficacy of less than universal vaccination," according to a University of Florida press release (1/10).

"The recently developed mathematical model might serve to settle or, at least, voice a compromise in an international debate over whether Haiti should vaccinate its population or clean up its sanitation systems to stave off the epidemic," the Gainesville Sun reports (Crane, 1/10). According to AFP, the researchers said "vaccination must be combined with programs to improve water quality." The news agency adds, "Talks between the Haitian health ministry, the WHO and Pan-American Health Organization on launching a vaccination campaign 'are taking place, but nothing has been agreed yet,'" the WHO said in response to an email query from AFP (1/10). In a related story, the U.N. released preliminary results from the Haiti Demographic and Health Survey, which show "substantial progress for children there in the education, nutrition, health, and sanitation sectors since 2006," according to the U.N. News Centre (1/10).

**Accountability Lacking For Cholera Outbreak In Haiti**

In a Foreign Policy opinion piece, former Associated Press reporter Jonathan Katz recounts his experience in Haiti after the January 2010 earthquake and during the October 2010 outbreak of cholera. In the piece, adapted from a book he authored, Katz describes his investigation into how and where cholera was introduced to Haiti, which had not had a case of the disease in more than 100 years. He says after it was discovered that Nepalese peacekeepers brought the disease to the country and careless waste disposal had introduced the cholera bacteria into the water supply, "The U.N. and its allies went on the defense. ... If the U.N. were discovered to have caused the epidemic in Haiti, its credibility would be catastrophically compromised—Haitian lives destroyed by the very people sent to protect them."

"Authorities defended their refusal to investigate the origin of the outbreak on grounds that pursuing the source would detract from fighting the epidemic," but "[b]y refusing to take the concerns seriously, investigators would cede inquiry to the very agitators and xenophobes they feared," Katz writes. "In two years, more than 7,800 Haitians have died of cholera," he notes, concluding, "The United Nations has made grandiose, if seemingly empty, promises to fight and eradicate the disease, but refuses to consider its own accountability in starting the epidemic. Aid workers and donor governments have lost a critical opportunity—to demonstrate that they took Haitian lives and welfare as seriously as their own" (1/10).
New Treatment Could Combat Deadly Chemical Agents
Jan. 11, 2013 — An enzyme treatment which could neutralise the effects of lethal chemicals responsible for the deaths of hundreds of thousands of people across the world has been developed by experts at the University of Sheffield.

Organophosphorus agents (OP) are used as pesticides in developing countries and acute poisoning is common because of insufficient control, poor storage, ready availability, and inadequate education amongst farmers. It is estimated about 200,000 people die each year across the world from OP poisoning, through occupational exposure, unintentional use and misuse, mostly in developing countries like India, Pakistan, and Sri Lanka and through deliberate terrorist activities.

OPs include compounds like Tabun, which was developed in 1936 by German scientists during World War II, Sarin, Soman, Cyclosarin, VX, and VR.

Using a modified human enzyme, scientist Professor Mike Blackburn from the University of Sheffield’s Department of Molecular Biology and Biotechnology collaborated in a consultancy role with Professor Alexander Gabibov of the Shemyakin-Ovchinnikov Institute, Moscow, and Professor Patrick Masson of the Département de Toxicologie, Centre de Recherches du Service de Santé des Armées, to create a “bioscavenger” which was found to protect mice against the nerve agent VR and showed no lasting effects.

In studies performed at the Institute of Bioorganic Chemistry in Pushchino, Russia, a total of eight mice were treated with the new enzyme after being subjected to enough of the VR agent to kill several of the animals—about 63 mg—and all survived.

Professor Blackburn said: “This current publication describes a novel method to generate a bioscavenger for the Russian VR organophosphorus agent with the key property of being long-acting in the bloodstream.

“That has been achieved by a combination of chemical surface modification (polysialylation) and biotechnology of production (through the use of an in vitro CHO-based expression system employing genes encoding butyrylcholinesterase and a proline-rich peptide under special promoter control).

Journal Reference:

Virus Caught in the Act of Infecting a Cell
Jan. 10, 2013 — The detailed changes in the structure of a virus as it infects an E. coli bacterium have been observed for the first time, report researchers from The University of Texas at Austin and The University of Texas Health Science Center at Houston (UT Health) Medical School this week in Science Express.

To infect a cell, a virus must be able to first find a suitable cell and then eject its genetic material into its host. This robot-like process has been observed in a virus called T7 and visualized by Ian Molineux, professor of biology at The University of Texas at Austin, and his colleagues.

The researchers show that when searching for its prey, the virus briefly extends—like feelers—one or two of six ultra-thin fibers it normally keeps folded at the base of its head.

Once a suitable host has been located, the virus behaves a bit like a planetary rover, extending these fibers to walk randomly across the surface of the cell and find an optimal site for infection.

At the preferred infection site, the virus goes through a major change in structure in which it ejects some of its proteins through the bacterium’s cell membrane, creating a path for the virus’s genetic material to enter the host.

After the viral DNA has been ejected, the protein path collapses and the infected cell membrane reseals.
"Although many of these details are specific to T7," said Molineux, "the overall process completely changes our understanding of how a virus infects a cell."

For example, the researchers now know that most of the fibers are usually bound to the virus head rather than extended, as was previously thought. That those fibers are in a dynamic equilibrium between bound and extended states is also new.

Molineux said that the idea that phages "walk" over the cell surface was previously proposed, but their paper provides the first experimental evidence that this is the case.

This is also the first time that scientists have made actual images showing how the virus's tail extends into the host—the very action that allows it to infect a cell with its DNA.

"I first hypothesized that T7 made an extended tail more than 10 years ago," said Molineux, "but this is the first irrefutable experimental evidence for the idea and provides the first images of what it looks like."

The researchers used a combination of genetics and cryo-electron tomography to image the infection process. Cryo-electron tomography is a process similar to a CT scan, but it is scaled to study objects with a diameter a thousandth the thickness of a human hair.

**Journal Reference:**
Bo Hu, William Margolin, Ian J. Molineux, and Jun Liu. The Bacteriophage T7 Virion Undergoes Extensive Structural Remodeling During Infection. Science, 10 January 2013 DOI: 10.1126/science.1231887

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**Effects of Antibiotics On Gut Flora Analyzed**

Jan. 9, 2013 — A study co-led by researchers at the Universitat de València reveals that antibiotics produce changes in the microbial and metabolic patterns of the gut. The researchers that have analyzed for the first time the bacteria, genes, enzymes and molecules that form the gut microbiota of patients treated with antibiotics publish the results of their study in the online edition of the journal *Gut*.

In the gut live one trillion bacteria, which are known as microbiota or gut flora, and that have co-evolved in symbiosis with humans. According to this study, treatment with antibiotics can alter this symbiosis from early stages of the treatment. "Although some of the changes are oscillatory and can be reversed at the end of the treatment, others seem irreversible," says one of the coordinators of the study, Andrés Moya, who works at Cavanilles Institute of Biodiversity and Evolutionary Biology of the Science Park of the Universitat de València.

The research, which has had the collaboration of the CSIC, the Centre Superior d’Investigació en Salut Pública (CSISP) (Centre for Advanced Research in Public Health), the University CEU San Pablo and the Centre d’Investigació Biomèdica en Xarxa en Epidemiologia i Salut Pública (CIBEResp) (Centre for Biomedical Research in Epidemiology and Public Health), has compared stool samples of a patient taken before and after the treatment.

**Changes in gut bacteria**

The biodiversity of the bacteria that form the gut microbiota, according to the results, decreases **during the treatment to the point of reaching its minimum 11 days after the beginning.** However, at the end of the treatment, the situation is reversed and the patient presents a bacterial population similar to the first.

Although the research "shows for the first time that gut bacteria presents a lower capacity to produce proteins, as well as deficiencies in key activities, during and after the treatment," explains Moya. Specifically, the study suggests that the gut microbiota shows less capacity to absorb iron, digest certain foods and produce essential molecules for the organism.

The research also shows that less abundant bacteria in the gut flora, but little active at the beginning of the treatment, at the end they became active and they may play an important role in the gut as a consequence of the antibiotics, according to Manuel Ferrer, researcher of the CSIC. "**These bacteria could be responsible for improving the interconnection between the liver and colon and of the production of essential molecules such as bile acids, hormones and cholesterol derivatives,**" say the researchers.

"Personalized therapies and interventions can only be reached through a comprehensive and detailed analysis of the different antibiotics and people from different geographical origin, age or state of health," concludes Moya.

**Journal Reference:**
Treatment with raltegravir increases the risk of mild muscular side-effects
Michael Carter
Published: 14 January 2013

Treatment with the HIV integrase inhibitor raltegravir (Isentress) is associated with an increased risk of skeletomuscular side-effects, according to Australian research published in the online edition of the Journal of Acquired Immune Deficiency Syndromes. Toxicities included muscle pain and muscle weakness and wasting. However, in most instances, these side-effects were mild and in the case of muscle wasting/weakness disappeared with the cessation of raltegravir therapy.

“This study identifies a significantly higher prevalence of symptomatic skeletal muscle toxicity...in patients treated with raltegravir-based cART [combination antiretroviral therapy],” write the authors. “This association is not dependent upon either the duration of raltegravir exposure or raltegravir trough levels.”

Raltegravir is a potent antiretroviral drug with proven efficacy in both treatment-naive and treatment-experienced people. Its main side-effects are headache, diarrhoea and nausea. These are generally mild and time limited.

Nevertheless, four case reports have associated raltegravir with rhabdomyolysis – the breakdown of skeletal muscle fibre. Elevations in creatinine kinase levels have also been observed in people treated with raltegravir, a finding which is consistent with the hypothesis that the drug may cause low-grade muscular toxicities.

To get a clearer understanding of this question, doctors in Sydney designed a prospective study comparing the prevalence and risk factors for skeletomuscular side-effects between people taking HIV treatment based on raltegravir and individuals treated with alternative antiretroviral regimens.

A total of 318 participants were recruited to the study between 2011 and 2012. Half were treated with raltegravir.

Muscle toxicity was defined as any one of the following:

- Isolated elevation in creatinine kinase.
- Widespread muscle pain (myalgia).
- Muscle weakness or wasting (proximal myopathy).
- Rhabdomyolysis.

There were no significant differences between the participants treated with raltegravir and those taking other regimens. Almost all (98%) were male, 89% were white and their median age was 51 years. Strenuous exercise – which can cause muscle soreness or weakness – was reported by 42% of participants.

The overall prevalence of muscle toxicity was 28%. This was significantly higher among the participants taking raltegravir-based treatment compared to individuals treated with alternative regimens (37 vs 19%, p < 0.001).

Looking at individual muscle toxicities, the investigators found that participants taking raltegravir were more likely to be diagnosed with myalgia than those in the control arm (19 vs 3%, p < 0.001). “Myalgia, although a common clinical finding, is unlikely to be a sufficient reason alone to switch from raltegravir, but cases should be considered on an individual basis,” suggest the authors. Prevalence of proximal myopathy was also more common in those taking raltegravir (4 vs 0%, p = 0.03).

Prevalence of isolated elevation in creatinine kinase was similar between the two study arms (14 vs 16%). There were no cases of rhabdomyolysis.

After controlling for potential confounders, raltegravir (OR = 2.64; 95% CI, 1.57-4.45, p < 0.001) and recent strenuous exercise (OR = 2.15; 95% CI, 1.35-3.75, p = 0.002) were both identified as having an independent and significant association with muscle toxicity.

In addition, myalgia was associated with raltegravir treatment (p < 0.001) and strenuous exercise was a risk factor for isolated elevation in creatinine kinase.

“Additional, prospective studies are necessary to better assess the long-term sequelae of muscle toxicity and uncover associated factors that may predict the likelihood of damage,” conclude the authors. “Our findings suggest that all patients receiving raltegravir should be actively monitored for myalgia and myopathy.”

Reference
Africa: Study Confirms Role of Road Networks in HIV Spread

By Calvin Otieno, 11 January 2013

Nairobi — Road networks are strongly related to the spread of HIV-1—the HIV subtype responsible for the AIDS pandemic—across Sub-Saharan Africa, a study confirms.

The study, published online in AIDS, says that the travel of hundreds of thousands of people by road across the continent daily has played a significant role in the distribution and spread of HIV-1.

Researchers from the United Kingdom and United States mapped HIV-1 distribution patterns across Sub-Saharan Africa between 1998 and 2008 using molecular epidemiology data. Their work, which maps the data "at a finer level of detail than ever before", builds on prior local studies that "have shown that transport infrastructure and human mobility are strongly related to HIV spread in Africa, and are likely major driving forces".

Andrew Tatem, associate professor at the University of Florida, and lead author of the study, tells SciDev.Net that transport infrastructure and other geographic features can promote or inhibit goods and people’s movements but have also been linked to the spread of many kinds of diseases for many years—adding that this is not unique to HIV and not exclusive to Sub-Saharan Africa.

He adds that places with good transport infrastructure leads to more people accessing an area and this may lead to more exchange of HIV between those areas.

"Wherever people make trips they take pathogens with them, and the more they travel, the higher the chances that more pathogens will be carried and diffused to newer locations," he says. Tatem adds that while new, accessible and quality roads bring many benefits and convey infrastructural development, they also promote this movement of pathogens to new areas.

However, he says that the spread should not affect the development of infrastructure across Africa.

"What could be done is to ensure that adequate surveillance and health facilities providing prompt diagnosis and treatment are in place in areas where infrastructure development is planned."

Samoel Khamadi, a senior researcher at the Kenya Medical Research Institute’s Centre for Virus Research, says that major road networks are some of the worst "HIV hotspots" because of sex trade. He says that the spread of HIV/AIDS through road networks should be "a wakeup call" for emphasising the importance of preventative measures. These could include awareness creation among people on the importance of safe sex and providing alternative livelihoods for sex workers.

Labor and QAHC fire back

Posted on 11 January 2013

Queensland Health Minister Lawrence Springborg has lambasted the state’s AIDS Council and the former Labor Government for a five per cent rise in gay men having unprotected sex between 2011-12.

But Labor and the Queensland Association for Healthy Communities (QAHC) both claim that the minister is greatly confused over the issue and is being irresponsible and misleading the public by effectively blaming members and groups within the LGBTI community.

The Courier Mail reported fresh data from a draft report saying the proportion of gay men having unprotected sex rose from 34.1 per cent to 39.1 per cent between 2011 and 2012. The article mentions these figures however whoever approved the report and how the figures were attained and calculated were not reported.

In a statement that appears to once again reignite the debate over the defunding of QAHC, Springborg said safe sex campaigns had descended into a form of political advocacy rather than health advocacy.

This is a very similar line of argument that the minister used as reason to defund QAHC last year. “The previous Labor Government squandered the health dollar trying to buy and appease radical political lobby groups rather than investing in serious health outcomes and cultural changes,” he told the Courier Mail.

He said the safe-sex campaigns, costing millions in tax-payers money, were a “complete farce”.

“It means that the so-called gay community leaders that championed these campaigns have completely sold out the people they claim to represent.”

In a statement to the Star Observer, Shadow Health Minister Jo-Ann Miller said that Springborg would have been receiving advice from the same source that advised the former Bligh-Labor Government.

“Mr Springborg as Minister would be receiving advice on funding allocations for HIV education campaigns from the same health officers who advised the former government,” Miller said.

“If he is rejecting expert departmental advice he needs to be upfront and say so.
“He also needs to explain the source of his alternative advice on which he now appears to be making funding decisions.

“But by using smear tactics to give the impression that some gay community groups are somehow involved in blatantly political campaigns is not being truthful.”

Executive Director of QAHC, Paul Martin said that the minister has a simplistic view of HIV prevention and has misled the state about gay health organisations.

“Minister Springborg fails to understand that ‘unprotected sex’ and ‘unsafe sex’ are two different things.” Martin said.

“Queensland research among gay men has found that there has been increasing levels of ‘sero-sorting’ – that is people of the same HIV status having sex together without condoms. Increasing levels of unprotected sex is not the same as unsafe sex.”

“In addition, men are increasingly using various risk reduction strategies to reduce the likelihood of HIV transmission in situations where condoms are not used. This shows that gay men are not ignoring the safe sex message, but are actively looking for ways to reduce HIV transmission.”

Martin found himself yet again defending QAHC against continued claims that the organisation was “a radical lobby group”.

“We are a health service organisation providing a range of evidence-based practical health services to the LGBT communities of Queensland. Part of our work also includes identifying wider structural barriers to health (e.g. stigma and discrimination) and advocating for healthy public policy.”

He also defended QAHC’s highly successful ‘Rip&Roll’ campaign, claiming that the safe-sex initiative was the most successful and highest profile campaign in the state’s history.

“Each year ‘Rip&Roll’ cost only around $150,000 to $200,000 – not the ‘millions of dollars’ claimed by Minister Springborg.”

Martin also vehemently defends the work done by QAHC volunteers and its staff against the ministers claims that QAHC had exploited the LGBTI community.

“Comments by Minister Springborg that ‘so-called gay community leaders’ have ‘completely sold out the people they claim to represent’ are deeply insulting and offensive to the volunteers and staff that have worked tirelessly for the LGBT community over the past 28 years.”

“Minister Springborg has declined to meet with Healthy Communities since becoming Health Minister, despite the organisation raising concerns about HIV prevention strategies, LGBT health concerns and requesting meetings with him.”

Drug-Resistant Gonorrhea Spreading in North America

*International Business Times (New York)*, (01.10.2013) Roxanne Palmer

Gonorrhea, one of the most common sexually transmitted infections, is continuing to develop drug-resistant strains. The bacteria became resistant to sulfonamides in the 1940s, then to penicillins and tetracyclines in the 1970s and 1980s. Fluorquinolones became ineffective by 2007 in the United States and cefixime and ceftriaxone have been used since then. Doctors have seen warning signs of gonorrhea resistance for years as they have had to use higher concentrations of cefixime to cure the disease. A strain of the disease is now resistant to the antibiotic cefixime. This strain was first discovered in Japan and has since spread to Asia and Europe.

A Canadian study has confirmed that cefixime resistance is now in North America. The researchers examined 291 people with gonorrhea infections at a Toronto health clinic. Of 133 patients who returned for follow-up examinations, approximately 7 percent did not respond to treatment.

In August 2012, the US Centers for Disease Control and Prevention changed its recommendations for treating gonorrhea from cefixime to a combination therapy with ceftriaxone and a week-long course of another antibiotic like azithromycin for doxycycline. With the global spread of drug-resistant gonorrhea, the change in treatment recommendations may only be a temporary measure. CDC has suggested, “Reinvestment in gonorrhea prevention and control,” and warned that new treatment options for the disease are urgently needed.


India Marks Two Years Since Last Diagnosed Polio Case

On January 13, India "completed two years since the last case of the crippling disease was reported ... a huge achievement for a country that as recently as 2009 reported 741 cases of polio—more than any other country in the world, and almost half of cases reported globally that year," the Wall Street Journal’s "India..."
Real Time" blog reports (Dutta, 1/13). "India's accomplishment was a triumph of consistent and strong political will as well as international coordination and has given a huge lift to the global fight against polio, a disease that as recently as 1988 claimed 350,000 people each year," TIME writes in an article examining the history of how the country's success "offers important lessons both for the complicated international effort to eradicate the disease for good and for India's own health care system" (Mahr, 1/13).

"Today, the wild polio virus circulates in only three countries: Afghanistan, Nigeria, and [India's neighbor], Pakistan, where the polio eradication campaign has been in the news lately, but, unfortunately, not because of the impressive 65 percent reduction in cases Pakistan has achieved since 2011," the New York Times' "India Ink" blog reports. "Sadly, the news out of Pakistan has focused on a recent spate of violence targeting polio vaccinators, the dedicated army of health workers and volunteers who go door-to-door to reach the most at-risk children with the oral polio vaccine," the blog continues (Mahajan, 1/11).

TIME also features a cover story examining how politics is hindering the fight against polio, particularly in Pakistan (Kluger, 1/14). BBC News examines challenges to eradicating polio in Nigeria, which "is being watched more closely than anywhere else: its cases reached a three-year high with more than 100 in 2012" (Dreaper, 1/14).

NPR's 'Shots' Blog Examines Cholera Epidemic in Haiti; U.N. SG Calls For Continued International Support Of Country

NPR's "Shots" blog examines the cholera epidemic in Haiti and addresses the controversy surrounding the U.N.'s role in the outbreak, noting, "Most scientists now think Nepalese soldiers unwittingly brought cholera to Haiti when they joined a U.N. peacekeeping force there in 2010." The blog also discusses plans to control cholera in Haiti. "The Haitian government is expected to release a detailed blueprint for the first two years of the effort sometime this month. The entire project is expected to cost $2.2 billion and take at least 10 years," the blog reports. According to the blog, Pan American Health Organization Deputy Director Jon Andrus said financing the effort will be challenging. "The question is: Can it be done? I believe it can. So we're ramping up efforts to do that," Andrus said, the blog notes. The blog also discusses cholera vaccination in Haiti, citing a recent study that "suggests that vaccinating around half the population would provide enough 'herd immunity' to make cholera transmission much less likely. ... But, so far, the U.N. says nothing has been decided about launching a cholera vaccination program of any sort in Haiti" (Knox, 1/12).

In a related story, U.N. Secretary-General Ban Ki-moon on Friday "called on the international community to continue its support for Haiti as he marked the third anniversary of the devastating earthquake that struck the Caribbean country, while praising the progress achieved so far," the U.N. News Centre reports (1/11).

Less reaction to DTaP vaccine given in kids' thighs than arms

Vaccine Safety Datalink study of 1.4 million children at Group Health, etc., in Pediatrics

SEATTLE—Children age 12 to 35 months who receive DTaP vaccine in their thigh muscle rather than their arm are around half as likely to be brought in for medical attention for an injection-site reaction. So says a new study of 1.4 million children at Group Health and seven other Vaccine Safety Datalink (VSD) centers across the country, e-published on January 14 in Pediatrics.

"These local reactions are the most common side effect of vaccinations," said study leader Lisa A. Jackson, MD, MPH, a senior investigator at Group Health Research Institute. "But we have known relatively little about how to prevent them." Local reactions go away after a day or two, but they can be painful, and the associated redness and swelling can concern parents. This study focused on "medically attended" local reactions: ones that resulted in a visit to a doctor, nurse, or emergency room. Ideally, medically attended local reactions would happen less often than the current nearly one in 100 vaccinated children.

"Our findings support current recommendations to give intramuscular vaccinations in the thigh for children younger than 3 years," Dr. Jackson said. Since 2011, the U.S. Advisory Committee on Immunization Practices (ACIP) has recommended that intramuscular vaccinations be given to toddlers aged 12 to 35 months preferably in the thigh muscle (or in the deltoid muscle of the arm only if it's big enough)—and to children age 3 years older in the deltoid muscle of the arm. But in practice, health care providers tend to vary in their choice of vaccine injection sites for children; and parents can influence that decision.
The research team also tracked local reactions in children age 3 to 6 years and from intramuscular vaccines other than DTaP, including inactivated influenza and hepatitis A. But they found no statistically significant differences between vaccinating in the thigh and arm in the older age group or for the other intramuscular vaccines.

Previous evaluations of local reactions after the fifth DTaP vaccine in children age 4 to 6 years found that vaccination in the thigh was linked to a lower risk of local reactions than was vaccination in the arm. Dr. Jackson also led an earlier study that showed that neither ibuprofen (Advil) nor acetaminophen (Tylenol) help prevent local reactions after that vaccine.

The current research followed children age 1 to 6 years who received intramuscular vaccines from 2002 to 2009 at the eight VSD sites: Group Health; Harvard Pilgrim Health Care in Boston; HealthPartners in Minneapolis; Marshfield Clinic in Wisconsin; Kaiser Permanente Colorado in Denver; Kaiser Permanente Northwest in Portland; Kaiser Permanente Northern California in Oakland; and Kaiser Permanente Southern California in Los Angeles. The VSD project is a collaborative effort between the Centers for Disease Control and Prevention (CDC)'s Immunization Safety Office and 10 managed care organizations, including these eight (whose research institutes also happen to be members of the HMO Research Network).

**Medicinal toothbrush tree yields antibiotic to treat TB in new way**

A compound from the South African toothbrush tree inactivates a drug target for tuberculosis in a previously unseen way.

Tuberculosis causes more deaths worldwide than any other bacterial disease. At the same time as rates are increasing, resistance strains are emerging due, in part, to non-compliance with the treatment required. Many current drugs are nearly 50 years old and alternatives are needed to the long, demanding treatment schedules.

The compound under research, diospyrin, binds to a novel site on a well-known enzyme, called DNA gyrase, and inactivates the enzyme. DNA gyrase is essential for bacteria and plants but is not present in animals or humans. It is established as an effective and safe drug target for antibiotics.

"The way that diospyrin works helps to explain why it is effective against drug-sensitive and drug-resistant strains of tuberculosis," said Professor Tony Maxwell from the John Innes Centre.

In traditional medicine the antibacterial properties of the tree are used for oral health and to treat medical complaints such bronchitis, pleurisy and venereal disease. Twigs from the tree are traditionally used as toothbrushes.

Most antibiotics originate from naturals sources, such as the soil bacteria *Streptomyces*. Antibiotics derived from plants are less common, but they are potentially rich sources of new medicines.

"Extracts from plants used in traditional medicine provide a source for novel compounds that may have antibacterial properties, which may then be developed as antibiotics," said Professor Maxwell.

"This highlights the value of ethnobotany and the value of maintaining biodiversity to help us address global problems."

The work on diospyrin and related naphthoquinone compounds is being continued by Professor Maxwell as part of the efforts of a consortium of European researchers, More Medicines For Tuberculosis (MM4TB). The collaboration between 25 labs across Europe is dedicated to the development of new drugs for TB.

The work was carried out by postdoctoral researcher Fred Collin and will be continued by South African research assistant Natassja Bush. It is published in the *Journal of Biological Chemistry*; [http://www.jbc.org/cgi/doi/10.1074/jbc.M112.419069](http://www.jbc.org/cgi/doi/10.1074/jbc.M112.419069).

**NIH scientists identify protective role for antibodies in Ebola vaccine study**

**What:**

Researchers at the National Institutes of Health (NIH) and Oregon Health & Science University (OHSU) have found that an experimental vaccine elicits antibodies that can protect nonhuman primates from Ebola virus infection. Ebola virus causes severe hemorrhagic fever in humans and nonhuman primates, meaning that infection may lead to shock, bleeding and multi-organ failure. According to the World Health Organization, Ebola hemorrhagic fever has a fatality rate of up to 90 percent. There is no licensed treatment or vaccine for Ebola virus infection.

Several research groups have developed experimental vaccine approaches that protect nonhuman primates from Ebola virus and the closely related Marburg virus. These approaches include vaccines based on DNA, recombinant adenovirus, virus-like particles, and human parainfluenza virus 3. But how
these vaccine candidates confer protection is an area that is still being explored: Do they activate immune cells to kill the invading virus? Or do they elicit antibodies that block infection?

In this study, scientists at NIH’s National Institute of Allergy and Infectious Diseases and OHSU’s Vaccine & Gene Therapy Institute built on earlier work with an experimental vaccine composed of an attenuated vesicular stomatitis virus carrying a gene that codes for an Ebola virus protein. They observed how cynomolgus macaques responded to a challenge of Ebola virus before and during treatment with the vaccine and in conjunction with depleted levels of immune cells. Their results showed that important immune cells—CD4+ T cells and CD8+ T cells—had a minimal role in providing protection, while antibodies induced by the vaccine appeared to be critical to protecting the animals.

The scientists say this finding will help improve future Ebola virus vaccine development. They plan to focus their studies on what level of antibody production is needed to establish protection from Ebola virus infection in humans.


**Diet may not impact certain health outcomes in older persons**

UNIVERSITY PARK, Pa.—Eating diets high in sugar and fat may not affect the health outcomes of older adults ages 75 and up, suggesting that placing people of such advanced age on overly restrictive diets to treat their excess weight or other conditions may have little benefit, according to researchers at Penn State and Geisinger Healthcare System.

"Historically people thought of older persons as tiny and frail," said Gordon Jensen, head of the Department of Nutritional Sciences at Penn State, "but that paradigm has changed for many older persons. Currently, 30 percent or more may be overweight, and by 2030, almost 30 percent are projected to be obese, not just overweight. Recent reports even suggest that there may be survival benefits associated with overweight and mild obesity status among the elderly."

"We all know that adverse dietary patterns, such as a Western diet containing high amounts of fat or a diet containing high amounts of refined sugar, both of which may contribute to obesity, are associated with adverse medical conditions and health outcomes for many people, but until now, the health effects of these types of poor diets have not been characterized for people who live to 75 years of age and older," said Pao Ying Hsao, postdoctoral fellow at Penn State.

The team’s research is part of a decades-long collaborative study between Penn State and the Geisinger Healthcare System on the effects of nutritional status and diet on the health of more than 20,000 older people living in Pennsylvania. In the current study, the team followed 449 individuals for five years who were on average 76.5 years old at the beginning of the study.

"This is one of the first studies to examine obesity-related health outcomes and dietary patterns in such aged persons," Jensen said.

At study baseline, the team assessed the participants' dietary patterns by calling each of them by telephone four or five times during a 10-month period and asking them about their diets over the previous 24 hours. The participants were categorized as adhering to one of three different dietary patterns. The "sweets and dairy" pattern was characterized by the largest proportions of energy from baked goods, milk, sweetened coffee and tea and dairy-based desserts, and the lowest intakes of poultry. The "health-conscious" pattern was characterized by relatively higher intakes of pasta, noodles, rice, whole fruit, poultry, nuts, fish and vegetables, and lower intakes of fried vegetables, processed meats and soft drinks. The "Western" pattern was characterized by higher intakes of bread, eggs, fats, fried vegetables, alcohol and soft drinks, and the lowest intakes of milk and whole fruit.

Using outpatient electronic medical records, the researchers identified whether the participants developed cardiovascular disease, diabetes mellitus, hypertension (high blood pressure) and metabolic syndrome during the five-year period. They found no relationship between dietary pattern and prevalence of cardiovascular disease, diabetes, metabolic syndrome or mortality in the participants; however, they did find an increased risk of hypertension in people who followed the "sweets and dairy" pattern.

The results appeared in this month's issue of the *Journal of Nutrition Health and Aging*.

"We don’t know if the participants had been following these dietary patterns their entire adult lives, but we suspect they had been because people don’t usually change dietary practices all that much," Jensen said. "The results suggest that if you live to be this old, then there may be little to support the use of overly restrictive dietary prescriptions, especially where food intake may already be inadequate. However, people who live on prudent diets all their lives are likely to have better health outcomes."
Tissue Engineers Report Knee Cartilage Repair Success With New Biomaterial

Jan. 14, 2013 — In a small study, researchers reported increased healthy tissue growth after surgical repair of damaged cartilage if they put a “hydrogel” scaffolding into the wound to support and nourish the healing process. The squishy hydrogel material was implanted in 15 patients during standard microfracture surgery, in which tiny holes are punched in a bone near the injured cartilage. The holes stimulate patients’ own specialized stem cells to emerge from bone marrow and grow new cartilage atop the bone.

Results of the study, published in the Jan. 9 issue of Science Translational Medicine, are a proof of concept that paves the way for larger trials of the hydrogel’s safety and effectiveness, the researchers say.

“Our pilot study indicates that the new implant works as well in patients as it does in the lab, so we hope it will become a routine part of care and improve healing,” says Jennifer Elisseeff, Ph.D., Jules Stein Professor of Ophthalmology and director of the Johns Hopkins University School of Medicine’s Translational Tissue Engineering Center (TTEC). Damage to cartilage, the tough-yet-flexible material that gives shape to ears and noses and lines the surface of joints so they can move easily, can be caused by injury, disease or faulty genes. Microfracture is a standard of care for cartilage repair, but for holes in cartilage caused by injury, it often either fails to stimulate new cartilage growth or grows cartilage that is less hardy than the original tissue.

Tissue engineering researchers, including Elisseeff, theorized that the specialized stem cells needed a nourishing scaffold on which to grow, but demonstrating the clinical value of hydrogels has “taken a lot of time,” Elisseeff says. By experimenting with various materials, her group eventually developed a promising hydrogel, and then an adhesive that could bind it to the bone.

After testing the combination for several years in the lab and in goats, with promising results, she says, the group and their surgeon collaborators conducted their first clinical study, in which 15 patients with holes in the cartilage of their knees received a hydrogel and adhesive implant along with microfracture. For comparative purposes, another three patients were treated with microfracture alone. After six months, the researchers reported that the implants had caused no major problems, and MRIs showed that patients with implants had new cartilage filling an average 86 percent of the defect in their knees, while patients with only microfracture had an average of 64 percent of the tissue replaced. Patients with the implant also reported a greater decrease in knee pain in the six months following surgery, according to the investigators.

The trial continues, has enrolled more patients and is now being managed by a company called Biomet. The trial is part of efforts to win European regulatory approval for the device.

In the meantime, Elisseeff says her team has begun developing a next-generation implant, one in which the hydrogel and adhesive will be combined in a single material. In addition, they are working on technologies to lubricate joints and reduce inflammation.
Journal Reference:

Surprising Twist to Protein Misfolding Discovered
Jan. 14, 2013 — An effort to develop software that unravels the complexities of how proteins fold is paying dividends in new findings on how they misfold, according to researchers at Rice University.

The study published this week in the Proceedings of the National Academy of Sciences by chemist Peter Wolynes and his team at Rice’s BioScience Research Collaborative should be of particular interest to those who probe the roots of degenerative diseases associated with the aggregation of amyloid fibers in the body. These include Alzheimer’s and Parkinson’s diseases and Type 2 diabetes.

The molecular dynamics software to predict how strands of residues bend and twist into their functional shapes is designed to follow Wolynes’ and his colleagues’ groundbreaking “principle of minimal frustration.” These residues, the molecular beads that make up proteins, follow the path of least resistance as they fold into their native states. The principle describes how evolution has shaped the path a protein takes toward stability.

The software, called AWSEM-MD (for associative memory, water-mediated structure and energy model) simulates the possible ways beads in a strand should fold, based on the energies at play down to the submolecular level, and accurately predicts the final structure. Two developers of the current version, Weihua Zheng, a postdoctoral researcher at Rice, and Nicholas Schafer, a graduate student, are co-authors of the new paper, the latest in a series on folding dynamics dependent on the software.

The researchers set out to confirm that a process seen by experimentalists called domain swapping is one cause of protein misfolding. Domains are conserved parts of protein chains. Occasionally, a domain in one chain may encounter its doppelgänger in a nearby chain and become entangled with it via interactions similar to those in the correctly folded state.

The result is often a dimer—a kind of protein Siamese twin—that probably won’t be able to perform its intended biological task and may become part of a damaging amyloid fibril. "Experimentalists had some strong laboratory evidence that dimerization is a consequence of minimal frustration, an idea proposed earlier by our group on more general grounds," Wolynes said. "So we figured it would be nice to do a simulation to check it."

The team did indeed see domain swapping in their models of human cardiac titin, a muscle protein. But they were surprised to see something they weren’t looking for: evidence that identical sequences in neighboring chains, as short as five to seven residues, had the unfortunate tendency to find each other and stick together.

They found instances of such "self-recognition" tipped the balance of energies that dictated whether a protein would fold properly. Replacing just a few residues in one fragment eliminated self-recognition and lowered the incidence of domain swapping, Wolynes said.

"We weren’t the people who thought of this as a possibility," he said. "It had been suggested by others, although I never really believed it because it doesn’t have an obvious connection to the principle of
minimal frustration." But the simulations showed instances where sticky self-recognition in one segment of a chain could affect the energy of residues down the line and effectively introduce "frustration" that keeps the rest of the protein from folding at all and results in high disorder, or entropy.

While the models don't directly connect to the formation of amyloid fibrils, Wolynes said, anecdotal evidence indicates protein-folding diseases have some correlation with fevers that allow the extra entropy to stabilize the misfolded forms. "Our results would provide a new explanation," he said, for how a disordered part of the chain can contribute to the stability of these misfolded states at high temperature.

"When you hear 'take two aspirins and call me in the morning,' your doctor is doing you a bigger favor than you know," Wolynes said.

The discovery could open paths for researchers to design drugs that inhibit specific interactions. "Very minor changes seem to destroy this self-recognition in the computer simulation, and that's what we want the experimentalists to do: Make those changes to see if they decrease the self-recognition effect," he said.

"Our simulations provide structural details of misfolded proteins at the molecular level that are difficult for experiments to probe," Zheng said. "These can generate specific hypotheses they can test."

The researchers hope their work will be useful to both experimentalists and other computational protein-folding researchers.

"AWSEM is hosted on Google Code, which requires all code to be open-source," Schafer said. "So it's available to anyone who wants to use it. What we're seeing with these studies is that the values we get by applying the principle of minimal frustration are appropriate globally, not just for predicting the native structures of proteins. It can predict bound structures (like dimers) and misfolded structures as well.

"You always have to be careful about using models that 'rig the deck' in favor of a particular anticipated result," he said. "But what's interesting is that our model doesn't have any information a priori about these specific types of misfolded structures. Our model is parameterized using as input only experimental data for properly folded structures and then applying the principle of minimal frustration. The wide range of successes we've had this year tells me that we have a decent method for deriving the strengths of the interactions."

"We never really thought about specific kinds of misfolding or the aggregation process when we built our model around the principle of minimal frustration," Zheng said. "But they all fall into place."

Journal Reference:
Weihua Zheng, Nicholas P. Schafer, and Peter G. Wolynes. Frustration in the energy landscapes of multidomain protein misfolding. PNAS, January 14, 2013 DOI: 10.1073/pnas.1222130110

Why Down Syndrome Boosts Susceptibility to Other Conditions
Jan. 10, 2013 — A study led by UC Irvine researchers has revealed some of the underlying neural factors that explain why people with Down syndrome are more susceptible to Alzheimer's disease, diabetes and autistic spectrum disorders. Jorge Busciglio, associate professor of neurobiology & behavior, and colleagues analyzed the cellular and molecular mechanisms leading to oxidative stress and mitochondrial dysfunction in Down syndrome individuals.

They found that this breakdown in energy metabolism within brain cells contributes to the higher probability of these other conditions.

Down syndrome occurs when a person has 47 chromosomes instead of the usual 46. Estimates suggest that 25 percent or more of individuals over 35 with Down syndrome show signs of Alzheimer’s-type dementia. This percentage increases with age.

The incidence of Alzheimer’s disease in people with Down syndrome is roughly three to five times greater than in the general population.

Journal Reference:

Breath Test Identifies Bacteria's Fingerprint
Jan. 8, 2013 — Scientists have identified the chemical 'fingerprints' given off by specific bacteria when present in the lungs, potentially allowing for a quick and simple breath test to diagnose infections such as tuberculosis.

Publishing their study January 11, in IOP Publishing’s Journal of Breath Research, the researchers have successfully distinguished between different types of bacteria, as well as different strains of the same bacteria, in the lungs of mice by analysing the volatile organic compounds (VOCs) present in exhaled breath.
It is hoped that a simple breath test could reduce the diagnosis time of lung infections from days and weeks to just minutes.

Co-author of the paper, Jane Hill, from the University of Vermont, said: "Traditional methods employed to diagnose bacterial infections of the lung require the collection of a sample that is then used to grow bacteria. The isolated colony of bacteria is then biochemically tested to classify it and to see how resistant it is to antibiotics.

"This whole process can take days for some of the common bacteria and even weeks for the causative agent for tuberculosis. Breath analysis would reduce the time-to-diagnosis to just minutes"".

Clinicians see breath-testing as an attractive method for diagnosing disease due to its ease of use and non-invasiveness. Scientists have already investigated breath-based diagnostics for multiple cancers, asthma and diabetes.

In this study, the researchers, from the University of Vermont, analysed the VOCs given off by Pseudomonas aeruginosa and Staphylococcus aureus, both of which are common in acute and chronic lung infections.

They infected mice with the two bacteria and sampled their breath after 24 hours. The VOCs were analysed using a technique called secondary electrospray ionization mass spectrometry (SESI-MS), which is capable of detecting VOCs down to parts per trillion.

They found a statistically significant difference between the breath profiles of the mice infected with the bacteria and the mice that were uninfected. The two different species of bacteria could also be distinguished to a statistically significant level, as could the two different strains of the P. aeruginosa that were used.

They hypothesise that bacteria in the lungs produce unique VOCs that are not found in regular human breath due to their differing metabolism.

"We have strong evidence that we can distinguish between bacterial infections of the lung in mice very effectively using the breathprint SESI-MS approach and I suspect that we will also be able to distinguish between bacterial, viral and fungal infections of the lung."

"To that end, we are now collaborating with colleagues to sample patients in order to demonstrate the strengths, as well as limitations, of breath analysis more comprehensively," continued Hill.

**Journal Reference:**

**Granzyme A Produced by γδ T Cells Induces Human Macrophages to Inhibit Growth of an Intracellular Pathogen**

**Abstract**

Human γδ T cells potently inhibit pathogenic microbes, including intracellular mycobacteria, but the key inhibitory mechanism(s) involved have not been identified. We report a novel mechanism involving the inhibition of intracellular mycobacteria by soluble granzyme A. γδ T cells produced soluble factors that could pass through 0.45 µm membranes and inhibit intracellular mycobacteria in human monocytes cultured below transwell inserts. Neutralization of TNF-α in co-cultures of infected monocytes and γδ T cells prevented inhibition, suggesting that TNF-α was the critical inhibitory factor produced by γδ T cells. However, only siRNA- mediated knockdown of TNF-α in infected monocytes, but not in γδ T cells, prevented mycobacterial growth inhibition. Investigations of other soluble factors produced by γδ T cells identified a highly significant correlation between the levels of granzyme A produced and intracellular mycobacterial growth inhibition. Furthermore, purified granzyme A alone induced inhibition of intracellular mycobacteria, while knockdown of granzyme A in γδ T cell clones blocked their inhibitory effects. The inhibitory mechanism was independent of autophagy, apoptosis, nitric oxide production, type I interferons, Fas/FasL and perforin. These results demonstrate a novel microbial defense mechanism involving granzyme A-mediated triggering of TNF-α production by monocytes leading to intracellular mycobacterial growth suppression. This pathway may provide a protective mechanism relevant for the development of new vaccines and/or immunotherapies for macrophage-resident chronic microbial infections.

**Author Summary**

A small subset of human T cells express γδ T cell receptors and recognize unique non-peptide phosphoantigens expressed by microbes and damaged cells, such as cancer. These cells are important because: 1) they reside within skin and mucosal surfaces at critical points of initial pathogen invasion, and
2) they are not restricted by polymorphic HLA types and thus can be activated by the same cognate antigens in highly diverse populations. Many important human pathogens such as the causes of AIDS, malaria, tuberculosis and others induce potent responses in γδ T cells that can be protective. However, the key mechanisms involved in γδ T cell-mediated protective immunity are not well defined. We have found that γδ T cells produce soluble granzyme A which correlates with their ability to protect against intracellular mycobacterial growth. We show directly that highly purified granzyme A alone can trigger human monocytes to control intracellular mycobacteria. We further show that the granzyme A-induced mycrobacterial inhibition required production of TNF-α by infected monocytes. These studies may have important implications for future vaccine development and novel therapeutic strategies.


Lipid Exchange between Borrelia burgdorferi and Host Cells

Abstract

Borrelia burgdorferi, the agent of Lyme disease, has cholesterol and cholesterol-glycolipids that are essential for bacterial fitness, are antigenic, and could be important in mediating interactions with cells of the eukaryotic host. We show that the spirochetes can acquire cholesterol from plasma membranes of epithelial cells. In addition, through fluorescent and confocal microscopy combined with biochemical approaches, we demonstrated that B. burgdorferi labeled with the fluorescent cholesterol analog BODIPY-cholesterol or 3H-labeled cholesterol transfer both cholesterol and cholesterol-glycolipids to HeLa cells. The transfer occurs through two different mechanisms, by direct contact between the bacteria and eukaryotic cell and/or through release of outer membrane vesicles. Thus, two-way lipid exchange between spirochetes and host cells can occur. This lipid exchange could be an important process that contributes to the pathogenesis of Lyme disease.

Author Summary

Lyme disease, the most prevalent arthropod-borne disease in North America, is caused by the spirochete Borrelia burgdorferi. Cholesterol is a significant component of the B. burgdorferi membrane lipids, and is processed to make cholesterol-glycolipids. Our interest in the presence of cholesterol in B. burgdorferi recently led to the identification and characterization of eukaryotic-like lipid rafts in the spirochete. The presence of free cholesterol and cholesterol-glycolipids in B. burgdorferi creates an opportunity for lipid-lipid interactions with constituents of the lipid rafts in eukaryotic cells. We present evidence that there is a two-way exchange of lipids between B. burgdorferi and epithelial cells. Spirochetes are unable to synthesize cholesterol, but can acquire it from the plasma membrane of epithelial cells. In addition, free cholesterol and cholesterol-glycolipids from B. burgdorferi are transferred to epithelial cells through direct contact and through outer membrane vesicles. The exchange of cholesterol between spirochete and host could be an important aspect of the pathogenesis of Lyme disease.


Universal Flu Vaccines Charge Ahead

Researchers and biotech companies are bringing a universal flu vaccine closer to reality.

By Sabrina Richards | January 14, 2013

It’s a frustrating fact of life that coming down with influenza one year doesn’t guarantee anyone a flu-free season the next year. Even the flu vaccine doesn’t provide full-proof protection, as it covers only a select few strains of the virus— a selection that’s based on the World Health Organization’s best bet as to which strains around the world will be most prevalent in the coming flu season.

Unfortunately, those predictions are proved wrong about one time out of 20, explained Sarah Gilbert, who leads the Human Influenza Vaccine Programme at the University of Oxford’s Jenner Institute.

However, some researchers are getting closer to creating the ever-elusive universal flu vaccine, which could protect against a number of influenza viruses at once, including pandemic strains. If successful, universal flu vaccines would take the guesswork out of vaccine planning, and only require booster shots every few years.

One antibody to bind them all

Influenza is a RNA virus that uses its hemagglutinin (HA) protein like a key to allow it to enter and infect target host cells. In response to infection, or to a typical flu vaccine, the body produces antibodies that bind the head of the HA molecule, preventing free-floating virus from entering and infecting cells.
However, the head is also the part of the HA protein that the virus most frequently changes via mutation, making the antibodies produced against one strain ineffective against another.

The answer to creating a vaccine that protects against many strains lies in forcing the immune system to make antibodies against the portions of the HA molecule that are shared, or genetically conserved, among most influenza viruses, thus creating a more universal vaccine. But, for unknown reasons, most vaccines don’t elicit such antibodies. So researchers are now trying new ways of enticing the immune system into making antibodies that recognize these general targets and neutralize many types of influenza at once.

“Up until about 4 years ago, we didn’t know much about human broadly neutralizing antibodies,” said Ian Wilson, a structural biologist at The Scripps Research Institute. But the last few years, researchers have found individuals who produce antibodies that neutralize a wide variety of both influenza A and B strains, showing that “a universal vaccine is possible if you can elicit the same types of antibodies” in others, said Wilson.

Wilson’s lab helped solve the structure of some of these broadly neutralizing antibodies and the region of HA they target—the conserved stem of HA. More recently, Wilson and his collaborators have shown that because HA’s head region has tiny conserved areas, occasionally even an antibody directed at the HA head can have some cross-reactivity among influenza types.

But most researchers think a stronger antibody can be made against regions in the HA stem. Specifically, some researchers think that a “headless” HA proteins could focus the antibody response on the conserved stem region. Others are looking to design vaccines that contain only small portions of the most important conserved segments of the stem region. Still others are focused on understanding the basic immunology of how antibodies bind and recognize their targets in order to improve vaccines from a different angle, and possibly understand why antibodies aren’t often naturally made to the stalk region, said Wilson.

Several biotech companies are preparing what they hope will become the first universal flu vaccines on the market, though none have been tested as a universal vaccine yet. Most have been tested for safety and ability to stimulate an immune response in healthy volunteers, or boost efficacy of current vaccines with mostly positive results. One strategy being tested combines several conserved regions of flu proteins into one molecule to produce a vaccine that hopefully stimulates an antibody response against a wide variety of strains. This includes the M-001 vaccine from Israel-based BiondVax, which contains regions from HA and two internal virus proteins. When M-001 was combined with the seasonal vaccine, it enhanced immunity to the strains contained in the seasonal vaccine. Other companies are pursuing similar methods, said Gilbert. “They’re all trying to use only very small [conserved] regions, and they all have their own strategies to identify which regions” are the best, as well as ways to produce stronger immune responses, she said.

**Delivery service**

Changing how vaccines are delivered also has the potential to produce more broadly cross neutralizing antibodies. Last year, researchers at the NIH elicited antibodies against the conserved HA stem region by presenting bird flu HA in two different forms. First they primed with a DNA vaccine—a segment of DNA encoding the HA protein, which host cells produce and present to immune cells—and followed this with a protein-based inactivated H5N1 boost. Using this prime-boost method produced neutralizing antibodies targeting the conserved stem region of HA.

John Schrader, an immunologist at the University of British Columbia says that it may be possible to generate broadly neutralizing antibodies using currently available vaccines, if it’s done correctly, he says. Schrader and his colleagues found that infection with, or vaccination against, the pandemic 2009 H1N1 strain (swine flu) produces the elusive broadly cross-neutralizing antibodies that seasonal vaccines do not. This may be because H1N1 is radically different from the other viruses commonly circulating in the human population. That distinctiveness may allow the virus to be recognized by a rare set of memory B cells, Schrader said.

Normally, the seasonal flu virus activates a wide array of B cells, most against the head region, a few against the stalk. Some of each persist after the infection as “memory” cells. When the next seasonal flu virus infects, it has similar head regions to previous viruses, so it’s the memory cells that bind to the head region that are activated, while the rare B cells against the conserved stem region get lost in the shuffle. But a drastically different virus like H1N1 only shares stem regions with previous viruses, so it can activate rare anti-stem memory B cells without also activating the anti-stem memory cells—producing large amounts of broadly neutralizing antibodies, Schrader said.
Therefore, prompting the production of broadly neutralizing antibodies could be as simple as vaccinating with a rare virus strain, and boosting with different rare strains, to ensure that only memory B cells that recognize the stem are activated. It would be key, in Schrader’s strategy, to avoid vaccinating someone twice with the same vaccine, so that B cells that recognize the head regions don’t also get re-activated.

**A different target**

Rather than trying to find the perfect region or regions of the HA molecule, some researchers are looking to other conserved viral proteins. The M2 protein, which helps the flu virus empty its contents into its target cell, is one of only three viral proteins dotting its surface—and one of the least variable between strains. But M2 presents several challenges for investigators hoping to produce an M2-targeted vaccine, cautioned Sang-Moo Kang, an immunologist at Georgia State University. First, there are many fewer M2 proteins than HA proteins, and secondly, the antibody-targeted region of M2 is about 20 times smaller than HA’s, “so M2 can’t compete in terms of host response,” said Kang. Also, rather than stimulating the generation of antibodies that prevent infection by blocking viral entry into cells, anti-M2 antibodies target infected cells, leading to their lysis. Such a vaccine would likely just contain an infection rather than prevent cells from becoming infected in the first place.

Despite these hurdles, at least one company is targeting M2 in their bid to produce a universal vaccine. VaxInnate, a New Jersey-based biotech company, has performed clinical trials using M2 epitope (M2e) fused to a bacterial protein. Like other vaccines being touted as future universal vaccines, VaxInnate’s method has yet to be shown to be effective against infection with a variety of strains. So far, VaxInnate has used their M2 vaccine to boost immune responses to a current influenza vaccine.

**A new direction**

Although most of the work to date has focused on antibody or B-cell-mediated responses, some researchers think that T cells—which kill virally infected cells—will be an important facet of universal vaccines. Because T cells kill flu-infected cells, they can prevent newly replicated virions from escaping infected cells and thus keep the infection from spreading through the body (sometimes so well that a patient notices no symptoms). Current vaccines don’t do much to activate T cells, which explains why previous infection with seasonal flu can protect against pandemic strains, but previous vaccination does not. T cells react to viral proteins that are chopped up and presented by infected cells, allowing them to recognize regions of conserved internal proteins that B cells—which generally target surface proteins—miss.

Gilbert at the Jenner Institute and her colleagues created a vaccine made of two conserved internal influenza proteins attached to a live vaccinia virus that is rendered unable to replicate. When patients were exposed to a strain of flu they had not encountered before, only 2 out of 11 patients who’d been vaccinated with Gilbert’s vaccine contracted the flu compared to 5 out of 11 un-vaccinated controls. Despite the promising results, “I wouldn’t want to sell a vaccine that only targets T cells,” noted Gilbert, who is currently working on combining her T cell vaccine with proteins to stimulate neutralizing antibodies as well.

Even if researchers do create vaccines that protect against all influenza viruses, we’ll still need to get vaccinated regularly—just not every year, said Gilbert. Unlike some other viruses, the flu doesn’t stimulate strong enough immune memory to keep us protected for life, even using a more universal vaccine. Gilbert estimates that future vaccines may stretch our yearly needle jabs to once every 5 years or so.

**Economist Intelligence Unit Report Calls for Global Policy Innovation to Tackle the ‘Silent Pandemic’ that is Hepatitis C**

Experts recommend comprehensive approach to combat global health issue

*London, 15 January 2013, PRNewswire* – A new Economist Intelligence Unit (EIU) report titled *The Silent Pandemic: Tackling Hepatitis C with Policy Innovation*, made possible as a result of an educational grant from Janssen Pharmaceutica NV and published today, highlights the urgent need for countries around the world to develop strategies to tackle head-on the growing social and economic issues associated with Hepatitis C (HCV).¹

While the total number of infected individuals is unknown due to a lack of available data, the World Health Organization (WHO) estimates that approximately 150 million people globally are currently living with the blood-borne infectious disease, HCV.² Of these, up to two thirds will develop chronic liver disease and one in five will develop cirrhosis.² HCV is also the leading cause of liver transplantation worldwide and in the US the disease now accounts for more deaths than HIV.¹
“The report highlights that worldwide, despite the significant burden of HCV, governments have failed to get a grip on the scale and impact of the disease,” said Charles Gore, President of The World Hepatitis Alliance. “In both developed and developing countries, the true human and economic cost of HCV will continue to rise unless policy makers confront this urgent public health issue now.”

Despite the devastating effects of HCV, the report states that it is now considered preventable and with modern treatments, the majority of sufferers can become clear of the virus. The report notes, however, that as few as 10% of patients are currently receiving treatments and there is a large disparity in care across countries. As a result, the report calls for countries to take a “comprehensive approach,” which takes into account local needs and resources available. This includes the following:

- **Effective disease surveillance** to create an accurate picture of the problem and ensure effective policies can be developed. The report claims that too few countries – developed or developing – have recently conducted the epidemiological studies necessary for good policy-making at a national, let alone a local, level. According to the EIU, 16 countries in the EU alone have epidemiological data that is either poor or non-existent.

- **Better public awareness** is needed to help remove the stigma associated with the disease and create better understanding of HCV. A survey by the European Liver Patients Association found that only 20% of those diagnosed had heard of hepatitis B or C before being told they had it (full survey results are available at: [http://www.hepbeppa.org/wp-content/uploads/2011/11/Report-on-Patient-Self-Help.pdf](http://www.hepbeppa.org/wp-content/uploads/2011/11/Report-on-Patient-Self-Help.pdf)).

- **Prevention measures** to reduce high-risk behaviour and improve education on healthy lifestyle choices for those already infected. The report also calls for measures to prevent transmission via healthcare systems, which is the major route of transmission of HCV in developing countries.

- **Innovative ways to reach out to patients** to ensure those who need treatment receive it before irreversible conditions develop.

“The report highlights that each country has different needs and resources; however, we urge all those involved in the management of HCV and public health to help increase awareness of the disease and look at the most effective ways of delivering effective treatment to those most in need,” said Gaston Picchio, Global Hepatitis Disease Area Leader, Janssen. “Janssen is committed to working with the HCV community and will continue to engage with healthcare professionals, government officials and patient advocates around the world to support their efforts to reduce the individual and societal burden of this devastating disease.”

A full copy of the EIU report and supporting materials, including an info-graphic, is available at: [http://www.janssen-emea.com/The-silent-pandemic](http://www.janssen-emea.com/The-silent-pandemic)

### About HCV

Hepatitis C (HCV) is a blood-borne infectious disease that affects the liver. With an estimated 150 million people infected worldwide, and three to four million people newly infected each year, HCV puts a significant burden on patients and society. Estimations indicate that HCV caused more than 86,000 deaths and 1.2 million disability-adjusted life-years (DALYs) in the WHO European region in 2002 (latest data available). Chronic infection with HCV can lead to liver cancer and other serious and fatal liver diseases. About one-quarter of the liver transplants performed in 25 European countries in 2004 were attributable to HCV (latest data available).

### References


### WHO Recommends Switching To Injectable Polio Vaccine

"This month the World Health Organization (WHO) in Geneva, Switzerland, proposed a shift in [polio] vaccination strategy from oral vaccines to injected ones that may have to be administered in clinics,"
Nature reports, adding, "The change is needed to mop up the last remaining pockets of polio, but experts say that it poses challenges in [rural areas], which have poor access to health care." The oral polio vaccine, developed by Albert Sabin and in widespread use through the Global Polio Eradication Initiative (GPEI), contains three inactivated strains of polio, and while the vaccine is cheap and easy to administer, the inactivated virus can revert to disease-causing forms, the journal notes.

"In a 4 January announcement, the WHO called for oral polio vaccine containing the polio strain type 2, one of the Sabin vaccine strains, to be phased out" because wild type 2 polio has been eliminated worldwide, and the policy also called for "the introduction, as quickly as possible, of the oral vaccine’s old competitor: the inactivated Salk vaccine," a more expensive, injectable vaccine, according to the journal. "But it carries no risk of causing polio," Nature writes, adding, "By giving children an inactivated vaccine that protects against all three subtypes of polio, health workers hope to gradually stamp out vaccine-derived outbreaks." The journal notes, "The high cost of the inactivated polio vaccine remains a significant hurdle for the plan," as does the lack of health care infrastructure in affected areas. However, health experts hope the injectable vaccine can be included in routine immunizations, the journal adds (Callaway, 1/14).

Experts Blame Lack Of Immunization Coverage For Pakistan’s Measles Outbreak

In 2012, measles "claimed the lives of more than 300 children in Pakistan," with more than 200 of those deaths from Sindh province, and health experts and the WHO are saying "the huge difference in routine immunization coverage between the provinces, districts and cities is at the root of the measles outbreak," Inter Press Service reports. "The government has started a mass immunization campaign from January 1 for children aged nine months to 10 years in eight districts of Sindh," according to the news service. "The outbreak casts serious doubts over official claims that 82 percent of under-fives in Sindh are immunized," IPS writes, noting D.S. Akram, a pediatrician with the non-governmental organization HELP, which works on maternal and child health in Sindh, said, "These figures are an overestimate and in measles vaccination it is around 50 percent at best" (Ebrahim, 1/12).

Some health officials said flooding and heavy rains over the past five years have contributed to health workers’ inability to reach certain areas, and others said malnutrition contributed to the measles deaths, BMJ reports (Kazi, 1/14). IPS adds, "Many experts have long held that with much money and political commitment directed towards eradication of polio, routine immunization took a backseat" (1/12).

Research Shows Genetic Factors Increase Risk Of Visceral Leishmaniasis

A new study published in Nature Genetics last week shows that genetics likely influence whether an individual develops visceral leishmaniasis, a lethal form of the parasitic disease transmitted by sandflies, the New York Times reports. In 80 percent of cases, leishmaniasis causes painful skin boils, but in 20 percent of cases, the disease—also called kala azar—spreads to the organs and is fatal if untreated, the newspaper notes. Researchers "compared DNA in almost 6,000 blood samples from India and Brazil," and they found "[h]oth Indians and Brazilians who got visceral leishmaniasis had similar DNA variations," the New York Times writes (McNeil, 1/14). A University of Western Australia press release says the discovery brings researchers "a step closer to developing a vaccine." The press release notes, "Leishmaniasis affects 12 million people and there are an estimated 1.5 million new cases annually mainly in India, Bangladesh, Nepal, Sudan, South Sudan, Ethiopia, and Brazil" (1/8).

Designer bacteria may lead to better vaccines

61 new strains of genetically engineered bacteria may improve the efficacy of vaccines for diseases such as flu, pertussis, cholera and HPV

AUSTIN, Texas — Researchers at The University of Texas at Austin have developed a menu of 61 new strains of genetically engineered bacteria that may improve the efficacy of vaccines for diseases such as flu, pertussis, cholera and HPV.

The strains of E. coli, which were described in a paper published this month in the journal PNAS, are part of a new class of biological "adjuvants" that is poised to transform vaccine design. Adjuvants are substances added to vaccines to boost the human immune response.

"For 70 years the only adjuvants being used were aluminum salts," said Stephen Trent, associate professor of biology in the College of Natural Sciences. "They worked, but we didn't fully understand why, and there were limitations. Then four years ago the first biological adjuvant was approved by the Food
and Drug Administration. I think what we're doing is a step forward from that. It's going to allow us to
design vaccines in a much more intentional way."

Adjuvants were discovered in the early years of commercial vaccine production, when it was noticed
that batches of vaccine that were accidentally contaminated often seemed to be more effective than those
that were pure.

"They're called the 'dirty little secret' of immunology," said Trent. "If the vials were dirty, they elicited
a better immune response."

What researchers eventually realized was that they could produce a one-two punch by intentionally
adding their own dirt (adjuvant) to the mix. The main ingredient of the vaccine, which was a killed or
inactivated version of the bacteria or virus that the vaccine was meant to protect against, did what it was
supposed to do. It "taught" the body's immune system to recognize it and produce antibodies in response
to it.

The adjuvant amplifies that response by triggering a more general alarm, which puts more agents of
the immune system in circulation in the bloodstream, where they can then learn to recognize the key
antigen. The result is an immune system more heavily armed to fight the virus or bacteria when it
encounters it in the future.

For about 70 years the adjuvant of choice, in nearly every vaccine worldwide, was an aluminum salt.
Then in 2009, the FDA approved a new vaccine for human papillomavirus (HPV). It included a new kind
of adjuvant that's a modified version of an endotoxin molecule.

These molecules, which can be dangerous, appear on the cell surface of a wide range of bacteria. As a
result, humans have evolved over millions of years to detect and respond to them quickly. They trigger an
immediate red alert.

"In some of its forms an endotoxin can kill you," said Trent. "But the adjuvant, which is called MPL, is
a very small, carefully modified piece of it, so it's able to trigger the immune response without overdoing
it."

What Trent and his colleagues have done is expand on that basic premise. Rather than just work with
an inert piece of endotoxin, they've engineered E. coli bacteria to express the endotoxin in many
configurations on the cell surface.

"These 61 E. coli strains each have a different profile on their surface," said Brittany Needham, a
doctoral student in Trent's lab and the first author on the paper. "In every case the surface structure of the
endotoxin is safe, but it will interact with the immune system in a range of ways. Suddenly we have a huge
potential menu of adjuvants to test out with different kinds of vaccines."

One form might work better with cholera vaccine, another with pertussis (whooping cough) and
another with a future HIV vaccine. Trent, Needham and their colleagues should be able to fine-tune the
adjuvants with increasing precision as more E. coli strains are engineered and tested, and as their
understanding of how they interact with the immune system deepens.

"I think we're at the dawn of a new age of vaccine design," said Trent. "For a long time vaccinology
was really a trial-and-error field. It was a black box. We knew certain things worked. We knew certain
vaccines had certain side effects. But we didn't entirely know why. Now that's changing."

Trent said that an additional advantage of their system is that the E. coli can be engineered to express
key viral and bacterial antigens along with the endotoxin. A single cell could deliver both parts of the one-
two punch, or even a one-two-three punch, if antigens from multiple diseases were expressed in a single
E. coli.

"It makes possible a vaccine that provides protection from multiple pathogens at the same time," said
Trent.

Trent and his colleagues are working on a second round of designer E. coli. They have also filed a
provisional patent on their system and are working with the university to find a corporate partner to pay
for clinical trials.

"This is ready to go," said Trent. "I can't predict whether it will actually make it to the market. But it's
very similar to the adjuvant that has already been approved, and my instinct is that if a company will
undertake to do the trials, it will get approved. A company could call us tomorrow, we could send them a
strain, and they could start working."
Generics Could Cut Costs of HIV Treatment


HIV-infected patients may soon be able to switch from a branded one-pill combination of antiretroviral drugs to a less expensive protocol that combines generic and branded drugs. Current guidelines recommend HIV-infected people take the single-pill combination of efavirenz (Sustiva), emtricitabine (Emtriva), and tenofovir (Atripla). The cheaper three-pill regimen would include a generic version of efavirenz, lamivudine (similar to emtricitabine), and Atripla. According to Rochelle Walensky, MD, the United States could see a savings of $920 million in the first year if every US resident on antiretroviral therapy switched to the three-pill generic regimen.

However, Walensky noted that it is harder to adhere to the schedule of taking three pills, and lack of adherence can make treatment less effective. In addition, there is evidence that lamivudine is less effective than emtricitabine, and patients are more likely to develop resistance to lamivudine.

Massachusetts General Hospital researchers compared the cost and effectiveness of no treatment with the recommended single pill dose, a three-pill regimen, and an intermediate treatment consisting of two pills. The two-pill alternative would include a generic form of efavirenz and a branded combination of tenofovir and emtricitabine (Truvada). An HIV-infected person who receives no treatment from age 43 has a life expectancy of 4.05 quality-adjusted life-years (QALY). The branded single-pill treatment results in 12.45 QALY, compared with 12.25 QALY for the two-pill intermediate treatment, and 12.08 QALY for the three-pill generic treatment.

Lifetime cost for the person taking the branded one-pill dose is $342,800, whereas lifetime cost for the generic-based three-pill regimen is estimated to be $300,300.


Health Dept. Addresses New Perception of HIV, AIDS


Because of better treatment and prevention, people view HIV and AIDS as less threatening than when the virus was discovered in 1981, reported Christine Schuyler, commissioner of human services for Chautauqua County Health Department. However, the virus is still a major threat to health, and people who do not know they have the virus can pass it to others. HIV occurs in all population groups.

HIV incidence rates for Chautauqua County—6.7 per 100,000 persons in 2009—are well below New York State and U.S. averages. A 2010 New York state law requires that healthcare providers offer HIV testing to “everyone between the ages of 13 and 64.”

HIV is transmitted through direct contact with HIV-infected blood, semen, vaginal fluids, and breast milk. The risk of HIV infection increases through unprotected sex and the sharing of needles or syringes. The virus does not spread via kissing or the exchange of saliva. People with HIV may not have symptoms for up to 10 years. Schuyler recommends abstinence and avoiding unprotected sex to avoid HIV infection.

The health department offers free and confidential HIV and STD testing. Interested persons should call (800) 604–6789. The health department connects HIV-infected people with Erie County Medical Center’s Immunodeficiency Services Clinic for care and case management services. There are two locations: the Jamestown office at 110 E. Fourth Street and the Dunkirk office at 319 Central Avenue.

Evergreen Health Services offers free, walk-in rapid HIV testing from 10:00 a.m. to 3:00 p.m. on Mondays at 111. W. Second Street in Jamestown. Testing is offered by appointment only Tuesday through Friday.

Chautauqua Opportunities, Inc. (COI) can help HIV-infected people find permanent housing. Interested persons should call the Jamestown office at (716) 661–9430 or the Dunkirk office at (716) 366–8176 or visit the COI website at http://chautauquaopportunities.com/

CMV infection may contribute to the size of the latent HIV reservoir

Michael Carter
Published: 16 January 2013

The presence of cytomegalovirus (CMV) in blood and semen is associated with higher levels of HIV DNA in blood, investigators from the United States report in the online edition of *Journal of Infectious Diseases*. The study involved gay men recently infected with HIV. The authors believe that CMV replication may increase the reservoir of cells latently infected with HIV.
This study demonstrated that presence of CMV in PBMC [peripheral blood mononuclear cells] and in seminal plasma of HIV infected ART-naïve MSM was associated with higher levels of proviral HIV DNA," write the authors. "It also found that simultaneous detectable CMV in semen and PBMC was associated with the highest levels of HIV DNA in PBMC."

Over 75% of HIV-positive gay men have at least one herpes virus actively replicating in their semen and the most common is CMV. Co-infection with CMV has been associated with accelerated HIV disease progression and increased immune activation. Investigators from San Diego hypothesised that it could also be an important factor in determining the size of the reservoir of cells with latent HIV infection.

They therefore designed an observation study involving 113 gay men recently infected with HIV. None were taking antiretroviral therapy. Paired semen and blood samples were provided for analysis. CMV DNA was quantified, as was proviral HIV DNA in PBMC, HIV viral load and CD4 cell count.

The participants had been infected with HIV for a median of 70 days at baseline. Median CD4 cell count at this time was 523 cells/mm³ and median blood plasma viral load was 50,000 copies/ml. Approximately 46% of participants provided semen samples positive for CMV (median peak viral load 4.52 log₁₀ DNA copies/ml).

Just over half the cohort (52%) provided paired longitudinal samples for analysis (median follow-up, 67 days). Approximately a fifth had intermittent CMV shedding in semen and 10% had intermittently detectable CMV DNA in PBMC. HIV DNA was detected in 91% of PBMC samples.

Analysis of the entire cohort showed that higher levels of HIV in DNA were associated with longer duration of HIV infection, and the presence of CMV in PBMC. However, blood plasma viral load and CD4 cell count were not associated with HIV DNA levels. The investigators were surprised by this finding and performed two sub-analyses. The first excluded participants with low-level HIV DNA. This revealed a positive association between HIV viral load and HIV DNA (p = 0.01). The second excluded participants with an estimated duration of infection of up to 120 days. This showed no association between HIV viral load and HIV DNA. Nor was the presence of a sexually transmitted infection at baseline associated with HIV DNA levels.

In multivariate analysis, the association between CMV in PBMC and higher levels of HIV DNA in PBMC was significant (p = 0.05).

Participants with detectable CMV in both semen and PBMC were more likely to have higher HIV DNA levels in PBMC than individuals with undetectable CMV in both semen and PBMC (p = 0.02).

"This study provides important insights in regard of one possible mechanism contributing to the establishment of the viral reservoir during early HIV infection," the investigators conclude. "Future studies should determine if persistent CMV replication can be targeted as a strategy to reduce the size of the latent HIV reservoir."

Reference
Gianella S et al. CMV DNA in semen and blood is associated with higher levels of proviral HIV DNA. J Infect Dis, online edition, 2013.

Queensland researcher David Harrich develops gene therapy which could stop HIV from turning deadly
A QUEENSLAND researcher has developed a gene therapy for HIV which has the potential to stop the virus from turning deadly.
Queensland Institute of Medical Research scientist David Harrich will begin animal trials this year, with experiments in humans are still five years away.

Associate Professor Harrich has manipulated an HIV protein involved in gene expression, known as Tat, and turned it into a weapon against the virus.

Using human immune system cells, known as T cells, in the laboratory, he's shown the mutant protein prevents HIV replication.

At the same time, Prof Harrich said the modified protein, dubbed Nullbasic, did not appear to adversely affect the human cells.

"So far we haven't found that Nullbasic causes toxicity in the cells we've tested," he said.
"I'm excited. Every test I've done with this agent has succeeded. It makes me optimistic it will work in humans. At the same time, I'm a sceptical scientist and I'm going to require proof it can jump every hurdle." QIMR researchers will soon begin testing the protein in mice.

"Before you can trial it on humans, it's going to have to go through rigorous testing in animals for safety," Professor Harrich said.
In order for human cells to make the HIV-inhibitory protein in the laboratory, he had to insert a new gene—a process known as gene therapy.

He said the idea of gene therapy being used as a treatment for HIV had gained momentum since the case of a man known as the Berlin Patient, considered by doctors to have been cured of the virus.

"He had a bone marrow transplant because he had cancer. The bone marrow from a human donor contained a mutant form of a normal protein that stopped the virus from being able to infect his cells," Prof Harrich said.

"He now has no HIV detectable in his body."

HIV, which cripples a person's immune system, has killed more than 25 million people since it emerged in the 1980s.

Patients are frequently treated with daily doses of anti-retroviral drugs which have been credited with lengthening the lives of people with HIV.

Prof Harrich said if the Nullbasic protein worked in humans, it potentially would be a one-off therapy.

"You would still be infected with HIV, it's not a cure. But the virus would stay latent, it wouldn't wake up, so it wouldn't develop into AIDS," he said.

**WHO Warns Of Dengue's Spread, Says Progress Made Against NTDs In New Report**

"Dengue is the world's fastest-spreading tropical disease and represents a 'pandemic threat,' infecting an estimated 50 million people across all continents, the World Health Organization (WHO) said on Wednesday," Reuters reports. In a statement, the WHO said dengue "registered a 30-fold increase in disease incidence over the past 50 years," and the agency noted though malaria causes more deaths, its incidence is declining, the news service adds. Speaking at a news briefing marking the WHO's release of a report (.pdf) on neglected tropical diseases (NTDs), Raman Velayudhan, a WHO NTD specialist, said, "You have to bear in mind that [dengue] has no treatment and vaccines are still in the research stage," according to Reuters (Nebehay, 1/16).

In the publication, titled "Sustaining the drive to overcome the global impact of neglected tropical diseases," the "WHO reports unprecedented progress against 17 neglected tropical diseases, thanks to a new global strategy, a regular supply of quality assured, cost-effective medicines and support from global partners," a WHO press release states. "The publication charts progress in controlling, eliminating and eradicating these [NTDs]. Two are targeted for global eradication, dracunculiasis (guinea worm disease) in 2015 and yaws in 2020," the press release says, adding, "The report outlines six targets set for the elimination of five diseases in 2015 and a further 10 targets for nine diseases for 2020, either globally or in selected geographical areas" (1/16). Uniting to Combat NTDs, a group of organizations focused on
fighting NTDs, also released a report on Wednesday, titled "From Promises to Progress," to mark the first anniversary of the London Declaration, "which brought public and private partners together under the shared goal of controlling and eliminating 10 NTDs by 2020," a press release from the group states (1/16).

**Cuban Authorities Work To Contain Cholera Outbreak In Capital City**

"Cuban authorities are scrambling to contain a cholera outbreak that has sickened dozens of people in Havana, the capital city of 2.2 million residents and a popular tourism destination," Reuters reports (Frank, 1/15). The country's "second cholera outbreak in four months—after 130 years without the disease—has sickened more than 50 people and killed one in Havana, authorities and the family of the deceased said Tuesday," Agence France-Presse writes (Jara, 1/15). "The outbreak was detected on 6 January," BBC News reports, adding, "According to the health ministry, measures taken since then mean the disease is in its 'extinction phase'" (1/15). A statement from the health ministry released on Tuesday "said the latest outbreak appeared to be caused by a food vendor who had not followed proper sanitary procedures," CNN notes (Oppmann, 1/15). "Community clinics and family doctors are on high alert and giving out instructions to prevent the disease, transportation hubs have passengers sterilizing their shoes before leaving town, and eateries are being systematically inspected and sometimes closed, residents say," Reuters reports (1/15).

**Could probiotics help HIV patients?**

Antiretroviral (ARV) drugs are the first line therapy for patients with HIV; however, ARV-treated, HIV-infected individuals still have a higher mortality rate than uninfected individuals. During the course of infection, HIV patients develop inflammation that damages the walls of the intestines, known as the gut mucosa, allowing intestinal microbes to escape and enter the bloodstream to cause a life-threatening systemic infection. The health of the gut mucosa is significantly influenced by the complement of bacteria in the gut and there is mounting evidence that probiotic supplements benefit patients intestinal disorders, such as irritable bowel syndrome, *C. difficile* infection, and inflammatory bowel disease.

In this issue of the Journal of Clinical Investigation, researchers led by Jason Brenchley at the National Institute of Allergy and Infectious Disease, demonstrated that probiotic supplementation may also be beneficial for ARV-treated HIV patients. Brenchley and colleagues treated SIV-infected macaques (a model of human HIV-infection) with either ARV alone or ARV in combination with a mixture of probiotics. Macaques treated with probiotics had enhanced gastrointestinal immune function and decreased inflammation compared to macaques treated with ARV alone. In a companion article, Judith Aberg and colleagues at New York University School of Medicine discuss how these findings could benefit HIV patients.

View this article at: [http://www.jci.org/articles/view/66227?key=1cff041937d9040dfed7](http://www.jci.org/articles/view/66227?key=1cff041937d9040dfed7)

**New study finds malaria, typhoid—not Ebola—biggest health threat for travelers to tropics**

DEERFIELD, IL. (January 16, 2013)—Feeling feverish after a visit to the tropics? It may not just be a bout with this year's flu. If you're a Western traveler, malaria and typhoid fever should top the list of diseases to discuss with your doctor when you return, especially following travel to Western Africa or India.

In a study of more than 80,000 returned travelers who sought medical care for illnesses, around 3,000 (4 percent) were affected by malaria, typhoid fever and other potentially life-threatening tropical diseases. Many would be surprised to know that not a single traveler contracted the highly contagious and lethal Ebola virus, which is typically one of the tropical diseases most feared by travelers. The findings were published online today in the American Journal of Tropical Medicine and Hygiene.

"While diagnosis and treatment of malaria and typhoid fever and many other tropical diseases have improved greatly over the years, people still can die from them if they are not treated quickly after their symptoms begin," said University of Oslo researcher Mogens Jensenius, MD, PhD, who with his colleagues analyzed 15 years of data entered into the GeoSentinel surveillance network database. "Doctors and nurses in Western countries need to be vigilant in considering these potentially life-threatening tropical infections in recently-returned travelers with fevers, and identify and treat them quickly."

Jensenius and fellow researchers at the U.S. Centers for Disease Control and Prevention (CDC), and several other universities throughout Europe, Israel, Australia and the United States looked at data from 82,825 ill travelers from Europe, North America, Israel, Japan, Australia and New Zealand. The travelers
sought care at clinics associated with GeoSentinel from June 1996 through August 2011 with illnesses contracted during travel to the tropics.

They found that 3,655 patients—4.4 percent of the total—had one of 13 life-threatening diseases. There were a total of 13 deaths, 10 of which occurred in patients with malaria.

Of the diseases, the researchers found:

- Malaria—caused by a parasite spread by the bite of infected female mosquitoes—was by far the most common condition, making up 76.9 percent of the diagnoses
- Fevers such as typhoid fever—a potentially life-threatening bacterial infection contracted from contaminated food and water in areas with poor sanitation—were found in 18.1 percent of the patients
- Leptospirosis, the rare bacterial infection, which is usually caused by exposure to contaminated water, was diagnosed in 2.4 percent of the ill travelers

Malaria was mostly seen in travelers to West Africa, while most cases of typhoid fever were contracted by visitors to the Indian subcontinent. There were no cases of Ebola, Lassa fever or yellow fever among the more than 82,000 ill Western travelers included in the study, according to Jensenius and his fellow researchers.

"We were quite surprised that these much-feared viral infectious diseases were completely absent," said Jensenius, who is also an infectious disease physician at Oslo University Hospital. "People talk about them all the time, but our paper suggests that these are still very, very rare among travelers."

European clinics reported more than half of all of the life-threatening diagnoses. Jensenius said this may reflect the fact that most European (as well as New Zealand and Australian) GeoSentinel sites are located in hospitals whereas sites in the United States and Canada more often are travelers' clinics. "In many of the North American GeoSentinel sites, they are more focused on pre-travel care," he noted, "and don't see as many patients post-travel as we do in Europe."

Every year, an estimated 50 million Western travelers visit tropical countries in Central and South America, Africa, Oceania and Asia, and their numbers are expected to grow, according to the World Tourism Organization (UNWTO). They may be tourists, adventure or eco-travelers on holiday or those traveling for business. But the group also includes an increasing number of immigrants returning to their home countries to visit friends and relatives.

"While tropical illnesses are rare in the Western world, these findings remind us that infectious disease pays no attention to geographic borders and affects the world at large," said David H. Walker, MD, president of the American Society of Tropical Medicine and Hygiene and chair of the department of pathology at the University of Texas Medical Branch in Galveston. "Our membership includes an exceptional cadre of skilled physician-scientists who are civilian, military and governmental clinical experts in travelers' health and diagnosing and treating tropical infection and disease. It is noteworthy that three of the leading life-threatening diseases are neglected rickettsioses, scrub typhus, murine typhus, and spotted fever rickettsioses." (For a list of physicians who specialize in Tropical Medicine, Medical Parasitology and Travelers' Health, go to: [http://www.astmh.org/source/ClinicalDirectory/](http://www.astmh.org/source/ClinicalDirectory/))

Each year, thousands of ill travelers seek health care at one of the 57 clinics associated with GeoSentinel around the world when they return from their visits. Their anonymous diagnoses are uploaded to GeoSentinel's database to track disease trends among travelers. The GeoSentinel network was initiated in 1995 by the International Society of Travel Medicine (ISTM), and is funded by ISTM and the U.S. Centers for Disease Control and Prevention to track travel-related illnesses and deaths.

Researchers have published more than 20 studies using GeoSentinel data, but the new study focuses only on tropical travel and "the life-threatening conditions that we as physicians need to identify rapidly," Jensenius said.

**Travel Advice for Returning Immigrants and Western Travelers**

Many of the malaria cases seen in the study were in immigrants returning to their countries of origin to visit friends and relatives, the researchers discovered. Jensenius said these travelers may have battled malaria when they once lived in the tropics, and "have this misconception that they are immune to the disease."

"When they go back from Europe 10 years later, they believe they don't need the protection of a prophylaxis," he said. "But that's wrong." Similar misconceptions might occur among returning immigrants to the Indian subcontinent, who believe they have immunity against typhoid fever.
The researchers advise all visitors to tropical regions to seek pre-travel advice on vaccinations and medications required for the countries they plan to visit, and while traveling take precautions to prevent insect bites, and drink bottled water.

Travelers who become ill with fever or flu-like illness while traveling or soon after returning home from high-risk areas should seek immediate medical attention and share their travel history with their physician, Jensensius cautioned. "Nearly all the diseases identified in our paper presented with a fever and an incubation period of just a couple of weeks."

**Immunology research sheds new light on cell function, response**

MANHATTAN, Kan.—A Kansas State University-led study has uncovered new information that helps scientists better understand the complex workings of cells in the innate immune system. The findings may also lead to new avenues in disease control and prevention.

Philip Hardwidge, associate professor of diagnostic medicine and pathobiology, was the study's principal investigator. He and colleagues looked at the relationship between a bacterial protein and the innate immune system—a system of defensive cells that responds rapidly to an infection in a nonspecific manner.

Among their findings, the researchers characterized a new protein that affects how cells in the innate immune system function and protect humans against invading bacteria such as *E. coli* O157:H7. The study, "NleB, a Bacterial Effector with Glycosyltransferase Activity, Targets GAPDH Function to Inhibit NF-kappaB Activation," was published in the most recent issue of the scientific journal *Cell Host and Microbe*. The National Institutes of Health's National Institute of Allergy and Infectious Diseases funded the study.

Hardwidge conducted the study with lead author Xiaofei Gao, a doctoral student at the University of Kansas Medical Center and now employed as a postdoctoral fellow at the Whitehead Institute; and with Thanh Pham and Leigh Ann Feuerbacher, postdoctoral research fellows in diagnostic medicine and pathobiology at Kansas State University. Colleagues at the University of Kansas Medical Center; the Institute of Infectiology in Muenster, Germany; and the Stowers Institute for Medical Research also contributed to the study.

The research team studied a bacterium that infects mice, named *Citrobacter rodentium*. The bacterium is similar to *E. coli* O157:H7, which causes diarrheal illness in humans. Both bacteria use the protein NleB to inhibit the innate immune system from fighting the bacteria.

"NleB is very important to the ability to cause disease," Hardwidge said. "Epidemiological and functional studies on *E. coli* and *C. rodentium* have shown that the presence of the NleB protein is associated with the ability of *E. coli* and *C. rodentium* to cause severe disease in humans and mice, respectively. But how the NleB protein did this was unknown."

According to Hardwidge, once bacteria such as *C. rodentium* and *E. coli* enter the body, the pathogens use a needle-like secretion apparatus to inject bacterial proteins into intestinal cells. Some of these proteins prevent the innate immune system from fighting the bacterium. One of these injected proteins is NleB.

Hardwidge and colleagues observed that the NleB protein binds with a protein in human cells named GAPDH. NleB modifies the GAPDH protein with a specific sugar molecule and prevents it from participating in a complex biochemical pathway that ultimately allows the innate immune system to respond efficiently to pathogens.

"The function of GAPDH in this pathway was less clear before we did these experiments," Hardwidge said. "GAPDH has well-known functions in the metabolism, but we observed that it also participates in how a cell responds to an infecting bacterium. We're very interested in the fact that this metabolic enzyme has apparently evolved also to be an important part of the innate immune system."

Hardwidge said that *E. coli* and *C. rodentium* using the NleB protein to target GAPDH and inhibit innate immunity is also an interesting finding, which will be characterized in greater detail in continuing studies.

With a more advanced understanding about how the innate immune system responds biochemically to invading bacteria—and how those bacteria suppress the response—scientists may be able to advance research and therapeutic drug development in other diseases, Hardwidge said. For example, cancers, Crohn's disease and Rheumatoid arthritis all are tied to overactive inflammation. In some cases, the same pathway in which GAPDH participates regulates the inflammation.
"The cell is so complicated, it's amazing that it even works at all, especially when you consider that it is three-dimensional and compartmentalized," Hardwidge said. "We have a general understanding about this important pathway that triggers a defensive response. But when you get into the details of how this pathway is regulated, we’re still learning and understanding what exactly is going on. Now, low and behold, there is a new protein involved."

**Mindfulness meditation may relieve chronic inflammation**

MADISON — People suffering from chronic inflammatory conditions, such as rheumatoid arthritis, inflammatory bowel disease and asthma — in which psychological stress plays a major role — may benefit from mindfulness meditation techniques, according to a study by University of Wisconsin–Madison neuroscientists with the Center for Investigating Healthy Minds at the Waisman Center.

Mindfulness-based stress reduction, originally designed for patients with chronic pain, consists of continuously focusing attention on the breath, bodily sensations and mental content while seated, walking or practicing yoga.

While interest in meditation as a means of reducing stress has grown over the years, there has been little evidence to support benefits specific to mindfulness meditation practice. This was the first study designed to control for other therapeutic mechanisms, such as supportive social interaction, expert instruction, or learning new skills.

A class in stress reduction can be beneficial in many ways, some of which have little to do with mindfulness, according to Melissa Rosenkranz, assistant scientist at the center and lead author on the paper, which was published recently in the journal *Brain, Behavior and Immunity*. For example, learning to manage stress by engaging in regular physical activity may be therapeutic.

"We wanted to develop an intervention that was meant to produce positive change and compare the mindfulness approach to an intervention that was structurally equivalent," Rosenkranz says.

The study compared two methods of reducing stress: a mindfulness meditation-based approach, and a program designed to enhance health in ways unrelated to mindfulness.

The comparison group participated in the Health Enhancement Program, which consisted of nutritional education; physical activity, such as walking; balance, agility and core strengthening; and music therapy. The content of the program was meant to match aspects of the mindfulness instruction in some way.

For example, physical exercise was meant to match walking meditation, without the mindfulness component.

Both groups had the same amount of training, the same level of expertise in the instructors, and the same amount of home practice required by participants.

"In this setting, we could see if there were changes that we could detect that were specific to mindfulness," Rosenkranz explains.

Using a tool called the Trier Social Stress Test to induce psychological stress, and a capsaicin cream to produce inflammation on the skin, immune and endocrine measures were collected before and after training in the two methods. While both techniques were proven effective in reducing stress, the mindfulness-based stress reduction approach was more effective at reducing stress-induced inflammation.

The results show that behavioral interventions designed to reduce emotional reactivity are beneficial to people suffering from chronic inflammatory conditions. The study also suggests that mindfulness techniques may be more effective in relieving inflammatory symptoms than other activities that promote well-being.

Rosenkranz emphasizes that the mindfulness-based approach is not a magic bullet. "This is not a cure-all, but our study does show that there are specific ways that mindfulness can be beneficial, and that there are specific people who may be more likely to benefit from this approach than other interventions."

Significant portions of the population do not benefit from available pharmaceutical treatment options, for example. Some of these patients suffer from negative side effects of the drugs, or simply do not respond to the standard-of-care for treatment of the disorder.

"The mindfulness-based approach to stress reduction may offer a lower-cost alternative or complement to standard treatment, and it can be practiced easily by patients in their own homes, whenever they need," Rosenkranz says.
Computer Methods Reveal How Hospital-Acquired Bacteria Spread

Jan. 16, 2013 — The new methods are used to develop models of the evolution of bacteria and viruses. "Essential for the evolution of the bacteria that cause hospital-acquired infections is the horizontal gene transfer. It means that several different cell processes transfer genes between the lineages of the same and different species so that the bacterium becomes resistant to antibiotics and the virulence factor rapidly spreads in the population," explains group leader, Professor Jukka Corander. Corander's group is part of the Centre of Excellence in Computational Inference Research.

This so-called recombination of bacteria makes it much more complicated to carry out evolution analyses. To facilitate such analyses, Corander's group in cooperation with researchers from Harvard University and the Wellcome Trust Sanger Institute has developed a number of methods based on smart randomised algorithms. These methods facilitate efficient and reliable analyses of extensive genomic data. With the current, most commonly used computational methods this work would take several months or even several years.

Two of the group's methods have recently been applied by an international study. This study demonstrated that more than half of the genetic variation of the MRSA bacteria (i.e. methicillin-resistant strains of Staphylococcus aureus) is caused by horizontal genomic transfer. This shows that the evolutionary analyses of the strains of bacteria are necessary when investigating the spread of bacteria in a host population. This horizontal variation significantly distorts the results received from normal evolutionary analyses.

"On the basis of the results from these analyses, i.e. the evolutionary variation, we're able to estimate when a certain strain of the MRSA bacterium has entered a country and started to spread to hospitals. This is the first time we have been able to prove that the interplay between the horizontal genomic variation and the mutational genomic variation may vary significantly across geographical locations and even between individual hospitals," Corander says. According to Corander, these insights open up new opportunities for in-depth studies on the spread and variation of MRSA and related causalities.

In another recently published study, Corander's group investigated the origin and evolution of the Enterococcus faecium bacterium that has adapted to survive in hospital environments. By using its analysis methods, the group found out that the forms of the bacteria originate from several independent sources, which is contrary to previous knowledge. In the nuclear genome of hospital strains of E. faecium, fewer signs of horizontal transfer were found than expected. This discovery led to a hypothesis that strains of bacteria that have adapted to survive in hospital environments may become either genetically or ecologically more isolated after horizontal transfer.

MRSA is a globally spread bacterium that is especially troublesome in hospitals. It is resistant to most antibiotics and annually causes the death of tens of thousands of people in the US, for instance. According to cautious estimates, the annual costs incurred by MRSA infections amount to several billion US dollars. In recent years, the E. faecium bacterium has become one of the major causes of hospital-acquired infections and its antibiotic-resistant strains have caused severe hospital epidemics worldwide.

Journal References:

New warnings over a rise in counterfeit condoms
By Greg Dawson

The government's health regulator has warned there are a rising number of counterfeit condoms being smuggled into the UK.

The Medicines and Healthcare products Regulation Agency (MHRA) claims millions have been illegally imported in the last 18 months.

Family planning experts say the bogus condoms don't provide protection against STIs or pregnancy.

Tests carried out on many of the fakes show they have a high burst rate.

Senior investigator Danny Lee-Frost said: "These products are made in the Far East for pennies and then sold over here for pounds.

"They will cut corners. They will cut costs. They will use cheaper ingredients and materials."

He says the condoms are mainly being found on sale in corner shops, newsagents and market stalls.
He said: "It’s vital that people buy condoms from well-known reputable retailers and pharmacies."

In August 2012 £1.5m worth of counterfeit condoms were seized at Heathrow Airport. A similar haul was discovered in Yorkshire.

Trading Standards say they are also regularly intercepting them across the country.

Counterfeiters have managed to copy major brands like Durex to convince people. A sample of fakes we were shown fooled Jay Dhadwa, 25, and 24 year-old Ricky Dixon.

Jay said: "I can't believe they aren't the real deal. They look and feel exactly like real ones. They've got the expiry date on the back too and the kite mark. It's impossible to tell."

Danny Lee-Frost admitted: "They certainly look the part. Many people would think it's the proper article."

He says the best way to avoid being caught out is to make sure you buy condoms from reliable places. "If you're not buying it from a reputable source, it's odds on that it is counterfeit and you shouldn't go anywhere near it."

**Sniffer dogs**

The MHRA has now employed the help of the UK’s first sniffer dogs trained to try to detect counterfeit condoms.

The dogs might be able to tell the difference but authorities are worried many of the counterfeits are difficult to detect because they look so similar to the real thing.

Paul Maddox is responsible for the dogs' training and said: "I was really surprised when I found out about the problem. I've heard about counterfeit medicines but I never thought condoms would ever be an issue."

"When we've trained the dogs up we managed to find a chink in the counterfeiters' armour and we've exploited that. That's why the dogs have been successful."

**Howard Stern Producer on HIV, Lifebeat, and Launching “The Arches of Hope”**

*Advocate*, (01.16.2013) Diane Anderson

Gary Dell’Abate, president of the HIV-advocacy organization Lifebeat, announced the installation of an interactive artwork, “The Arches of Hope,” in New York City. The artwork is part of a national campaign to increase HIV/AIDS awareness among young people and bring about an HIV-free generation. Antonio Pio Saracino designed “The Arches of Hope,” which was the idea of Patrick Duffy, creative director of gay-oriented hotel The Out NYC.

The awareness campaign kicked off with a week-long celebration that will culminate in a January 17 reception at The Out NYC. During the week preceding the reception, Lifebeat asked people across the country to tweet “messages of hope for an HIV-free generation” using the hashtag #Arches of Hope. Messages were displayed on JumboTron screens in Times Square and on digital tickertape embedded in the interactive art installation. These Twitter messages were also shared across 12 social networking sites.

Salt-N-Pepa’s Sandra “Pepa” Denton, long-time safe sex advocate, participated in the reception. Unveiling of “The Arches of Hope” is timed to coincide with President Obama’s inauguration.

Dell’Abate—also known as “Baba Booey,” the producer of “The Howard Stern Show”—became an HIV/AIDS activist after his brother’s death from AIDS. Dell’Abate stated that Lifebeat launched the awareness campaign because young people have become “cavalier” about unprotected sex after the development of effective HIV treatment.

**Schumer, Higgins Want Feds to Review Buffalo VA Following Potential HIV, Hepatitis Exposure**

*The Republic (Columbus)*, (01.16.2013) The Associated Press

On January 15, Sen. Charles Schumer (D-N.Y.) and Rep. Brian Higgins (D-N.Y.) issued separate requests to the Department of Veterans Affairs’ (VA) Inspector General for an independent review of the Buffalo VA Medical Center. The motivation for this inquiry comes from reports that more than 700 patients may have been exposed to HIV, hepatitis B, or hepatitis C within the past two years through the use of multi-dose insulin pens on more than one patient. Medical center officials say that needles were changed with each use, but the risk of contamination remained for the patients involved. Both Schumer and Higgins question how those involved let this practice continue undetected from October 2010 to November 2012, and why the VA took two months to contact those who may have been affected. Patients who may have been affected are being advised to get tested.
Mount Sinai researchers discover how the flu virus tells time
Discovery provides new targets for antiviral drugs and vaccine designs

Scientists have discovered that the flu virus can essentially tell time, thereby giving scientists the ability to reset the virus' clock and combat it in more effective ways. According to researchers at the Icahn School of Medicine at Mount Sinai, the flu knows how much time it has to multiply, infect other cells, and spread to another human being. If it leaves a cell too soon, the virus is too weak. If it leaves too late, the immune system has time to kill the virus.

The finding provides a novel design platform for the flu vaccine and could lead to new antiviral drugs that make this viral clock dysfunctional. The research, led by Benjamin tenOever, PhD, Fishberg Professor of Microbiology at Mount Sinai, is published in the January 17th issue of Cell Reports.

With only ten major components, the virus needs to steal most of its resources from the human cell in order to multiply. During this process, the virus often trips various "alarms" that equate to our immune system detecting, and then killing the virus. Dr. tenOever hypothesized that the virus must have a mechanism in place to keep track of how much time it has to steal these resources before the immune system springs into action. If the virus moves too fast, it will not have time to multiply. If it moves too slowly it will be stopped by the immune response. Dr. tenOever and his team wanted to find out how the virus knows exactly how much time it needs to multiply and move on.

"We knew that the virus has about eight hours in a cell to create enough copies of itself to continue spreading before the cell's antiviral alarm would be set off," said Dr. tenOever. "On a broader level, the virus needs two days of continuous activity to infect enough cells to permit spread to another human being. We wanted to tap into the flu's internal clock and find a way to dismantle it to prevent the spread of the virus."

Dr. tenOever and his team examined the processes that control the timing of infection. This research led to the discovery that, by relying on a quirk in our cell biology, the virus slowly accumulates one particular protein that it needs to exit the cell and subsequently spread to other cells, and eventually other humans—just in time before the immune system is activated.

Armed with this knowledge, Dr. tenOever and his team manipulated this timer by making the virus acquire this protein too fast, which caused flu to exit the cell too quickly and not have time to make more viruses. The next step was to manipulate the process to make flu acquire this protein too slowly, giving the immune system time to launch a response before the virus could escape, thereby killing the virus and preventing infection. Dr. tenOever hopes this discovery will lead to new antiviral drugs that target the virus's internal clock and that it will provide a new design platform for the flu vaccine. Currently, individuals have the option to receive a shot, which delivers dead virus through a needle, or a nasal spray, which contains live but weakened flu virus. Although the nasal spray vaccine is believed to be more effective than the shot, it is only FDA approved for individuals between the ages of 2-49. With data from the Cell Reports study, scientists will be able to develop a new type of spray vaccine that is composed of a virus with a "defective clock". This new option for protecting against flu may prove safer for the very old and very young who are unable to receive the current spray vaccine.
**Sniffing immune cells**

Research at IST Austria shows how immune cells navigate through the skin by sensing graded patterns of immobilized directional cues

Immune cells constantly patrol our body to check for foreign invaders, such as bacteria or viruses. To do so they leave the blood stream, actively crawl through tissues and finally re-enter the circulation via lymphatic vessels. Research from the laboratory of Michael Sixt elucidates how the cells are guided through tissues like the skin. It is thought that cells either sense their environment by 'touching' or 'smelling': They adhere to structural molecules like connective tissue proteins using adhesion receptors. Or they 'smell' soluble signal molecules with specialized surface receptors. Especially solutes are thought to act as directional cues as they tend to be more concentrated closer to the production source. Like one can find a flower by following its scent, cells are able to follow such soluble gradients. Both principles, touching and smelling, have been demonstrated to work in cell culture experiments. But how cell guidance functions in real tissues is still not known.

According to the new study, immune cells in mouse skin use a mixed strategy. They follow gradients of guidance cues, which are not soluble but immobilized to sugar molecules in the connective tissue. In their newly published work, the scientists around Michael Sixt visualized both the immune cells, in this case dendritic cells, and the cue, the chemokine CCL21, and recorded movies of how the cells navigate through living tissues. The researchers found that the chemokine is exclusively produced by the lymphatic vessel. From there it distributes into the surrounding tissue, forming a concentration gradient. In collaboration with Robert Hauschild and Tobias Bollenbach, two physicists at IST Austria, detailed quantitative maps of the chemokine distribution were drawn and compared with the migratory routes of the cells. Observation and quantitative prediction matched well: a cell can find the next lymphatic vessel by comparing the concentration of chemokine across its surface and then crawling towards the higher concentration. For this to work the cell only needs to be of a certain size because the gradients are noisy. A small cell would easily get trapped on a local concentration peak as it cannot "see" that there is an even higher peak nearby. To prove their concept, the scientists outcompeted the chemokine gradients in the tissue by applying excess chemokine from the outside. They found that this confuses the cells on their way to the lymphatic vessel. When they released the anchoring of the chemokine to the tissue, cells also got confused, demonstrating that the gradients are not soluble but bound to the tissue.

Michael Sixt points out: "This is the first time someone could directly visualize and quantify a chemokine gradient, and show how these gradients guide migratory cells. The finding that the guidance cue is anchored to the tissue makes a lot of sense: if it would be soluble, even a slight massage of the skin would likely cause fluid shifts and destroy the gradient. In contrast, an immobilized gradient is a permanent and robust infrastructure and rather insensitive to the fluid turbulences occurring in most tissues. It is important to understand how immune cells move and navigate. Only then can we think about strategies to alter their behavior".

For more see [http://ist.ac.at/research/research-groups/sixt-group/](http://ist.ac.at/research/research-groups/sixt-group/).
How Cells Know When It’s Time to Eat Themselves
Jan. 17, 2013 — Researchers at the University of California, San Diego School of Medicine have identified a molecular mechanism regulating autophagy, a fundamental stress response used by cells to help ensure their survival in adverse conditions.

The findings are published online in the January 17 issue of Cell.

Senior author Kun-Liang Guan, PhD, a professor of pharmacology at UC San Diego Moores Cancer Center, and colleagues report that an enzyme called AMPK, typically involved in sensing and modulating energy use in cells, also regulates autophagic enzymes.

Autophagy, which derives from the Greek words for "self" and "eat," is triggered to protect cells when times are tough, such as when cells are starved for nutrients, infected or suffering from damaged organelles, such as ribosomes and mitochondria. Much like the human body in freezing conditions will reduce operations in extremities to preserve core temperatures and organ functions, cellular autophagy involves the degradation and synthesis of some internal cellular elements to ensure survival of the whole.

The scientists found that AMPK regulates different complexes of an enzyme class called Vps34 kinase in different ways. Some Vps34 enzymes are involved in normal cellular vesicle trafficking—the vital movement of molecules inside a cell. Other Vps34 complexes are involved in autophagy. Guan and colleagues say AMPK inhibits some non-autophagy enzymes, but activates autophagous ones.

The study more fully illuminates a process essential to healthy cell function and survival. "Autophagy is an important way for cells to clear damaged parts that could be harmful to them and to digest parts for nutrients when cells are experiencing starvation conditions," Guan said.

More broadly, he noted that "defects in autophagy have been associated with human disease, such as cancer and neurodegenerative disorders." Failure of normal autophagy has also been associated with accumulated cell damage and aging.

Journal Reference:

GI Tract Bacteria May Protect Against Autoimmune Disease
Jan. 17, 2013 — Early life exposure to normal bacteria of the GI tract (gut microbes) protects against autoimmune disease in mice, according to research published on-line in the January 17 edition of Science. The study may also have uncovered reasons why females are at greater risk of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and lupus compared to males.

Researchers from The Hospital for Sick Children (SickKids) found that when female mice at high risk of autoimmune (type 1) diabetes were exposed to normal gut bacteria from adult male mice, they were strongly protected against the disease. In this type of mouse strain, more than 85% of females develop autoimmune diabetes due to strong genetic risk factors. In contrast, only 25% of the females developed the disease after they were given normal male gut microbes early in life.

"Our findings suggest potential strategies for using normal gut bacteria to block progression of insulin-dependent diabetes in kids who have high genetic risk," says principal investigator Dr. Jayne Danska. She is Senior Scientist in Genetics & Genome Biology at SickKids and Professor in the Departments of Immunology and Medical Biophysics at the University of Toronto.

A second unexpected finding was the effects of the gut microbe treatments on sex hormones. "We were surprised to see that when young female mice received normal gut microbes from adult males, their testosterone levels rose. We then showed that this hormone was essential for the gut microbe treatment to protect against the disease. It was completely unexpected to find that the sex of an animal determines
aspects of their gut microbiome composition, that these microbes affect sex hormone levels, and that the hormones in turn regulate an immune-mediated disease," says Dr. Danska.

She adds, "We don't know yet how transfer of male gut microbes into females increases their testosterone, or how this process protects against autoimmunity. This study opens up a new research arena to explore the clinical potential of altering the gut microbiome community to prevent or treat immune-mediated diseases."

**The hygiene hypothesis**
The findings support the 'hygiene hypothesis,' which suggests that the dramatic increase in autoimmune and inflammatory diseases over the past 50 years results from changes in our exposure to microbes. Gut microbes are essential for normal development and training of the immune system, for extracting nutrients from our food, and for protecting us from some infectious diseases. "Our gut microbial community is an essential part of ourselves—bacterial cells outnumber human cells in our bodies by more than ten to one—and we live with them as partners," explains Dr. Danska.

Previous research has shown that children living on farms, exposed to a denser and more complex microbial environment, have fewer immune-mediated diseases compared to their village or urban-dwelling peers.

This new publication is the first to identify a difference between normal gut microbes in males and females reared in identical conditions, and to show that transfer of male-sourced gut bacteria protects against autoimmune disease in females with high genetic risk.

"Our findings point to a direct relationship between normal gut microbe composition and prevention of autoimmune disease. From these discoveries we can move on to characterize the relationships between gut microbes, sex hormones, and ways to control unwanted immune responses," says Dr. Danska.

**Implications for diabetes and other autoimmune diseases**
The researchers' success in preventing type 1 diabetes from developing in high-risk mice suggests that similar approaches may be applicable in preventing and treating other immune diseases, particularly those showing a female sex bias, Dr. Danska says.

**Journal Reference:**

**Scientists Shed Light On the 'Dark Matter' of DNA**

Jan. 17, 2013 — In each cell, thousands of regulatory regions control which genes are active at any time. Scientists at the Research Institute of Molecular Pathology (IMP) in Vienna have developed a method that reliably detects these regions and measures their activity.

Information on the new technology was just published online in the journal *Science*.

Genome sequences store the information about an organism's development in the DNA's four-letter alphabet. Genes carry the instruction for proteins, which are the building blocks of our bodies. However, genes make up only a minority of the entire genome sequence—roughly two percent in humans. The remainder was once dismissed as "junk," mostly because its function remained elusive. "Dark matter" might be more appropriate, but gradually light is being shed on this part of the genome, too.

Far from being useless, the non-coding part of DNA contains so-called regulatory regions or enhancers that determine when and where each gene is expressed. This regulation ensures that each gene is only active in appropriate cell-types and tissues, e.g. hemoglobin in red blood cell precursors, digestive enzymes in the stomach, or ion channels in neurons. If gene regulation fails, cells express the wrong genes and acquire inappropriate functions such as the ability to divide and proliferate, leading to diseases such as cancer.

Despite the importance of gene regulatory regions, scientists have been limited in their ability to study them on a genome-wide scale. Their identification relied on indirect means, which were error prone and required tedious experiments for validating and quantifying enhancer activities.

Alexander Stark and his team at the IMP in Vienna now closed this gap with the development of a new technology called STARR-seq (self-transcribing active regulatory region sequencing), published online by *Science* this week. STARR-seq allows the direct identification of DNA sequences that function as enhancers and simultaneously measures their activity quantitatively in entire genomes.

Applying their technology to *Drosophila* cells, the IMP-scientists surprisingly find that the strongest enhancers reside in both regulatory genes that determine the respective cell-types as well as in broadly active "housekeeping" genes that are required for basic cell survival in most or all cells. In addition, they
find several enhancers for each active gene, which might provide redundancy to ensure robustness of gene regulation.

The new method combines advanced sequencing technology and highly specialized know-how in bio-computing. It is a powerful tool which, according to Alexander Stark, will prove immensely valuable in the future. "STARR-seq is like a magic microscope that lets us zoom in on the regulatory regions of DNA. It will be crucial to study gene regulation and how it is encoded in the genome—both during normal development and when it goes wrong in disease."

**Journal Reference:**
Arnold Cosmas D. Arnold, Daniel Gerlach, Christoph Stelzer, Łukasz M. Boryń, Martina Rath, Alexander Stark. **Genome-Wide Quantitative Enhancer Activity Maps Revealing Complex cis-Regulation of Transcription.** Science, January 17, 2013
DOI: 10.1126/science.1232542

**Fecal transplant more effective than antibiotics for bacterial infection: study**
By Samantha Kimmey
Thursday, January 17, 2013 10:08 EST
While many people might be more comfortable taking pills to fight off a dangerous infection, it turns out that there may be a more effective treatment: excrement.

A new study found that fecal transplants can be a dramatically more effective course of treatment than antibiotics in the case of at least one kind of bacterial infection, reported the Los Angeles Times. The study found that transplanting the feces of a healthy individual into someone with the infection *Clostridium difficile*, or CDI, which kills about 100,000 people annually, cured three times as many people as those who took just antibiotics.

In fact, the study ended early because the researchers decided it would be unethical to continue to provide some participants with only antibiotics, reported the New York Times. Scientists believe that the treatment works through the microbial diversity in healthy feces, as the normal balance of microbes may be diminished in those with CDI. They hope that, eventually, fecal transplants may help treat other health problems, such as irritable bowel syndrome and anorexia.

The leader of the study, Dr. Els van Nood from the University of Amsterdam Department of Internal Medicine, said that though they were hopeful, “we did not anticipate such a big difference.” But he also said that the treatment had a “gross factor,” especially with younger patients.

**European Commission Approves PREZISTA® (Darunavir) 800mg Tablet Once A Day Reducing The Number Of Pills Taken By People Living With HIV**
Article Date: 17 Jan 2013—9:00 PST

**Current ratings for:**
European Commission Approves PREZISTA® (Darunavir) 800mg Tablet Once A Day Reducing The Number Of Pills Taken By People Living With HIV

Janssen R&D Ireland has announced that the European Commission (EC) has approved a new PREZISTA(R) (darunavir) 800mg tablet allowing people living with HIV to take one darunavir tablet once a day. Darunavir is indicated in combination with other antiretrovirals for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced and treatment-naive patients with no darunavir resistance-associated mutations[1]. Darunavir is always taken in combination with ritonavir and other HIV medicines together with food. This new tablet strength has been developed to allow patients taking darunavir once daily to reduce the number of darunavir tablets by half.

The approval is based on study C176[2] which evaluated the 400 mg tablet formulation versus the 800 mg formulation. One hundred and twenty eight healthy volunteers, were included in this study and received treatment under fasting (n=83) or under fed conditions (n=45). The results of this study show that the rate and extent of absorption were similar between intake of a single 800 mg dose of darunavir formulated as one 800 mg tablet or two 400 mg tablets.[2]

“Strict adherence to treatment regimens is crucial to prevent virological failure and the development of drug resistance when treating HIV,” said Brian Woodfall, Vice President, Medical Affairs, Janssen EMEA. “This single 800 mg tablet formulation is a direct reflection of the ongoing commitment of Janssen to further develop treatment options for people living with HIV. With this approval we are providing an alternative solution and a reduced pill burden which should make it easier for patients to
manage their treatment on a day-by-day basis and keep their HIV at undetectable levels."

**Diospyrin Inactivates a Drug Target for Tuberculosis in New Way**

*News-Medical.net*, (01.18.2013)

Professor Tony Maxwell, a researcher at the John Innes Centre, reported that diospyrin, a compound from the South African toothbrush tree, is effective in treating drug-sensitive and drug-resistant TB. Maxwell stated that diospyrin binds to an enzyme known as DNA gyrase and inactivates the enzyme, which is essential for bacteria.

Traditional medicine has used the toothbrush tree's antibiotic properties to treat bronchitis, pleurisy, and STDs. People also use the tree's twigs as toothbrushes.

Most antibiotics come from natural sources like the soil bacteria Streptomyces, but naturally occurring compounds in plants are another potential source for new antibiotics. It may be possible to learn of other cures from the field of ethnombology, according to Maxwell, which underscores the importance of preserving biodiversity.

[Editor's Note: The full report, "The Naphthoquinone Diospyrin is an Inhibitor of DNA Gyrase with a Novel Mechanism of Action," was published in the Journal of Biological Chemistry and is available at www.jbc.org/cgi/doi/10.1074/jbc.M112.419669].

**WHO Reports Significant Decrease In Measles Deaths Over Past Decade But Warns Large Outbreaks In Certain Regions Threaten Progress**

"While the number of measles deaths around the world has significantly decreased over the past decade, large outbreaks in certain regions are jeopardizing progress, the United Nations health agency said [Thursday], adding that improved vaccination rates are critical to eliminate the disease," the *[U.N. News Centre]* reports. "Between 2000 and 2011, measles deaths dropped from 542,000 to 158,000 globally, representing a 71 percent decrease," the news service writes, adding, "New cases also dropped during the same period by 58 percent, according to new data" from the WHO (1/17).

"The highly contagious disease is a leading cause of death among young children around the world, especially the poor, malnourished and unvaccinated, it said," *[Reuters]* notes (Nebehay, 1/17). "Despite this global progress, some populations remain unprotected," according to a WHO press release, which adds, "An estimated 20 million children worldwide did not receive the first dose of vaccine in 2011" (1/17).

"More than half live in five countries: Democratic Republic of Congo (DRC), Ethiopia, India, Nigeria and Pakistan," Reuters notes (1/17).

**Cell: Protein folding via charge zippers**

Membrane proteins are the "molecular machines" in biological cell envelopes. They control diverse processes, such as the transport of molecules across the lipid membrane, signal transduction, and photosynthesis. Their shape, i.e. folding of the molecules, plays a decisive role in the formation of, e.g., pores in the cell membrane. In the *Cell* magazine, researchers of Karlsruhe Institute of Technology and the University of Cagliari are now reporting a novel charge zipper principle used by proteins to form functional units (DOI: 10.1016/j.cell.2012.12.017).

"It is fascinating to see the elegant basic principles that are used by nature to construct molecular assemblies," explains Anne Ulrich, Director of the KIT Institute for Biological Interfaces. "A charge zipper between the charged side chains is an entirely unexpected mechanism used by membrane proteins to neutralize their charges such that they can be immersed into hydrophobic cell membranes."

In the study published now, Ulrich and her team investigate the so-called Twin-arginine translocase (Tat) that is used in the cell membrane of bacteria as an export machinery for folded proteins. Several TatA subunits assemble as a pore that can adapt its diameter to the size of the cargo to be transported. "But how can such a pore be built up from TatA proteins? How can they reversibly form a huge hole in the membrane for a variety of molecules to pass through, but without causing leakage of the cell?" Ulrich formulates the questions studied.
To answer these questions, the researchers studied the molecular structure of TatA protein from the bacterium B. subtilis, which consists of a chain of 70 amino acids. The analysis showed that it folds into a rather rigid, rod-shaped helix that is followed by a flexible, extended stretch. Many amino acids in the helix and the adjacent stretch carry positive or negative charges. Surprisingly, the sequence of charges on the helix is complementary to those in the adjacent stretch of the protein. When the protein is folded up at the connection point like a pocket knife, positive and negative charges will always meet and attract each other. Hence, the protein links up both of its segments, similar to the interlocking teeth of a zipper.

"The clue is that this binding principle also works with the neighboring proteins," Ulrich says. Instead of folding up alone, every TatA protein also forms charge zippers with both of its neighbors. Computer simulations showed that this leads to stable and, at the same time, flexible connections between the adjacent molecules. In this way, any number of proteins can be linked together to form an uncharged ring, which thus lines the TatA pore in the hydrophobic membrane. This novel charge zipper principle does not only seem to play a role in protein transport, but also in the attack of certain antimicrobial peptides on bacteria, or in their formation of biofilms as a response to stress.

**Which nutritional factors help preserve muscle mass, strength and performance in seniors?**

January 18, 2013

New review by International Osteoporosis Foundation (IOF) Nutrition Working Group examines role of nutrition in sarcopenia, with focus on protein, vitamins D and B, and acid-base diet.

Sarcopenia, or the gradual loss of muscle mass, is a common consequence of ageing, and poses a significant risk factor for disability in older adults. As muscle strength plays an important role in the tendency to fall, sarcopenia leads to an increased risk of fractures and other injuries.

The International Osteoporosis Foundation (IOF) Nutrition Working Group has published a new review which identifies nutritional factors that contribute to loss of muscle mass, or conversely, are beneficial to the maintenance of muscle mass. The Group reviewed evidence from worldwide studies on the role of nutrition in sarcopenia, specifically looking at protein, acid–base balance, vitamin D/calcium, and other minor nutrients like B vitamins.

“The most obvious intervention against sarcopenia is exercise in the form of resistance training,” said Professor Jean-Philippe Bonjour, co-author and Professor of Medicine at the Service of Bone Diseases, University of Geneva. “However, adequate nutritional intake and an optimal dietary acid-base balance are also very important elements of any strategy to preserve muscle mass and strength during ageing.”

The review discusses and identifies the following important nutritional factors that have been shown to be beneficial to the maintenance of muscle mass and the treatment and prevention of sarcopenia:

- **Protein**: Protein intake plays an integral part in muscle health. The authors propose an intake of 1.0–1.2 g/kg of body weight per day as optimal for skeletal muscle and bone health in elderly people without severely impaired renal function.

- **Vitamin D**: As many studies indicate a role for vitamin D in the development and preservation of muscle mass and function, adequate vitamin D should be ensured through exposure to sunlight and/or supplementation if required. Vitamin D supplementation in seniors, and especially in institutionalized elderly, is recommended for optimal musculoskeletal health.

- **Avoiding dietary acid loads**: Excess intake of acid-producing nutrients (meat and cereal grains) in combination with low intake of alkalizing fruits and vegetables may have negative effects on musculoskeletal health. Modifying the diet to include more fruits and vegetables is likely to benefit both bones and muscles.

Emerging evidence also suggests that vitamin **B12** and/or folic acid play a role in improving muscle function and strength.

As well, the Review discusses non-nutritional interventions such as hormones, and calls for more studies to identify the potential of antioxidants and anti-inflammatory compounds in the prevention of sarcopenia.

Dr. Ambrish Mithal, co-author and Chair and Head of Endocrinology and Diabetes division at Medanta, New Delhi underlined the need for further research in the field. “Strategies to reduce the numbers of falls and fractures within our ageing populations must include measures to prevent sarcopenia. At present, the available evidence suggests that combining resistance training with optimal nutritional status has a synergistic affect in preventing and treating sarcopenia, “ said Mithal.
“We hope that further studies will shed light on other effective ways of preventing and treating this condition.”


Discovery of quadruple helix DNA could lead to cancer breakthrough

Scientists at the University of Cambridge reported Sunday that they have discovered quadruple helix DNA inside human cells by creating synthetic molecules that seek it out — raising the potential that future medicines may be able to pinpoint and shut down DNA replication within cancerous tumors.

Although the findings, published in the scientific journal Nature Chemistry, still leave a lot of unanswered questions about quadruple helix DNA, the work released Sunday is a breakthrough brought about by more than a decade of research.

Still, 60 years on from the discovery of DNA, scientists do not know why traditionally double helix structures loop back in on themselves sometimes during replication. They’ve known these structures exist in a laboratory setting, but the Cambridge findings are the first to pinpoint the formation of “quadruplexes” within living human cells.

Observing the structures was no easy feat, however. Scientists had to create synthetic bio-luminescent antibody proteins that seek out and bind to quadruplexes at various stages in cell division. The proteins were built in such a way that they glow more brightly during DNA replication.

Using those markers, researchers noticed that the proteins are able to “trap” quadruplexes and stabilize their production, potentially opening up a new avenue for cancer treatments.

“We are seeing links between trapping the quadruplexes with molecules and the ability to stop cells dividing, which is hugely exciting,” Professor Shankar Balasubramanian said in an advisory.

“The research indicates that quadruplexes are more likely to occur in genes of cells that are rapidly dividing, such as cancer cells,” he added. “For us, it strongly supports a new paradigm to be investigated – using these four-stranded structures as targets for personalized treatments in the future.”

Balasubramanian also warned that so little is known about quadruplexes that interfering with their production may not ultimately prove helpful. “One thought is that these quadruplex structures might be a bit of a nuisance during DNA replication – like knots or tangles that form,” he said.

“Did they evolve for a function?” Balasubramanian added. “It’s a philosophical question as to whether they are there by design or not – but they exist and nature has to deal with them. Maybe by targeting them we are contributing to the disruption they cause.”

Though much work is left to be done, the group that funded the study, Cancer Research UK, believes it could lead to a revolution in cancer therapies.

“This research further highlights the potential for exploiting these unusual DNA structures to beat cancer – the next part of this pipeline is to figure out how to target them in tumor cells,” Dr. Julie Sharp at Cancer Research UK said in an advisory. “It’s been sixty years since its structure was solved but work like this shows us that the story of DNA continues to twist and turn.”

U.S. Faces Drug Shortages in Treating Multidrug-Resistant TB

Chicago Tribune, (01.17.2013) David Beasley, Reuters

More than 80 percent of US health departments that treat multidrug-resistant tuberculosis (MDR TB) have difficulty obtaining treatment drugs. Based on the results of the National Tuberculosis Controllers Association’s 2010 survey, the difficulty is blamed on shortages, shipping delays, and a complicated new drug acquisition process.

Of the 33 health departments that responded to the survey, 26 had patients with MDR TB in the five years the survey covered and 21 of them had difficulty finding the second-line drugs needed. More than half of the 26 health departments that treated a drug-resistant strain of TB (81 percent) complained of difficulty finding drugs for the disease, and more than half said problems finding the proper drugs for MDR TB delayed patient treatment.

According to CDC statistics, the United States reported 10,258 TB cases in 2011, and 529 deaths from TB in 2009.

CDC noted that because only 54 percent of 61 health jurisdictions approached responded to the survey, the results might not accurately represent the national drug shortage problem.
Pre- and Probiotics Could Help HIV Patients, Suggests New Research

NutraIngredients.com, (01.18.2013) Nathan Gray

Researchers believe that supplementation with prebiotics and probiotics can help lower the risk of infection and inflammation for HIV patients taking antiretroviral drugs (ARVs). Jason Brenchley, of the US National Institute of Allergy and Infectious Disease, and others were aware that people treated with ARVs have a higher mortality rate than uninfected individuals, and that HIV infection causes gastrointestinal (GI) tract damage, microbial translocation, and immune activation. Based on the results of the research, the team suggested that pre- and probiotics could provide adjunctive therapy for HIV infection that is well tolerated and inexpensive.

Brenchley and colleagues treated macaques infected with simian immunodeficiency virus (SIV), a model of the human infection, with either ARVs alone or ARVs in combination with a symbiotic mixture of probiotics and prebiotics. Seven SIV-infected macaques received the symbiotic mixture of prebiotic inulin and a probiotic for 60 days. These macaques were found to have GI immune function and decreased inflammation compared to the control group. The subjects who received probiotics showed increased frequency and functionality of the GI tract. According to Brenchley and colleagues, symbiotic treatment resulted in increased frequency and functionality of GI tract APCs, enhanced reconstitution of and functionality of CD+ T cells, and reduced fibrosis of lymphoid follicles in the colon.

The study, “Probiotic/Prebiotic Supplementation of Antiretrovirals Improves Gastrointestinal Immunity in SIV-Infected Macaques,” was published online ahead of print in the Journal of Clinical Investigation (doi: 10.1172/JCI66227).

Immune system molecule with hidden talents

Fending off pathogens isn’t all antibodies do—they also help to convey messages between immune cells

22.01.2013

Dendritic cells, or DCs for short, perform a vital role for the immune system: They engulf pathogens, break them down into their component parts, and then display the pieces on their surface. This in turn signals other immune cells capable of recognizing these pieces to help kick-start their own default program for fighting off the invaders. In order to do their job, the DCs are dependent upon the support from a class of immune system molecules, which have never before been associated with dendritic cells: antibodies, best known for their role in vaccinations and diagnostics. Now, scientists at the Helmholtz Centre for Infection Research (HZI) and the Hannover Medical School (MHH) were able to show that antibodies are essential for dendritic cell maturation. The researchers’ findings have been published in the renowned scientific journal, Proceedings of the National Academy of Sciences (PNAS).

The human immune system is made up of some half a dozen different cell types that are all working in tandem. Team work is key since each cell type has a single unique job to perform, which is central to its ability to help defend the body against invaders and ward off disease. If one of these players is taken out of commission, the entire system is thrown out of whack.

This is precisely what Dr. Siegfried Weiss, head of HZI Department of Molecular Immunology, and his team of researchers observed when they looked at immunodeficient mice. “Our ‘RAG’ mice are lacking adaptive, or acquired immunity,” explains Weiss. “Basically, what this means is they are missing their antibody-producing B cells, among others.”

The dendritic cells belong to a different branch of the immune system—innate immunity, which, although far less pliable, is capable of a fairly rapid response. Which is why these cells should not be affected by a defect in acquired immunity. Still, the scientists noticed that DCs obtained from this particular murine strain were not working properly—their maturation process was faulty and instead of breaking down a pathogen into small pieces, they ended up destroying the pathogen altogether. "The
broken down pieces are called antigens. Presenting antigen is the dendritic cells’ main job,” explains Dr. Natalia Zietara, one of the scientists who worked on this study. “In fact, it is one of the most important points of intersection between the immune system’s innate and acquired branches. If it goes missing, any subsequent immune responses don’t ever get triggered,” adds her colleague, Dr. Marcin Lyszkiewicz. The cells’ normally highly precise interplay comes to a standstill and the acquired immune response becomes largely ineffective at a targeted defense against invading pathogens.

Starting with this observation, the immunologists were interested in identifying the cause behind the defect in the DCs’ function. To this end, they initially examined the dendritic cells’ surface markers for any potential deviation from the norm—albeit to no avail. Only once they began studying the transcriptome, the sum total of genes that are active in the cells that were being examined, the researchers found what it was they were looking for: The *activity of a select few genes, among them those encoding a family of receptors capable of binding antibodies, had been altered*. Through a series of subsequent experiments, the researchers were able to show that it was these very molecules, which stimulated dendritic cell maturation.

Antibodies, also called immunoglobulins, are proteins made by B cells. Their normal job is one of neutralizing toxins or viruses and labeling bacteria for destruction by other immune cells. The concept of vaccination is based on artificially prompting the organism to make antibodies, which, at a later stage—specifically, upon contact with the actual pathogen—helps the body ward off disease. Until now, this new role for antibodies was completely unknown. "We had no idea that B cells and dendritic cells use immunoglobulins to communicate with each other. It just goes to show you how complex the immune system really is and how we are a long way from truly grasping the full scope of its complexity," says Dr. Andreas Krueger, head of the Lymphocyte Biology research group at the MHH’s Institute of Immunology.

"In a way, you might say the researchers discovered a ‘hidden talent’ of antibodies.

**Original publication:**

**Evidence Mounts for Role of Mutated Genes in Development of Schizophrenia**

Jan. 22, 2013 — Johns Hopkins researchers have identified a rare gene mutation in a single family with a high rate of schizophrenia, adding to evidence that abnormal genes play a role in the development of the disease.

The researchers, in a report published in the journal *Molecular Psychiatry*, say that family members with the mutation in the gene Neuronal PAS domain protein 3 (NPAS3) appear at high risk of developing schizophrenia or another debilitating mental illnesses.

Normally functioning NPAS3 regulates the development of healthy neurons, especially in a region of the brain known as the hippocampus, which appears to be affected in schizophrenia. The Johns Hopkins researchers say they have evidence that the mutation found in the family may lead to abnormal activity of NPAS3, which has implications for brain development and function.

"Understanding the molecular and biological pathways of schizophrenia is a powerful way to advance the development of treatments that have fewer side effects and work better than the treatments now available," says study leader Frederick C. Nucifora Jr., Ph.D., D.O., M.H.S., an assistant professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. "We could definitely use better medicines."

Along with environmental factors, it is widely believed that many genes play some role in causing schizophrenia, a disease characterized by a variable combination of hallucinations, delusions, impaired cognition and a loss of drive and initiative. The disorder strikes an estimated seven in every 1,000 adults in the United States. While the Johns Hopkins experiments to date show that the NPAS3 mutation is rare, Nucifora says learning as much as possible about the biological role of NPAS3 will likely lead to a better understanding of how other genes contribute to the development of schizophrenia, even in the absence of the NPAS3 mutation.

For the study, Nucifora and his team used blood samples to search the DNA of 34 people with schizophrenia or a related condition, schizoaffective disorder. All 34 were members of families in which more than one person had the disease. The investigators were specifically looking for NPAS3 mutations—previous research suggested it could be involved in schizophrenia—and found it in one of the families.
By analyzing blood samples from that single family—two parents and four adult children—they found that the mother, who has schizophrenia, her two children with schizophrenia, and her child with major depression all had the mutant version of NPAS3. The NPAS3 gene provides instructions for the production of a protein that contains 933 amino acids. The altered gene led to a single flaw: a valine was switched to an isoleucine. Nucifora says it is not yet known how this single mutation affects the function or structure of NPAS3. A possible hint comes from the finding of other investigators that a change from valine to isoleucine in a protein known as APP is linked to Alzheimer's disease.

Nucifora cautions that, by itself, finding a mutation in a single family with mental illness doesn't establish the altered gene as the cause of the illness. Nucifora and his colleagues therefore set out to determine whether the mutation plays any role in the function of NPAS3, which serves as a master switch in cells, controlling the fate of many other genes involved in brain development and metabolism.

To do that, Nucifora and his colleagues grew neurons with either normal or mutated copies of NPAS3 in a dish, and found that the healthy neurons grew nice long extensions, a process that typically allows them to make good connections with other cells and is therefore critical for brain function. In neurons with the mutated gene, the extensions were abnormally short.

Other genes believed to be involved in mental illness also have been found to disrupt the growth of longer neuronal extensions. "We showed that the mutation does change the function of NPAS3, with potentially harmful effects in neurons," he says. "The next step is to figure out exactly how the genetic disruption alters neuronal function, and how these abnormal neurons influence the broader function of the brain."

Nucifora and his team are now working to create a mouse with the NPAS3 mutation. "If this mutation in NPAS3 is indeed important for human disease, then we should detect abnormalities in the neurons of mice with mutant NPAS3, and the mice should have impairments in learning, memory and social behavior," he says.

**Journal Reference:**

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**How Cells’ DNA Repair Machinery Can Destroy Viruses**

Jan. 21, 2013 — A team of researchers based at Johns Hopkins has decoded a system that makes certain types of immune cells impervious to HIV infection. The system’s two vital components are high levels of a molecule that becomes embedded in viral DNA like a code written in invisible ink, and an enzyme that, when it reads the code, switches from repairing the DNA to chopping it up into unusable pieces. The researchers, who report the find in the Jan. 21 early edition of the *Proceedings of the National Academy of Sciences*, say the discovery points toward a new approach to eradicating HIV from the body.

"For decades, we’ve seen conflicting reports on whether each of these components helped protect cells from viruses," says James Stivers, Ph.D., a professor of pharmacology and molecular sciences at the Johns Hopkins University School of Medicine's Institute for Basic Biomedical Sciences. "By plotting how much of each are found in different types of cells, as well as the cells’ response to HIV, we learned that both are needed to get the protective effect."

Researchers have long known that DNA’s code is made up of four building blocks called nucleotides, commonly abbreviated A, T, G, and C. Before a cell divides, DNA-copying enzymes string these nucleotides together based on existing templates, so that each of the new cells gets its own copy of the
genome. But because the T nucleotide, dTTP, is very similar to dUTP, a fifth nucleotide that doesn't belong in DNA, the copying enzyme sometimes mistakenly puts in a U where there should be a T.

To prevent this, says Stivers, most human cell types have an enzyme whose job is to break down dUTP, keeping its levels very low. Another quality control measure is the enzyme hUNG2, which snips stray Us out of newly copied DNA strands, leaving the resulting holes to be filled by a different repair enzyme. Certain immune cells called resting cells lack the first quality-control mechanism because, Stivers explains, "They're not replicating their DNA and dividing, so they couldn't care less if they have a lot of dUTP."

This is a critical piece of information, Stivers says, because when a retrovirus like HIV invades a cell, its first order of business is to make a DNA copy of its own genome, then insert that copy into the host cell's genome. If there are many dUTPs floating around in the cell, they will likely make their way into the new viral DNA, and, potentially, later be snipped out by hUNG2. The question, Stivers says, left open by the conflicting results of previous studies, was what effect, if any, this process has on HIV and other viruses.

To address this question, Amy Weil, a graduate student in Stivers' laboratory, measured dUTP levels and hUNG2 activity in a variety of human cells grown in the laboratory, then exposed them to HIV. Cells with high dUTP but little hUNG2 activity succumbed easily to the virus, which appeared to function just fine with a U-ridden genome. Similarly, cells with low dUTP levels but high hUNG2 activity were susceptible to HIV. For these cells, it seemed, hUNG2 would snip out the few stray Us, but the resulting holes would be repaired, leaving the viral DNA as good as new.

But in cells with both high dUTP and vigilant hUNG2, the repair process turned into a hack job, Stivers says, leaving the viral DNA so riddled with holes that it was beyond repair. "It's like dropping a nuclear bomb on the viral genome," he says.

By showing how dUTP and hUNG2 work together to protect resting cells from infection, Stivers says, the study identifies a new pathway that could restrict HIV infection in non-dividing cells. Current anti-retroviral drugs effectively suppress the virus, but, Stivers explains, they miss copies of the virus that hide out in non-dividing cells, and "the minute you stop taking anti-retrovirals, it starts replicating again." He suggests that drug strategies could be devised to target this pathway in affected cells, possibly lessening the pool of viruses hiding out in non-dividing cells. The principle could also be applied to other retroviruses, he says, since they, like HIV, all make DNA copies of their genomes as part of the infection process.

**UK experts: successful treatment is "as effective as consistent condom use" in reducing HIV transmission**

**Effectiveness depends on regular screening for viral load rebound and STIs**

Roger Pebody

Published: 23 January 2013

The British HIV Association (BHIVA) and the Department of Health's Expert Advisory Group on AIDS (EAGA) published this week a position statement on the use of HIV treatment by people with HIV to reduce the risk of transmission. For the first time, the document provides health professionals with a consensus statement, developed by UK experts, which can be used to guide discussions with individuals.

Clinicians, epidemiologists, policy experts and HIV-positive people contributed to the document. The key points are outlined below.

**As effective as condoms**

The statement notes that there is now conclusive randomised clinical trial evidence, from the HPTN 052 trial, to show that transmission of HIV through vaginal sex is significantly reduced when an HIV-positive person is taking effective antiretroviral therapy (ART). In this trial, early treatment reduced HIV transmission to an uninfected partner by 96%.

"The observed reduction in HIV transmission in a clinical trial setting demonstrates that successful ART use by the person who is HIV positive is as effective as consistent condom use in limiting viral transmission," it says.

The document includes some explanatory notes, which point out that there has never been a randomised controlled trial of the efficacy of condom use, compared to non-use. For that reason, there are no figures that can be directly compared. However, meta-analyses of observational studies of serodiscordant couples who maintained 100% condom use have found the strategy to be about 80% effective in reducing HIV infection.
Necessary conditions
The document states that the transmission risk during vaginal intercourse will be “extremely low”, provided certain conditions are fulfilled.

- There are no sexually transmitted infections in either partner. (The document clarifies requirements for STI screening, including following sexual relationships outside a primary partnership.)
- The person with HIV has had a sustained plasma viral load below 50 copies/ml for more than six months, including the most recent test.
- Viral load testing occurs every three to four months (i.e. more regularly than in standard clinical care).

In the document’s explanatory notes, it is explained that in HPTN 052 there was a single confirmed case of HIV transmission from a person on treatment. This individual had only recently begun ART and would not have met the UK position statement’s requirement for an undetectable viral load for at least six months.

The authors say that this justifies the use of the phrase “extremely low risk”. They clarify that this is not the same as “zero risk”. Moreover, with the data that are available, it is not possible to give accurate and meaningful figures for the risk of transmission during a single sexual act.

Anal intercourse
The published research was primarily done with heterosexual couples and is assumed to relate primarily to vaginal intercourse. Data are not available for anal intercourse, either between men, or between men and women. “However, it is expert opinion that an extremely low risk of transmission can also be anticipated for these practices, provided the same conditions stated above are met,” according to the statement.

Discussion with people with HIV
Healthcare professionals should discuss the impact of ART on sexual transmission with all people living with HIV. For people not currently on therapy, the possibility of starting treatment in order to reduce transmission risk should be discussed.

Limitations of ART
The position statement notes that no single prevention method can completely prevent HIV transmission. Moreover, antiretroviral treatment has no effect on other sexually transmitted infections, whereas condoms can prevent their spread.

Reference
British HIV Association (BHIVA) and Expert Advisory Group on AIDS (EAGA). Position statement on the use of antiretroviral therapy to reduce HIV transmission. 2013. (Free to download)

Mortality rates continue to fall in the Swiss HIV cohort
Michael Carter
Published: 25 January 2013
Mortality in people with HIV is continuing to fall, Swiss investigators report in HIV Medicine. The mortality rate in 2010 was a little over 1% and the majority of deaths were due to non-AIDS-related causes, many of which were associated with modifiable risk factors.

“Smoking and other modifiable cardiovascular risk factors, substance abuse, and HCV [hepatitis C virus] co-infection substantially influenced the distribution of causes of death,” write the authors.

They believe that more needs to be done to accurately record causes of death in people with HIV, especially as autopsies are performed in less than a fifth of cases.

The introduction of effective antiretroviral therapy in the mid 1990s was accompanied by a large fall in HIV-related mortality. However, mortality rates are still higher among people living with HIV compared to the general population. Understanding causes of death is of fundamental importance for HIV treatment, care and prevention.

Investigators from the Swiss HIV Cohort Study wanted to establish a better understanding of mortality rates and causes of death in the people in their care. They therefore designed a study involving everyone who received care between 1988 and 2010.

A total of 16,134 people were included in the analysis and 5023 (31%) died.

The investigators examined causes of death in three different time periods: the pre-treatment era (1988-1995); the early antiretroviral era (1996-2004); and the modern treatment era (2005-2010).

In the pre-treatment era, 78% of deaths were attributable to AIDS. This had fallen to 15% by 2005-2010. However, the proportion of deaths due to non-AIDS-related diseases increased from 17 to 71%.
AIDS-related mortality peaked in 1992, at a rate of 11 per 100 person-years. This fell to a rate of just 0.144 deaths per 100 person-years in 2006. Non-AIDS-related mortality also fell from a rate of 1.74 per 100 person-years in 1993 to 0.776 per 100 person-years in 2003. There was a simultaneous decline in mortality rates attributed to unknown causes, from 2.33 per 100 person-years in 1994 to 0.207 per 100 person-years in 2007.

In 2010, the mortality rates for AIDS, non-AIDS-related causes and unknown causes were 0.21, 0.86 and 0.26 per 100 person-years respectively.

The investigators then examined the characteristics of the people who died in the modern HIV treatment era.

A total of 459 people (5%) who received care between 2005 and 2009 died. This provided a mortality rate of 1.25 per 100 person-years. Median age at the time of death was 47 years; the median duration of diagnosed HIV infection was 14 years; 93% of those dying had experience of antiretroviral therapy; and the last median CD4 cell count was 251 cells/mm$^3$. Co-infection with viral hepatitis was highly prevalent. Some 45% of those dying were co-infected with hepatitis C and 11% were co-infected with hepatitis B.

The most frequent causes of death were non-AIDS-related cancers (19%); AIDS (16%); liver failure (15%); non-AIDS-related infections (9%); substance abuse (7%); suicide (6%); and heart attack (6%). Between 2005 and 2009, there were significant changes in the characteristics of the people who died. Their median age increased (45 vs 49 years, p < 0.001); their duration of infection with HIV was longer (13 vs 16 years, p = 0.002); their median CD4 cell counts were higher (257 vs 321 cells/mm$^3$, p = 0.005); and the proportion of people who had never taken HIV treatment fell (13 to 5%, p = 0.005).

Causes of death also changed significantly. The proportion dying from AIDS fell from 23 to 9%, whereas the percentage of deaths caused by non-AIDS-related cancers increased from 13 to 24%.

At the time of death, 40% of people in the study had a CD4 cell count below 200 cells/mm$^3$ and 20% had a CD4 cell count above 500 cells/mm$^3$.

Analysis of deaths among people with hepatitis C-co-infection showed that 32% were due to liver failure; 14% were caused by non-AIDS-related infections; 14% were attributed to substance abuse; and 8% were related to non-HIV-related cancers.

Overall, an increased risk of death was associated with injecting drug use, a lower CD4 cell count, smoking, diabetes, low body mass index, active hepatitis B or hepatitis C co-infection and interrupting HIV therapy.

“Many of these causes of death were associated with modifiable risk factors which require increased attention in primary and specialized care,” write the authors.

Only 19% of those dying in the most recent period were autopsied, and the investigators found discrepancies between the causes of death recorded using an HIV-specific coding system and those entered into national death registries. The investigators were concerned by these findings and stressed the importance of accurately establishing the probable cause of death.

Despite this, they were encouraged by their results, concluding: “Mortality in HIV-persons with access to care is continuously decreasing and causes of death are changing.”

Reference

Pitt team finds 'Achilles Heel' of key HIV replication protein
PITTSBURGH, Jan. 24, 2013 – Researchers at the University of Pittsburgh School of Medicine may have found an "Achilles heel" in a key HIV protein. In findings published online today in Chemistry and Biology, they showed that targeting this vulnerable spot could stop the virus from replicating, potentially thwarting HIV infection from progressing to full-blown AIDS.

Previous research demonstrated that a small HIV protein called Nef interacts with many other proteins in infected cells to help the virus multiply and hide from the immune system. The Pitt group developed a way to track Nef activity in high-throughput drug screening protocols by linking it to an enzyme called Hck, which is activated by Nef in HIV-infected cells, explained senior author Thomas E. Smithgall, Ph.D., William S. McEllroy Professor and Chair, Department of Microbiology and Molecular Genetics.

"We reasoned that agents that prevent Nef from its usual interactions with other proteins might be able to stop HIV from replicating and infecting other cells," Dr. Smithgall said. "For this study, we devised an automated screening procedure and tested nearly 250,000 compounds to find ones that could block Nef activity."
One of the compounds they discovered, called B9, seemed particularly potent at blocking Nef. In follow-up experiments, the research team examined how B9 accomplished this and found that it could prevent two Nef molecules from interacting to form dimers as effectively as a mutation in a critical area of the protein surface. The inability of Nef to dimerize consequently impairs its function in the viral replication process.

"This pocket where B9 binds to Nef and where Nef forms a dimer indicates it’s a hot spot, or Achilles heel, that could represent a new target for HIV drugs," Dr. Smithgall said. "Our test tube and cell culture experiments show that blocking this site brings HIV replication to a halt."

The team is working with medicinal chemists at the University of Pittsburgh Drug Discovery Institute (DDI) to find analogs of B9 that have therapeutic potential, and plan to assess them in animal models of HIV/AIDS.

**Gilead Petitions FDA Over Its Stribild AIDS Med**
By Ed Silverman // January 24th, 2013 // 8:47 am
In a challenge to FDA decision-making that will be closely watched by the pharmaceutical industry, Gilead Sciences has asked the agency to grant five years of exclusivity to its recently approved Stribild AIDS medication. The biotech filed a citizen’s petition arguing that exclusivity is warranted because its fixed-dose combination drug contains two so-called active moieties that have never before been approved in any other drug application.

An active moiety is the part of a drug that makes it work the way it does and the FDA has regularly interpreted the law to say that drugmakers do not receive 5-year exclusivity unless all ingredients are new active moieties. Currently, the FDA awards only three years of exclusivity if a fixed-dose combination drug contains a previously approved ingredient and if a drugmaker conducted new clinical studies that were essential to approval.

Stribild, a once-a-day pill that was approved last summer, contains four Gilead compounds, only two of which have new active moieties. So unless the FDA grants its request, Gilead (GILD) receives only three years of exclusivity. And the biotech hopes to wring as much revenue as possible from Stribild, which some Wall Street analysts believe can generate up to $2.7 billion in sales by 2016. The treatment costs about $28,500 per patient per year.

Since 1994, however, the agency has denied exclusivity to 10 fixed-dose combination drugs containing both new and previously approved active moieties, according to the Gilead petition. Until now, no drugmaker has challenged the guidelines used by the FDA to make such decisions, but Gilead believes the FDA’s historical interpretation “strongly discourages” the development of fixed-dose combinations to the detriment of patients (here is the citizen’s petition and related documents).

As a work around, some drugmakers have first sought approval of a new active moiety as a single-ingredient drug to secure five years of exclusivity and then seek FDA approval of a fixed-dose combination including that drug. Gilead argues such strategies are unnecessary, because the FDA interpretation amounts to a rule of thumb that is not binding and, on a broader level, a Gilead spokeswoman says the biotech wants the agency to modify its interpretation of the law in such a way that would encourage further development of fixed-dose combination drugs.

Of course, it is uncertain when the FDA will act on the petition, or whether Gilead will succeed in swaying the agency. But one source familiar with FDA regulations notes that it would be significant if the agency were to change course. Meanwhile, Gilead faces opposition over Stribild pricing from the AIDS Healthcare Foundation, which is angling to place a referendum in front of San Francisco voters to require city officials to hold talks with drugmakers about pricing for ‘essential medicines’ (backstory).

**HIV-like viruses in non-human primates have existed much longer than previously thought**
Viruses similar to those that cause AIDS in humans were present in non-human primates in Africa at least 5 million years ago and perhaps up to 12 million years ago, according to study published January 24 in the Open Access journal *PLOS Pathogens* by scientists at Fred Hutchinson Cancer Research Center. Until now, researchers have hypothesized that such viruses originated much more recently.

HIV-1, the virus responsible for AIDS, infiltrated the human population in the early 20th century following multiple transmissions of a similar chimpanzee virus known as SIVcpz. Previous work to determine the age of HIV-like viruses, called lentiviruses, by comparing their genetic blueprints has calculated their origin to be tens of thousands of years ago.
However, other researchers have suspected this time frame to be much too recent. Michael Emerman, Ph.D., a virologist and member of the Human Biology Division at Fred Hutchinson Cancer Research Center, and Alex Compton, a graduate student in the Emerman Lab, describe the use of a technique to estimate the extent to which primates and lentiviruses have coexisted by tracking the changes in a host immunity gene called APOBEC3G that were induced by ancient viral challenges.

They report that this host immunity factor is evolving in tandem with a viral gene that defends the virus against APOBEC3G, which allowed them to determine the minimum age for the association between primates and lentiviruses to be around 5 or 6 million years ago, and possibly up to 12 million years ago.

These findings suggest that HIV-like infections in primates are much older than previously thought, and they have driven selective changes in antiviral genes that have incited an evolutionary arms race that continues to this day. The study also confirms that viruses similar to HIV that are present in various monkey species today are the descendants of ancient pathogens in primates that have shaped how the immune system fights infections.

"More than 40 non-human primate species in sub-Saharan Africa are infected with strains of HIV-related viruses," Emerman said. "Since some of these viruses may have the potential to infect humans as well, it is important to know their origins."


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**Hepatitis C Linked to Tattoo Ink**

*Fox News*, (01.24.2013)

Fritz Francois, MD, a researcher from New York University Langone Medical Center, reports that people with hepatitis C are four times more likely to have tattoos, regardless of other risk factors. The estimate is based on a study of 2,000 hepatitis C-infected people who had not received a blood transfusion before 1992 or reported a history of injecting drugs.

According to CDC, 3.2 million people in the United States have hepatitis C, although some may not realize it because they have not yet developed symptoms. Injected drug use is responsible for 60 percent of new hepatitis C diagnoses each year; 70 percent of those infected develop chronic liver disease, the leading U.S. cause of liver transplants and liver cancer. CDC reports that 20 percent of hepatitis C-infected people say they have no history of injected drug use. A 2012 Harris poll estimated that 20 percent of people have a tattoo.

CDC spokesperson Scott Holmberg, MD recommends that people who want to be tattooed go to a trained professional for piercings or tattooing. Because there are no federal regulations for tattoo parlors and standards vary from state to state, Francois urges people to research tattoo parlors carefully. According to the Alliance for Professional Tattooists, it is important to find a tattooist who uses disposable gloves, "a clean workspace without blood spatters, and single-use, disposable needles."


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**Undetectable Viral Load Essentially Eliminates Transmission Risk in Straight Couples**

*AIDSMEDS*, (01.23.2013)

A recent review indicated that heterosexual serodiscordant couples have a low risk of HIV transmission if the HIV-infected partner has an undetectable viral load as a result of successful antiretroviral (ARV) therapy. The study by the National AIDS Treatment Advocacy Policy was presented at the Third International Workshop on HIV and Women in Toronto, Canada.

Researchers combined data from six studies of serodiscordant heterosexual couples. Three studies provided data on HIV transmission rates, ARV history, and viral load of the HIV-infected partner. These studies included 991 couples with 2,064 person-years of follow-up. The researchers found a 0.0 per 100 person-years transmission rate. The other three studies included rates of transmission and treatment history of 5,233 couples. When these three studies were combined with the previous three, the researchers found a pooled transmission risk of 0.14 per 100 person-years. This means that if 1,000 serodiscordant couples in which the HIV-infected partner is on ARV therapy with an undetectable viral load had sex for one year, approximately one or two non-infected partners would become infected with HIV.

In the six studies, the four transmissions took place before the HIV-infected partner had been on ARVs for six months; therefore, the seropositive partner may not have reached an undetectable viral load by that point. The researchers performed another analysis excluding the data from these transmissions. The result of this second analysis was a transmission risk of 0.0 per 100 person-years.
Sten H. Vermund, MD., Ph.D., director of the Institute for Global Health at Tennessee’s Vanderbilt University, warned that individuals who have what appears to be an undetectable viral load may have what he calls, “viral spikes,” which may intermittently put a partner at risk of HIV infection. He advised that to have a zero risk of transmitting the virus to others, individuals should “be on antiretrovirals religiously and also use condoms.”


Schumer Seeks Testing for Veterans’ Families

Buffalo News (01.24.2013) Jerry Zremski
On January 23, Sen. Charles E. Schumer (D-N.Y.), expressed his latest concerns regarding problems at the Buffalo Veterans Affairs (VA) Medical Center in a letter to Brian Stiller, medical director at VA Western New York Healthcare System. The problems occurred because of faulty labeling practices at the hospital in which insulin delivery devices possibly may have been used on more than one patient during the time period of October 19, 2010, to November 1, 2012. As many as 716 veterans could have been exposed to HIV, hepatitis B, or hepatitis C. In the letter, Schumer emphasized that the Buffalo VA Medical Center should not only provide health testing to possibly exposed veterans but also extend testing to their family members and caregivers. Schumer based his request upon information from relatives of the diabetic patients who were treated at the hospital.

Schumer states, “The VA must waste no time in testing the family members and caregivers of the 716 patients in Buffalo who were victims of the negligent and improper use of insulin pens. These veterans and their family members who may have been exposed to life-threatening illnesses need testing performed immediately, and every day that goes by is another day the families’ legitimate concerns go unanswered.” Schumer explained that family members continued to provide care to the veterans and were unaware of their own possible exposure. He requested that they be provided the same follow-up services as any potentially exposed veteran.

Buffalo VA Hospital spokesperson Evangeline Conley said that the hospital is reviewing this matter and investigating all options. According to Conley, currently the VA will provide free testing, care, and counseling to any veteran who tests positive for any blood-borne disease resulting from this incident.

Second NY Hospital Warns Patients About Potential HIV, Hepatitis Exposure From Insulin Pens

Fox News (01.24.2013) Associated Press
Olean General Hospital is the second western New York hospital to notify patients that they may have been exposed to HIV or hepatitis through the improper sharing of insulin pens. The hospital says it is mailing letters recommending blood screening to 1,915 patients who received insulin there from November 2009 through last week. According to hospital officials, the notifications follow an internal review conducted after the recent news of insulin pen-sharing at Buffalo’s Veterans Affairs hospital. In the Buffalo case, more than 700 patients may have been exposed to blood-borne pathogens over a two-year period after multi-use pens intended for use on a single individual may have been used on more than one person.

Antibiotics Not Being Used Properly, Leading To ‘Apocalyptic Scenario’ Of Drug-Resistant Infections, England’s Chief Medical Officer Says

"The rise in drug-resistant infections is comparable to the threat of global warming, according to the chief medical officer for England," BBC News reports. Professor Dame Sally Davies "said bacteria were becoming resistant to current drugs and there were few antibiotics to replace them," the news service adds (Gallagher, 1/24). "It is clear that we might not ever see global warming, the apocalyptic scenario is that when I need a new hip in 20 years I’ll die from a routine infection because we’ve run out of antibiotics,’ she announced,” adding, “It is very serious, and it’s very serious because we are not using our antibiotics effectively in countries," GlobalPost writes (Silverstein, 1/24).

"Some strains of bacteria, notably MRSA, are becoming feared in hospital wards around the world, and there are also reports of antibiotic resistance in strains of E. coli and tuberculosis," the National Post notes, adding, "Davies will issue a report in March with recommendations on what needs to be done, but in many areas of the U.K. press, calls were already being made for governments, doctors and drug manufacturers to come together to plot a strategy to avoid the worst-case scenarios” (Rehel, 1/24).
Devex Interviews WHO NTD Department Director On Roadmap For Eliminating 17 Diseases
"Lorenzo Savioli, director of WHO's department of neglected tropical diseases, spoke to Devex from Geneva in a phone interview on Wednesday, January 23, days after WHO released a progress report on its year-old roadmap to eliminate 17 tropical diseases," Devex's "Development Newswire" blog reports. "The conversation highlighted some of the main front lines in the fight against neglected diseases: increasing support from the Global South and the pharmaceutical sector, funding fatigue by cash-strapped Western governments, and the challenges posed by political turmoil and other crises," the blog notes before summarizing the conversation, which focused primarily on the eradication of Guinea worm and yaws (Lieberman, 1/24).

'Vaccine Diplomacy' Could Reduce Disease Burden On Korean Peninsula
"North Korean leader Kim Jong Un, in a New Year's Day speech, called for reductions in international tension and an end to confrontation with South Korea, while raising the prospect of reunification between the North and South," Peter Hotez, president and director of the Sabin Vaccine Institute, notes in a Los Angeles Times opinion piece, asking, "Could 'vaccine diplomacy' work on the Korean peninsula?" He writes, "The short answer is yes," adding, "Ultimately, science diplomacy could play an essential role in helping catalyze improved North-South relations in 2013, with joint programs for elimination of neglected diseases as a cornerstone."

Hotez "examine[s] how North Korea and South Korea diverged more than 50 years ago in their respective disease-control efforts," noting, "In contrast to South Koreans' public health and economic gains over the last five decades, North Koreans remain poor and sick." He provides examples of how "vaccine diplomacy can play a key role," and notes "there is the opportunity of true scientific alliances between nations." Hotez continues, "North Korean scientists also could become partners in biomedical research," and he concludes, "With adequate political will and support, this could become a breakout year for science and vaccine diplomacy to reduce the disease burden on the Korean peninsula and promote an unprecedented level of scientific collaboration" (1/24).

Frontiers publishes systematic review on the effects of yoga on major psychiatric disorders
Yoga on our minds: The 5,000-year-old Indian practice may have positive effects on major psychiatric disorders, including depression, schizophrenia, ADHD and sleep complaints
Yoga has positive effects on mild depression and sleep complaints, even in the absence of drug treatments, and improves symptoms associated with schizophrenia and ADHD in patients on medication, according to a systematic review of the exercise on major clinical psychiatric disorders.

Published in the open-access journal, Frontiers in Psychiatry, on January 25th, 2013, the review of more than one hundred studies focusing on 16 high-quality controlled studies looked at the effects of yoga on depression, schizophrenia, ADHD, sleep complaints, eating disorders and cognition problems.

Yoga in popular culture
Yoga is a popular exercise and is practiced by 15.8 million adults in the United States alone, according to a survey by the Harris Interactive Service Bureau, and its holistic goal of promoting psychical and mental health is widely held in popular belief.

"However, yoga has become such a cultural phenomenon that it has become difficult for physicians and patients to differentiate legitimate claims from hype," wrote the authors in their study. "Our goal was to examine whether the evidence matched the promise."

Benefits of the exercise were found for all mental health illnesses included in the review, except for eating disorders and cognition problems as the evidence for these was conflicting or lacking.

Dr. P. Murali Doraiswamy, a professor of psychiatry and medicine at Duke University Medical Center, US, and author of the study, explained that the emerging scientific evidence in support of the 5,000 year old Indian practice on psychiatric disorders is "highly promising" and showed that yoga may not only help to improve symptoms, but also may have an ancillary role in the prevention of stress-related mental illnesses.

The review found evidence from biomarker studies showing that yoga influences key elements of the human body thought to play a role in mental health in similar ways to that of antidepressants and psychotherapy. One study found that the exercise affects neurotransmitters, inflammation, oxidative stress, lipids, growth factors and second messengers.
Unmet need among mental health patients
Depression alone affects more than 350 million people globally and is the leading cause of disability worldwide, according to the World Health Organization (WHO). On World Mental Health Day last year, the WHO called for improved access to treatments.

While there has been an increase in the number of medications available for mental health disorders, many of which can be life saving for patients, there remains "a considerable unmet need," according to Dr. Meera Balasubramaniam, lead author of the study, who is also based at Duke University, US.

Poor compliance and relapse as well as treatment resistance are growing problems, and medications are expensive and can leave patients with significant side effects.

The Primary Care study, carried out by WHO, found that 60% of patients were still depressed after a year of being treated with an anti-depressant and a National Institute of Mental Health funded research showed remission in only one-third of patients.

"The search for improved treatments, including non-drug based, to meet the holistic needs of patients is of paramount importance and we call for more research into yoga as a global priority," said Doraiswamy. "If the promise of yoga on mental health was found in a drug, it would be the best selling medication world-wide," he added.

There are many benefits associated with practicing yoga for improving mental health, including, fewer side effects, relatively low cost, generally good access and the improvement of physical fitness, added the authors.

The authors also note that while the results are promising, the findings should be viewed as preliminary because all studies of yoga to date have consisted of small samples, and more rigorous research will be needed before the exercise can be applied to help patients with mental health disorders.


At least one in five were infected in flu pandemic, international study suggests 20-27 per cent of people were infected in countries for which data are available.
Date: 25 Jan 2013

At least one in five people in countries for which data are available were infected with influenza during the first year of the 2009 H1N1 pandemic, according to a new study. The highest rates of infection were in children, with 47 per cent of those aged five to 19 showing signs of having caught the virus. Older people were affected less, with only 11 per cent of people aged 65 or older becoming infected.

The findings come from an international collaboration led by the World Health Organization and Imperial College London, which analysed data from 19 countries, including the UK, US, China and India, to assess the global impact of the 2009 influenza pandemic.

The results, published in the journal Influenza and Other Respiratory Viruses, showed that 20-27 per cent of people studied were infected in the pandemic during the first year of circulation. The researchers believe the incidence of influenza is likely to have been similar in countries where data were not available, meaning that as many as a quarter of the world's population may have been infected.

The study collated results from more than two dozen research studies involving more than 90,000 blood samples collected before, during and after the pandemic. The samples were tested for antibodies produced by the body in response to the specific flu strain that caused the pandemic.

While this study did not set out to look at mortality, the authors also used previously published estimates of pandemic influenza mortality together with mortality estimates that are still in progress, to estimate the proportion of people infected who died from the pandemic virus. Based on an estimate of approximately 200,000 deaths, they suggest that the case fatality ratio was less than 0.02 per cent.

Multiple exposures to previously circulating influenza viruses may have given older people some protection against the strain that emerged in 2009. Blood samples from before the pandemic showed that 14 per cent of people aged 65 or over already had antibodies that reacted to the 2009 strain.

Dr Maria Van Kerkhove, from the Medical Research Council Centre for Outbreak Analysis and Modelling at Imperial College London, one of the lead authors of the study, said: "This study is the result of a combined effort by more than 27 research groups worldwide, who all shared their data and experience with us to help improve our understanding of the impact the pandemic had globally."

Dr Anthony Mounts of the World Health Organization, the senior author, said: "Knowing the proportion of the population infected in different age groups and the proportion of those infected who
died will help public health decision-makers plan for and respond to pandemics. This information will be used to quantify severity and develop mathematical models to predict how flu outbreaks spread and what effect different interventions may have."

The study was funded by the Medical Research Council.

Reference

Scientists Discover How Epigenetic Information Could Be Inherited: Mechanism of Epigenetic Reprogramming Revealed
Jan. 24, 2013 — New research reveals a potential way for how parents' experiences could be passed to their offspring's genes. The research was published January, 25 in the journal Science.

Epigenetics is a system that turns our genes on and off. The process works by chemical tags, known as epigenetic marks, attaching to DNA and telling a cell to either use or ignore a particular gene.

The most common epigenetic mark is a methyl group. When these groups fasten to DNA through a process called methylation they block the attachment of proteins which normally turn the genes on. As a result, the gene is turned off.

Scientists have witnessed epigenetic inheritance, the observation that offspring may inherit altered traits due to their parents' past experiences. For example, historical incidents of famine have resulted in health effects on the children and grandchildren of individuals who had restricted diets, possibly because of inheritance of altered epigenetic marks caused by a restricted diet.

However, it is thought that between each generation the epigenetic marks are erased in cells called primordial gene cells (PGC), the precursors to sperm and eggs. This 'reprogramming' allows all genes to be read afresh for each new person—leaving scientists to question how epigenetic inheritance could occur.

The new Cambridge study initially discovered how the DNA methylation marks are erased in PGCs, a question that has been under intense investigation over the past 10 years. The methylation marks are converted to hydroxymethylation which is then progressively diluted out as the cells divide. This process turns out to be remarkably efficient and seems to reset the genes for each new generation. Understanding the mechanism of epigenetic resetting could be exploited to deal with adult diseases linked with an accumulation of aberrant epigenetic marks, such as cancers, or in 'rejuvenating' aged cells.

However, the researchers, who were funded by the Wellcome Trust, also found that some rare methylation can 'escape' the reprogramming process and can thus be passed on to offspring—revealing how epigenetic inheritance could occur. This is important because aberrant methylation could accumulate at genes during a lifetime in response to environmental factors, such as chemical exposure or nutrition, and can cause abnormal use of genes, leading to disease. If these marks are then inherited by offspring, their genes could also be affected.

Dr Jamie Hackett from the University of Cambridge, who led the research, said: "Our research demonstrates how genes could retain some memory of their past experiences, revealing that one of the big barriers to the theory of epigenetic inheritance—that epigenetic information is erased between generations—should be reassessed."

"It seems that while the precursors to sperm and eggs are very effective in erasing most methylation marks, they are fallible and at a low frequency may allow some epigenetic information to be transmitted to subsequent generations. The inheritance of differential epigenetic information could potentially contribute to altered traits or disease susceptibility in offspring and future descendants."

"However, it is not yet clear what consequences, if any, epigenetic inheritance might have in humans. Further studies should give us a clearer understanding of the extent to which heritable traits can be derived from epigenetic inheritance, and not just from genes. That could have profound consequences for future generations."

Professor Azim Surani from the University of Cambridge, principal investigator of the research, said: "The new study has the potential to be exploited in two distinct ways. First, the work could provide information on how to erase aberrant epigenetic marks that may underlie some diseases in adults. Second, the study provides opportunities to address whether germ cells can acquire new epigenetic marks through environmental or dietary influences on parents that may evade erasure and be transmitted to subsequent generations, with potentially undesirable consequences."

Journal Reference:
Synthetic Corkscrew Peptide Kills Antibiotic-Resistant Gram-Negative Bacteria

Jan. 24, 2013 — An engineered peptide provides a new prototype for killing an entire category of resistant bacteria by shredding and dissolving their double-layered membranes, which are thought to protect those microbes from antibiotics.

The synthetic peptide was effective in lab experiments against antibiotic-resistant Gram-negative bacteria, which cause a variety of difficult-to-treat, potentially lethal infections such as pneumonia and sepsis.

The team led by scientists at The University of Texas MD Anderson Cancer Center reported its findings online in advance of print this week at the Proceedings of the National Academy of Sciences.

"The antibiotic pipeline against multidrug-resistant Gram-negative problem pathogens is a major unmet need in contemporary medicine; as such, our new antimicrobial agent holds immediate promise," said co-senior author Wadih Arap, M.D., professor in MD Anderson’s Department of Genitourinary Medical Oncology and the David H. Koch Center.

Arap, Renata Pasqualini, Ph.D., also a co-senior author, professor in genitourinary medical oncology and the Koch center, and colleagues have previously constructed peptide combinations that are in development against cancer and white fat cells.

"The prototype introduced here as an antibiotic candidate has a unique mechanism of action and translational applications readily identified," Pasqualini said.

Gram-negative bacteria that are highly resistant to existing treatments include E.coli, Acinetobacter baumanii, Pseudomonas aeruginosa, and kebsiella pneumonia. These infections are often present in health care settings and most threatening to people with weakened immune systems.

The spiral peptide called KLAKLAKKLAKLAK acts against bacteria by puncturing their lipid bilayer membranes and has only low toxicity toward mammalian cells. These antimicrobial peptides, however, are subject to routine destruction by host enzymes or those generated by the microbe. Combating that effect by increasing the dose heightens both toxicity to other cells and cost.

D- KLAKLAKKLAKLAK destroys microbes, biofilms
Arap, Pasqualini and colleagues engineered a version of KLAKLAKKLAKLAK to use in their combination therapies but had not tested the peptide alone as an antibiotic.

The peptide is made of L-amino acids, the building blocks of life, which makes them vulnerable to destruction. The researchers synthesized a peptidomimetic—a version of the peptide using D-amino acids with a reversed peptide sequence, making it more durable.

In a series of lab experiments, the researchers found that D-KLAKLAKKLAKLAK:

- Kills a variety of strains of E.coli, A.baumanii and P. aeruginosa, including multi-drug resistant strains.
- Works against Gram-negative bacteria at all phases of growth, including dormant cells that are prone to become resistant.
- Causes dose-dependent damage to the bacterial membrane resulting in its dissipation and cell death.
- Specifically disrupts lipids found in Gram-negative bacteria membranes while not affecting membranes in eukaryotic cells—cells with the nucleus and other structures enclosed in separate membranes found in mammals and other non-microbial life.
- Works in combination with the antibiotic piperacillin at lower doses to kill bacteria.
- Eliminates biofilms, layers of combinations of microbes that adhere to surfaces and provide an ideal setting for bacterial growth.

Next step: Animal model experiments
Arap and Pasqualini note that developing D-KLAKLAKKLAKLAK as a drug will next require experiments in animal models of sepsis and other infections to further gauge the peptide’s effectiveness and side effects.

In their cancer and anti-obesity research, the D-peptide is used with targeting agents to hit specific cells. Large preclinical studies in mice, rats and monkeys showed low toxicity at treatment-level concentrations. Their cancer drug in a first-in-human phase I clinical trial revealed side effects that were predictable, dose-dependent and reversible. Even so, toxicity may differ when it’s used against bacterial infections.

The peptide was not effective against Gram-positive bacteria, which have thicker cell walls but are generally more vulnerable to antibiotics and the immune system than are Gram-negative bacteria. Gram-
positive bacteria include those that cause anthrax, tuberculosis, strep throat and such treatment-resistant infections as *Staphylococcus aureus*.

Gram-negative bacteria, which have thinner membranes but are generally more resistant to antibiotics or immune system attack, also include those that cause typhoid fever, cholera, gonorrhea, syphilis and lyme disease.

**Journal Reference:**

**Pathogenic Bacteria Adhering to the Human Vascular Wall Triggers Vascular Damage During Meningococcal Sepsis**

Jan. 24, 2013 — Researchers at the Paris Cardiovascular Research Center (PARCC) have shown how adhesion of *Neisseria (N.) meningitidis* to human microvessels in a humanized mouse model leads to the characteristic cutaneous lesions of meningococcal sepsis. This work, published on January 24 in the Open Access journal *PLOS Pathogens*, is an important demonstration of the direct role of adhesion, specifically Type IV pili mediated adhesion, plays in the development of the disease.

Meningococcal sepsis is a rapidly developing and often fatal infection. Cutaneous lesions, often presenting clinically as purpuric or petechial skin rashes, are a hallmark feature of the infection hence the term purpura fulminans to describe this severe form of sepsis. Understanding the mechanisms behind the development of these lesions is important to understand disease progression because it reveals the underlying mechanisms of the pathological process. From the experimental point of view the strict human specificity of *N. meningitidis* has long been a limiting factor in the development of relevant in vivo models of this infection and for understanding how the bacteria interact with the blood vessels. It was previously thought that that the large number of circulating bacteria was responsible for the vascular damage through the release of LPS in particular.

In this research, investigators utilized a humanized mouse model, where human skin, containing an abundance of human microvessels, was grafted onto immunocompromised mice. Grafted mice thus had a hybrid vasculature, part mouse, and part human. In this context, *N. meningitidis* associated exclusively, and in significant numbers, with the human vessels. Once associated with the human vessels the bacteria rapidly led to an endothelial inflammatory response with expression of the human pro-inflammatory cytokines IL-6 and IL-8 and the infiltration of inflammatory cells. Vascular events such as clotting, thrombosis, congestion and vascular leak were all observed in the infected human vessels, mimicking the clinical pathology. The combination of these factors led to the development of a purpuric rash in 30% of the infections. The association of the bacteria with the human vessels was shown to be dependent on the adhesive properties of the bacterial Type IV pili, filamentous structures found at the surface of many pathogenic bacteria. Importantly, bacterial mutants deficient for these adhesive structures do not lead to any distinctive pathology despite normal numbers of circulating bacteria.

This work thus leads to a change in the paradigm in our understanding of the disease mechanism, with local adhesion events now considered central to the disease process. Because it recapitulates key features of human infection, the described experimental model opens new avenues of research to further understand the mechanisms of disease and to design new prevention and treatment strategies.

**Journal Reference:**

**False Beliefs Persist, Even After Instant Online Corrections**

Jan. 24, 2013 — It seems like a great idea: Provide instant corrections to web-surfers when they run across obviously false information on the Internet.

But a new study suggests that this type of tool may not be a panacea for dispelling inaccurate beliefs, particularly among people who already want to believe the falsehood.

"Real-time corrections do have some positive effect, but it is mostly with people who were predisposed to reject the false claim anyway," said R. Kelly Garrett, lead author of the study and assistant professor of communication at Ohio State University.

"The problem with trying to correct false information is that some people want to believe it, and simply telling them it is false won't convince them."
For example, the rumor that President Obama was not born in the United States was widely believed during the past election season, even though it was thoroughly debunked.

The prospect of correcting falsehoods like this online before they have a chance to spread widely has obvious appeal, Garrett said.

In fact, it has already been attempted: A team from Intel and the University of California, Berkeley, developed Dispute Finder, a plug-in for web browsers that was released in 2009 and would alert users when they opened a webpage with a disputed claim. That project has ended, but Garrett said similar efforts are under way.

"Although the average news user hasn’t encountered real-time correction software yet, it is in the works and I suspect it will see more widespread use soon," he said.

But will it work? In order to find out, Garrett conducted a study with Brian Weeks, a graduate student in communication at Ohio State. Their study (available here), which they will present Feb. 26 in Austin, Texas, appears in the 2013 Proceedings of the Computer Supported Cooperative Work and Social Computing conference.

Participants in the study were a diverse group of 574 adults from across the country who participated online.

The experiment was designed to see what would happen when participants read false statements copied from a “political blog” (actually text prepared by the researchers) about the issue of electronic health records.

While some of the information, collected from news stories and government sources, was correct, the researchers also inserted several false statements about who was allowed access to these records. For instance, the message falsely claimed that hospital administrators, health insurance companies and even government officials had unrestricted access to people’s electronic health records.

The participants were divided into three groups—some were presented with an immediate correction, saying that FactCheck.org, an independent fact-checking organization, had concluded this blog post contained factual errors. Inaccurate statements were italicized, enclosed in brackets and displayed in red, and a detailed correction appeared at the bottom of the page.

Others read the blog post with the errors, followed by completing an unrelated three-minute task, and then were presented with the exact same correction.

The final group was presented only with the inaccurate message during the study.

Afterwards, all participants were asked how easy or difficult it would be for several groups (including hospital administrators, government officials and others) to access electronic health records. Participants were graded based on the accuracy of their answers.

In general, those who received the immediate correction were just slightly more likely to be accurate than those who received the delayed correction. Those who received no corrections were, not surprisingly, the least accurate.

But the most interesting results came when the researchers analyzed who was influenced by each kind of correction.

The real-time correction worked well with participants who indicated at the beginning of the study that they supported electronic health records, also called EHRs.

"But for those who opposed EHRs, the effect of the immediate correction was essentially the same as if they had received no correction at all," Garrett said.

The reason appears to be that opponents of EHRs discounted the credibility of the source of the correction, Garrett said. On the other hand, the more favorably an individual felt about EHRs, the more credible the correction was perceived to be.

Although this pattern was also evident among those who received the delayed correction, the effect was significantly weaker.

Garrett said the results of this study cast doubt on the theory that people who believe false rumors need only to be educated about the truth to change their minds.

"Humans aren’t vessels into which you can just pour accurate information," he said.

"Correcting misperceptions is really a persuasion task. You have to convince people that, while there are competing claims, one claim is clearly more accurate."

Garrett noted that, while instant corrections were slightly more effective than delayed corrections, the problem is that instant corrections actually increase resistance among those whose attitudes are supported by the falsehood.
"We would anticipate that systems like Dispute Finder would do little to change the beliefs of the roughly one in six Americans who, despite exhaustive news coverage and fact checking, continue to question whether President Obama was born in the U.S.," he said.

Garrett said it may be better to find a way to deliver corrections later, when people may not be so defensive about their beliefs.

**Caloric Restriction Has a Protective Effect On Chromosomes**
Jan. 23, 2013 — One of the indicators of a cell’s health is the state of its DNA and containers—the chromosomes—so when these fuse together or suffer anomalies, they can become the source of illnesses like cancer and/or aging processes.

According to a study carried out by a team led by María Blasco, the director of the Spanish National Cancer Research Centre (CNIO) and head of the Telomeres and Telomerase Group, a sustained lowering of food intake over time results in an increase of telomere length—the ends of chromosomes—in adult mice, which has a protective effect on the DNA and genetic material.

These beneficial effects on the youth of the chromosomes translate to a lower incidence of cancer and other age-related illnesses. The journal *PLOS ONE* is to publish the details of this study in its online edition this week.

**A lower incidence of cancer and better health**
To carry out the study, researchers used young mice—just three months old—and reduced their caloric intake by 40% before observing them until the end of their life cycle.

"We see that mice that undergo caloric restriction show a lower telomere shortening rate than those fed with a normal diet," says Blasco. "These mice therefore have longer telomeres as adults, as well as lower rates of chromosome anomalies," she adds.

To study the effects of this phenomenon on the health of the mammals, researchers observed the incidence of age-related illnesses like cancer. The mice that had been fed a lower calorie intake showed a reduction in the incidence of cancer. Furthermore, these mice also showed a lower incidence of other age-related illnesses such as osteoporosis, greater glucose uptake or improvements in motor coordination.

When the researchers carried out these same experiments with a variety of mice that produce more telomerase—a protein that lengthens telomeres and protects chromosomes—they observed that these mice not only enjoyed better health but also lived up to 20% longer.

"We believe that such a significant increase in longevity is due to the protective effect against cancer produced by caloric restriction—incidents fall by 40% if we compare them with the mice that produce more telomerase and have a normal diet—and, added to the presence of longer telomeres, this makes the mice live longer and better," says Blasco.

Despite the effects of caloric restriction depending on the genetic characteristics of each organism, this study opens the way to studying the effect other factors and lifestyle habits, such as smoking or exercise, might have on aging.

Furthermore, it is calculated that there are currently more than 10,000 people in the world on some form of controlled caloric restriction, so the observation of these individuals will be decisive in discovering the effects of this type of diet on humans.

**Journal Reference:**
Elsa Vera, Bruno Bernardes de Jesus, Miguel Foronda, Juana M. Flores, Maria A. Blasco. *Telomerase Reverse Transcriptase Synergizes with Calorie Restriction to Increase Health Span and Extend Mouse Longevity.* *PLoS ONE*, 2013; 8 (1): e53760 DOI: 10.1371/journal.pone.0053760

**Microbiologists Eavesdrop On the Hidden Lives of Microbes**
Jan. 23, 2013 — Microbiologists who study wild marine microbes, as opposed to the lab-grown variety, face enormous challenges in getting a clear picture of the daily activities of their subjects. But a team of scientists from MIT and the Monterey Bay Aquarium Research Institute recently figured out how to make the equivalent of a nature film, showing the simultaneous activities of many coexisting species in their native habitat over time.

Instead of making a movie, the scientists used a robotic device that dangled below the surface of the ocean, drifting in the water with a neighborhood of microbial populations and gathering samples of one billion microbes every four hours. Similar to fast photography that stops action, the robotic device "fixed" each sample so that whatever genes the microbes were expressing at the moment of capture were preserved for later study in the lab, where the scientists used whole-genome gene-expression analysis to create a time-lapse montage of the daily labors of multiple microbial species over a two-day period.
"A naturalist like Sir David Attenborough can follow a herd of elk and see how the elk’s behavior changes hour to hour, day to day and week to week. But we haven’t been able to observe naturally occurring microbes with that kind of resolution until now," says Edward DeLong, the Morton and Claire Goulder Family Professor in Environmental Systems in the MIT Department of Civil and Environmental Engineering and Department of Biological Engineering.

DeLong is senior author of a paper on the study appearing online the week of Jan. 21 in the Proceedings of the National Academy of Sciences. Co-authors on the paper are Elizabeth Ottesen, a former MIT postdoc who is now an assistant professor at the University of Georgia; MIT postdoc Curtis Young and research engineer John Eppley; and senior research specialist John Ryan, senior scientist Francisco Chavez, and president Christopher Scholin of the Monterey Bay Aquarium Research Institute.

"We've essentially captured a life in the day of these microbes," DeLong says. "As little as three years ago, I wouldn't have even have considered it possible to get such a high resolution picture of microbial population dynamics and activity in the 'real world.'"

Because microbes are extraordinarily sensitive to slight environmental changes and alter their gene expression rapidly in response to fluctuations in temperature, light, nutrient availability and other environmental variables, the genes they express tell a story about their habitat and their interactions with it: In essence, changes in their gene expression provide information on the good times and the bad times they experience. In a sense, each naturally occurring microbe is a living sensor; the researchers read the sensors' outputs by studying their gene expression.

The montage showed that photosynthetic microbes, which create the oxygen, energy and organic carbon used by the rest of the food web, ramped up their light-utilizing activities in the morning and powered those down at night, just as their domestic brethren do in response to light and dark in the lab.

But the underwater scenes also showed something scientists had never seen before: Nonphotosynthetic, carbon-eating microbes of very different species displayed synchronized, rapidly varying metabolic gene expression. Some of the genes simultaneously expressed by different species shared the same function—for instance, genes associated with growth or respiration. Others encoded very different functions, mirroring the varied metabolic capabilities of the disparate species. The simultaneous expression of these genes indicates that the microbes were responding to similar environmental changes, probably in the nature or quantity of organic matter available in the immediate vicinity.

They all may have been responding to the same cue or possibly one species may have acted as a first responder, signaling other species when it changed its own gene expression.

"In this work, the scientists use robots on buoys to do the sampling, which allows excellent resolution in both time and space, and they're therefore able to look at the functions that a range of different types of plankton are expressing," says Rob Knight, an associate professor of molecular biophysics at the University of Colorado. "The information should be really useful for developing predictive models that help us understand how marine plankton will respond to factors such as climate change and ocean acidification, by revealing the networks by which genes interact with each other to produce complex biological functions."

**Retrovirus in the Human Genome Is Active in Pluripotent Stem Cells**

Jan. 23, 2013 — A retrovirus called HERV-H, which inserted itself into the human genome millions of years ago, may play an important role in pluripotent stem cells, according to a new study published in the journal Retrovirology by scientists at UMass Medical School. Pluripotent stem cells are capable of generating all tissue types, including blood cells, brain cells and heart cells. The discovery, which may help explain how these cells maintain a state of pluripotency and are able to differentiate into many types of cells, could have profound implications for therapies that would use pluripotent stem cells to treat a range of human diseases.

"What we've observed is that a group of endogenous retroviruses called HERV-H is extremely busy in human embryonic stem cells," said Jeremy Luban, MD, the David L. Freelander Memorial Professor in HIV/AIDS Research, professor of molecular medicine and lead author of the study. "In fact, HERV-H is one of the most abundantly expressed genes in pluripotent stem cells and it isn't found in any other cell types."

In the study, Dr. Luban and colleagues describe how RNA from the HERV-H sequence makes up as much as 2 percent of the total RNA found in pluripotent stem cells. The HERV-H sequence is controlled by the same factors that are used to reprogram skin cells into induced pluripotent stem (iPS) cells, a discovery that garnered the 2012 Nobel Prize in Physiology or Medicine. "In other words, HERV-H is a
new marker for pluripotency in humans that has the potential to aid in the development of iPS cells and transform current stem cell technology,” said Luban.

When a retrovirus infects a cell, it inserts its own genes into the chromosomal DNA of the host cell. As a result, the host cell treats the viral genome as part of its own DNA sequence and begins making the proteins required to assemble new copies of the virus. And because the retrovirus is now part of the host cell's genome, when the cell divides, the virus is inherited by all daughter cells.

In rare cases, it's believed that retroviruses can infect human sperm or egg cells. If this happens, and if the resulting embryo survives, the retrovirus can become a permanent part of the human genome, and be passed down from generation to generation. Scientists estimate that as much as 8 percent of the human genome may be composed of extinct retroviruses left over from infections that occurred millions of years ago. Yet these sequences of fossilized retrovirus were thought to have no discernible functional value.

"The human genome is filled with retrovirus DNA thought to be no more than fossilized junk," said Luban. "Increasingly, there are indications that these sequences might not be junk. They might play a role in gene expression after all."

An expert in HIV and other retroviruses, Luban and his colleagues were seeking to understand if there was a rationale behind where, in the expansive human genome, retroviruses inserted themselves. Knowing where along the chromosomal DNA retroviruses might attack could potentially lead to the development of drugs that protect against infection; better gene therapy treatments; or novel biomarkers that would predict where a retrovirus would insert itself in the genome, said Luban.

Turning these same techniques on the retrovirus sequences already in the human genome, they discovered a sequence, HERV-H, that appeared to be active. "The sequences weren’t making proteins because they had been so disrupted over millions of years, but they were making these long, noncoding RNAs," said Luban.

Specifically, the HERV-H sequence was making abundant amounts of RNA in human embryonic stem cells—and only stem cells. In total, there are more than 1,000 HERV-H retrovirus genomes scattered throughout the human genome. The Luban lab also found high levels of HERV-H RNA in some iPS cells. Other iPS cells, perhaps those lines that were not sufficiently reprogrammed to pluripotency, had lower levels of the HERV-H RNA, another indication that HERV-H may be an important marker for pluripotency.

Interestingly, the HERV-H genes that were expressed in human pluripotent stem cells are only found in the human and chimpanzee genomes, indicating that HERV-H infected a relatively recent ancestor to humans, said Luban.

"Once upon a time HERV-H was an invader to our genome and perhaps caused diseases like AIDS or cancer," said Luban. "Now it seems that a kind of détente has been reached. Not only that, but this ancient invader may one day be exploited by clinicians to cure people of a wide range of diseases using stem cell therapies."

Luban and colleagues will next try to determine the specific mechanisms by which HERV-H contributes to pluripotency.

Journal Reference:

The Future of Antibiotics and Resistance
Brad Spellberg, M.D., John G. Bartlett, M.D., and David N. Gilbert, M.D.

In its recent annual report on global risks, the World Economic Forum (WEF) concluded that “arguably the greatest risk . . . to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall.”

Traditional practices in infection control, antibiotic stewardship, and new antibiotic development are cornerstones of society’s approach to combating resistance and must be continued. But the WEF report underscores the facts that antibiotic resistance and the collapse of the antibiotic research-and-development pipeline continue to worsen despite our ongoing efforts on all these fronts. If we’re to develop countermeasures that have lasting effects, new ideas that complement traditional approaches will be needed.
New ideas are often based on the recognition of old truths. Prokaryotes (bacteria) “invented” antibiotics billions of years ago, and resistance is primarily the result of bacterial adaptation to eons of antibiotic exposure. What are the fundamental implications of this reality? First, in addition to antibiotics' curative power, their use naturally selects for preexisting resistant populations of bacteria in nature. Second, it is not just “inappropriate” antibiotic use that selects for resistance. Rather, the speed with which resistance spreads is driven by microbial exposure to all antibiotics, whether appropriately prescribed or not. Thus, even if all inappropriate antibiotic use were eliminated, antibiotic-resistant infections would still occur (albeit at lower frequency).

Third, after billions of years of evolution, microbes have most likely invented antibiotics against every biochemical target that can be attacked — and, of necessity, developed resistance mechanisms to protect all those biochemical targets. Indeed, widespread antibiotic resistance was recently discovered among bacteria found in underground caves that had been geologically isolated from the surface of the planet for 4 million years. Remarkably, resistance was found even to synthetic antibiotics that did not exist on earth until the 20th century. These results underscore a critical reality: antibiotic resistance already exists, widely disseminated in nature, to drugs we have not yet invented.

Thus, from the microbial perspective, all antibiotic targets are “old” targets. Yet since the early 1930s, when Gerhard Domagk and colleagues discovered that chemical red dyes (the sulfonamides) can kill bacteria, the singular arc of antibiotic research and development has been to discover “new” targets to attack in order to kill the microbes. This strategy has saved countless lives. Ironically, it has also driven the resistance that threatens the very miracle of antibiotics. Ultimately, over centuries or millennia of selective pressure, we will run out of targets, and resistance mechanisms will become so prevalent as to preclude effective clinical deployment of antibiotics.

Promising future strategies to combat resistance can be divided into five categories, each of which requires additional societal investment in basic and applied research and policy activities. These interventions aim to prevent infections from occurring in the first place, to encourage new economic models that spur investment in anti-infective treatments, to slow the spread of resistance in order to prolong the useful lives of antibiotics, to discover new ways to directly attack microbes in a manner that does not drive resistance, or to alter host–microbe interactions in order to modify disease without directly attacking microbes.

Infection prevention eliminates the need to use antibiotics. Traditional infection-prevention efforts must be buttressed by new technologies that can more effectively disinfect environmental surfaces, people, and food. We also need technology that enables intensive health care without requiring the implantation of foreign materials such as plastic or metal (e.g., improved drug delivery by means of the gut, skin, or respiratory mucosa to replace intravenous therapy and regenerative-tissue technology that obviates the need for prosthetic implants). Improvements in population health and health care delivery systems can reduce admissions to hospitals and skilled nursing facilities, thereby reducing infections. Finally, new vaccines hold great promise for preventing antibiotic-resistant infections.

Despite preventive efforts, though, infections will always occur, and we will always need safe and effective therapy for them. The collapse of the antibiotic research-and-development pipeline is the result of both economic and regulatory barriers. The solution is better alignment of economic and regulatory approaches to antibiotic development. For example, public–private partnerships could align the research-and-development focus of industry with unmet medical needs. Also, a new regulatory approach, such as the Limited Population Antibiotic Drug (LPAD) proposal from the Infectious Diseases Society of America, could allow drugs to be approved on the basis of small, relatively inexpensive clinical superiority trials focused on lethal infections caused by highly resistant pathogens. The antibiotic would receive a very narrow label, helping to protect against overuse. Thus, the LPAD would simultaneously empower antibiotic stewardship and provide economic incentives for investment by reducing the cost of clinical trials and creating the conditions for a pricing premium.

In a 1945 interview with the New York Times, Alexander Fleming called for stopping the overuse of penicillin in order to slow the development of resistance. Nearly 65 years later, in 2009, more than 3 million kg of antibiotics were administered to human patients in the United States alone; in 2010, a staggering 13 million kg were administered to animals. The majority of the animal antibiotic use was meant to promote the growth of livestock. We cannot confront resistance unless we stop exposing the environment to massive quantities of antibiotics and their resulting selective pressure. Promising but untapped strategies for slowing resistance include transparent, public reporting of data on antibiotic use across medical centers and individual providers to enable national benchmarking and reimbursement modification, development and use of rapid diagnostic and biomarker tests that empower providers to
withhold antibiotics from patients who don't have bacterial infections and shorten antibiotic courses for those who do, elimination of antibiotic use for the promotion of growth in animals, bioengineering efforts to degrade antibiotics in sewage so as to avoid environmental contamination and selection for resistance, and conducting of studies to determine the shortest effective course of therapy for common infections.

A more innovative form of stewardship is the development of therapies that do not drive resistance. For example, the infusion of monoclonal antibodies (a modern advance on serum therapy, which is more than a century old) or white cells that attack microbes holds promise for treating infections. Finally, what if we were able to treat infections without seeking to kill the microbe? Casadevall and Pirofski’s damage-response framework of microbial pathogenesis underscores the concept that clinical signs, symptoms, and outcomes of infection result as much, or more, from the host response to the microbe as from a direct effect of the microbe itself. Thus, we should be able to treat infections by attacking host targets rather than microbial targets. Indeed, recent preclinical research demonstrates that we can successfully deploy therapies that either moderate the inflammatory response to infection or that limit microbial growth by blocking access to host resources without attempting to kill microbes. For example, an antibiotic of a novel class (LpxC inhibitors), which blocks synthesis of gram-negative lipopolysaccharide, could not kill Acinetobacter baumannii but prevented the microbe from causing disease in vivo. Other examples include antiinflammatory monoclonal antibodies, probiotics to compete with microbial growth, and sequestration of host nutrients (e.g., iron) to create a resource-limited environment in which microbes cannot reproduce. Such strategies require clinical validation but have the potential to reduce resistance when pursued in concert with traditional antibiotic therapy.

The converging crises of increasing resistance and collapse of antibiotic research and development are the predictable results of policies and processes we have used to deal with infections for 75 years. If we want a long-term solution, the answer is not incremental tweaking of these policies and processes. Novel approaches, based on a reconceptualization of the nature of resistance, disease, and prevention, are needed.

Can Low Volume Syringes Help End HIV and HCV Transmission Among People Who Use Drugs?

Published on Thursday, 24 January 2013 00:00
Written by Cyd Nova
Syringes that have a lower "dead space" volume retain less fluid that can harbor HIV and hepatitis C virus (HCV), and switching to this type could help reduce viral transmission among injection drug users, according to an article in the January 2013 issue of International Journal of Drug Policy.

Researchers at RTI International and the Futures Institute propose that changing the type of syringes made available in areas where the local HIV epidemic is injection-driven may lower and eventually halt HIV transmission among people who inject drugs.

The key may lie in the difference between high dead-space syringes (HDSS) and low dead-space syringes (LDSS). Dead-space refers to the parts of a syringe where blood and other fluid remains after the plunger has been fully depressed. In contrast with high dead-space syringes—which have detachable needles and retain an average 84 ml of fluid when expressed—low dead-space syringes generally have permanently attached needles and only retain an average 2 ml of fluid in the needle itself.

Thus, a person who shares a high dead-space syringe with an HIV positive partner is more likely to be exposed to the virus than those who use a low dead-space syringe.

In laboratory experiments simulating the process of aspirating blood into the syringe and rinsing it out with water, high dead-space syringes retained 1000 times more HIV than low-dead space syringes. In similar experiments testing for hepatitis C, low-dead space syringes were also shown to be less likely to transmit the virus. Studies showed that HCV was only able to live for 1 day in a low dead-space syringe, as opposed to 60 days in a high dead-space syringe.

Using a mathematical model, the authors projected that replacing high dead-space syringes with low dead-space syringes in countries with injection-driven epidemics—such as China, Indonesia, Russia, and
Ukraine—would lead to major reductions in HIV transmission, with a foreseeable outcome of reducing transmissions to nearly zero within 8 years.

A survey of current HIV rates across cities with high levels of injection drug use seems to support this claim. In countries where high dead-space syringes are mostly used, HIV prevalence was low among people who inject drugs in 18 cities, moderate in 15 cities, and high in 25 cities/areas. In cities/areas where low dead-space syringe are most common, HIV prevalence was low in 8 cities/areas and high in only 1 city.

Further research is required, but the authors highlight the need for prompt feasibility studies and randomized controlled trials, as well as rapid assessments with people who inject drugs to identify potential barriers in practicality.

"Although additional research is needed, this intervention should be implemented and evaluated as soon as possible," stated lead author William Zule. "Switching from high dead-space to low dead-space syringes should be viewed as an additional component to comprehensive HIV prevention packages."

A low-cost initiative, the primary concern is the difficulty of getting the word out to educate drug users, care providers, and pharmacists about the reasons for making this change. Another potential barrier is that most low dead-space syringes have a shorter barrel and permanently affixed needles, which will not work for injecting drugs that must be dissolved in a larger volume of liquid. Drug users may also often prefer detachable needles, as they can be replaced if they become clogged. There is currently only 1 manufacturer of low dead-space detachable needles, which are expensively priced.

Despite these potential obstacles, drug user advocates have heralded this study. "This study makes a compelling case for syringe access programs to review their policies and education," said Daniel Raymond, Policy Director for the Harm Reduction Coalition. "Globally, a switch to low dead-space syringes has the potential to reduce not only HIV infections, but also hepatitis C infections among people who inject drugs."

Zule states that he is collaborating with the North Carolina HIV/AIDS division to disseminate education within the community, and moving forward from there to gather information about the types of syringes used in the U.S. and working towards a national shift to using low dead-space syringes. 1/18/13

Reference

The Berlin Patient: The HIV Cure Case Report with a Name
Published on Friday, 15 June 2012 00:00
Written by Matt Sharp
Controversy has been stirring among scientists, activists, and the media during the past week due to developments in the case of the Berlin Patient, Timothy Brown. So far there have been a dozen or more reports that have interpreted new information in a variety of ways. Even expert researchers are not exactly sure what to make of these developments.

The controversy began with a poster and oral presentation of Brown’s case by Steven Yukl from the University of California San Francisco at the International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies last week in Sitges, Spain. Yukl presented new findings from extensive tests to determine whether HIV eradication has occurred and to define the potential role of various viral reservoir measurements.

Brown became widely known as the only person cured of HIV after he received bone marrow transplants to treat leukemia. His doctor, Gero Hütte—a hematologist with no special experience in HIV—found a donor who was both a genetic match and had an uncommon mutation, known as CCR5-delta32, that makes CD4 cells resistant to HIV entry.

Over the last 5 years Brown has endured multiple high-volume blood draws, leukapheresis, flexible sigmoidoscopy with 30 biopsies from the rectum, and a lumbar puncture for this study. His blood plasma, peripheral blood mononuclear cells (PBMCs), and gut and cerebrospinal fluid (CSF) samples were sent to several labs with expertise in detecting extremely small amounts of virus. Researchers including Tae-Wook Chun from the National Institute of Allergy and Infectious Diseases, Douglas Richman from the
University of California San Diego, and Robert Siliciano from Johns Hopkins used a variety of different measurements and techniques.

The results showed that Brown’s CD4 T-cell counts remained fairly stable and were within the normal range. **HIV genetic material was found in plasma by 2 of 4 labs at 3 different time points, and once in a rectal sample**, but it was barely detectable by the most sensitive assays and was lower than levels typically seen in patients with viral suppression on antiretroviral therapy.

**No HIV RNA or DNA was detected in Brown’s CSF**, and 2 labs with co-culture experience could detect no replication-competent virus in 9 billion PBMCs obtained through leukapheresis. HIV-specific antibody levels were detectable, but tended to decrease over time.

Furthermore, cloned HIV sequences bore little resemblance to each other or to pre-transplant virus. Even stranger, 2 sequences were almost the same as a common lab strain, suggesting possible contamination.

Like looking for a needle in a haystack, this intensive analysis provided a collection of evidence that investigators hoped would provoke discussion about what tests are useful in people with extremely low-level virus, thereby advancing cure research.

Unfortunately, one researcher—Alain Lafeuillade from the Department of Infectious Diseases at General Hospital in Toulon, France—has morphed the conversation into mockery by misrepresenting the results in a blog post on the HIV Reservoirs and Eradication Strategies reference portal and in a widely distributed press release.

Lafeuillade stated that "although HIV could have evolved and persist[ed] over the last 5 years, these data also raise the possibility that the patient has been reinfected. More studies are in progress to know if this seronegative HIV individual can infect other subjects if he has unsafe sex."

As Richard Jefferys from the Treatment Action Group in New York stated in an email, "It is not yet certain if the analyses that did show evidence of HIV genetic material are accurate or represent false positives, but if they do turn out to be accurate it would not be a surprise: HIV can infect multiple different cell types but can only replicate in some of them, and Brown did not have every cell in his body replaced."

Paula Cannon from the University of Southern California Keck School of Medicine told HIVandHepatitis.com, "The important thing is that Timothy remains free of any replicating or infectious virus, that he continues to have no symptoms of being HIV infected, and that he continues to be in good health—that he continues to be cured."

Jefferys’ and Cannon’s statements appear to represent the consensus of cure researchers and activists, yet it depends on what definition of cure is used. The field is so new, with so many unknowns, that what researchers mean by a cure is controversial in itself. However, if Brown is able to control HIV without medication, he is considered functionally cured, despite not being able to completely eradicate every last bit of non-replicating HIV in his body.

Lafeuillade’s statement suggesting that Brown may infect other people if he has unsafe sex is "vile," "appalling," and "shameful," according to several AIDS cure activists. Debate is necessary in science—especially when a field is new—but when blatant misinterpretation demonizes the patient, the goal is crushed.

I’ve got to hand it to Timothy Brown, who is still the first person known to be cured of AIDS. As he eventually decided to make his name known to the world, he has had to live with scientific commentary and interpretation, accurate or not. He has had to endure countless tests and procedures, and at least one close call with death. Yet all along he has graciously allowed himself to be poked and prodded, volunteering his body—his blood, sweat, and tears—for some of the most important scientific research in the history of AIDS.
Dung Defeats Drugs
Fecal transplants outcompeted traditional antibiotics at curing a deadly intestinal infection.

By Beth Marie Mole | January 18, 2013

Infusing a healthy person’s stool into the intestines of another—a treatment known as a fecal transplant—successfully cured 15 out of 16 patients (94 percent) suffering from a recurrent and dangerous diarrheal infection of *Clostridium difficile*, according to clinical trial results published this week (January 16) in the *New England Journal of Medicine*. In contrast, traditional treatment with the antibiotic vancomycin only cured 7 out of 26 patients (27 percent). Though the success of the transplants convinced researchers to end the trial early, many physicians expected the results since fecal transplants have been used to treat hundreds of patients before, yielding a 90 percent success rate.

“Those of us who’ve been doing this procedure for some time didn’t need any more convincing, but the larger medical community needs to go through these steps,” gastroenterologist Alexander Khoruts, of the University of Minnesota in Minneapolis, who was not involved in the trial, told *Nature*. “It’s an unusual situation where we have more than 50 years of worldwide experience and more than 500 published cases, and only this far along does a randomized trial appear.”

The reason for the delayed trials and reluctant community, Khoruts and others say, is due to squeamishness by doctors and patients about the procedure, which aims to restore a healthy population of gut microbes in a sick person’s intestines. In particular, this latest infused healthy fecal material into a patient’s small intestine through a tube inserted in the patient’s nose. Though the study authors claim the nasal route is quicker and easier than the more common enema method, some doctors fear that patients will find the option repulsive. Researchers have even developed synthetic stool in hopes that it will increase patient acceptance.

Nevertheless, the authors say patients suffering from *C. difficile infections* are anxious to try the transplant. “We get e-mails from everywhere, from desperate patients asking to come to the hospital to get this treatment,” Els van Nood, an internal medicine researcher at the University of Amsterdam and a co-author of the study, told *Nature*. “They can still find a lot of reluctance [among doctors], and we hope that this will change.”

Double DNA
Scientists provide evidence for the existence of four-stranded human DNA, which has previously only been theorized and synthesized.

By Bob Grant | January 22, 2013

HeLa cells, one type of cancer cell where G-quadruplexes were located, WIKIMEDIA, TenOfAllTrades

Researchers at the University of Cambridge in the United Kingdom have reportedly identified quadruple-helix human DNA for the first time ever. Though four-stranded DNA molecules were synthesized in the lab more than 50 years ago, never before have such “G-quadruplexes,” so named because they were thought to occur in guanine-rich regions of the genome, been observed in human cells. The Cambridge scientists provide strong evidence that such four-helix DNA does exist in humans, and suggested that it may play a central role in human disease.
“It’s early days, but if we can map exactly where these G-quadruplex structures pop up in the genome, we may learn how better to control genes or other cellular processes that go awry in diseases like cancer,” study leader Shankar Balasubramanian told *Nature*. “That’s the long-term vision anyway.”

Balasubramanian and his team made an antibody that bound tightly to G-quadruplex structures, but not to traditional double-helix DNA, and found that it bound to many different sites on human chromosomes in cultured tumor cells. They published their findings earlier this week (January 20) in *Nature Chemistry*.

**Is Cannabis Really That Bad?**

**Though some studies point to negative consequences of pot use in adolescents, data on marijuana’s dangers are mixed.**

By Sabrina Richards | January 23, 2013

Marijuana is a tricky drug, alternately demonized as a gateway drug and lionized for its medical promise. And while the juries remain out on both sides of the coin, one thing is clear: its use is on the rise.

According to the US Department of Human Health and Services, the number of people in the United States who admit to smoking pot in the last month climbed from 14.4 million in 2007 to over 18 million in 2011.

This increase may in part be due to the lack of strong evidence supporting the suspected risks of cannabis use. Indeed, though marijuana smoke carries carcinogens and tar just as tobacco smoke does, definitive data linking marijuana to lung damage is lacking. And a recent long-term study that seemed to conclusively link chronic marijuana initiated in adolescence to a lowered IQ in New Zealanders was quickly challenged by a counter-analysis that pointed to socioeconomic status as a confounding factor.

According to survey data from the Centers for Disease Control and Prevention, cannabis use increases in teenagers as marijuana’s perceived risks decline, and researchers—and undoubtedly some parents—are anxious to get to the bottom of the matter.

**Take a deep breath**

In 2012, a study at the University of California, San Francisco (UCSF) calculated that even smoking a single joint every day for 20 years might be benign, though most participants only smoked two or three joints each month. “I was surprised we didn’t see effects [of marijuana use],” said UCSF epidemiologist Mark Pletcher, who led the study.

One assessment of various epidemiological studies points to small sample size and poor study design as reasons for scientists’ inability to nail down a link between cannabis and cancer risk. But some suspect that such a link doesn’t exist, and that marijuana may even have cancer-preventive effects. A 2008 study, for example, suggested that smoking marijuana may reduce the risk of tobacco-associated lung cancer, calculating that people who smoke both marijuana and tobacco have a lower risk of cancer than those who smoke only tobacco (though still a higher risk than non-smokers).

But even Pletcher isn’t sanguine about marijuana’s effects on the lungs, and suspects that there may still be long-term lung damage that can be hard to detect. “We really can’t reassure ourselves about heavy use,” he explained.

**Your brain on drugs**

There is some evidence to suggest that stoned subjects exhibit increased risk-taking and impaired decision-making, and score worse on memory tasks—and residual impairments have been detected days or even weeks after use. Some studies also link years of regular marijuana use to deficits in memory, learning, and concentration. A recent and widely discussed report on the IQs of New Zealanders followed since birth found that cannabis users who’d started their habit in adolescence had lower IQs than non-users.

In this study, led by researchers at Duke University, “you could clearly see as a consequence of cannabis use, IQ goes down,” said Derik Hermann, a clinical neuroscientist at the Central Institute of Mental Health in Germany who was not involved in the research.

But not 4 months later, a re-analysis and computer simulation at the Ragnar Frisch Center for Economic Research in Oslo countered the Duke findings. Ole Rogeberg contended that socioeconomic factors, not marijuana use, contributed to the lower IQs seen in cannabis users.

Rogeberg’s conclusion counters a sizeable literature, however, which supports a link between pot use and neurophysiological decline. Studies in both humans and animals suggest that people who acquiring a marijuana habit in adolescence face long-term negative impacts on brain function, with some users finding it difficult to concentrate and learn new tasks.
Notably, most studies on the subject suggest that while there may be negative consequences of smoking as a teen, users who begin in adulthood are generally unaffected. This may be due to endocannabinoid-directed reorganization of the brain during puberty, Hermann explained. The intake of cannabinoids that comes with pot use may cause irreversible “misleading of the neural growth,” he said.

In addition to the consequences for intelligence, many studies suggest that smoking marijuana raises the risk of schizophrenia, and may have similar effects on the brain. Hermann’s group used MRI to detect cannabis-associated neuron damage in the pre-frontal cortex and found that it was similar to brain changes seen in schizophrenia patients. Other studies further suggest that weed-smoking schizophrenics have greater disease-associated brain changes and perform worse on cognitive tests than their non-smoking counterparts.

But much of this research can’t distinguish between brain changes resulting from marijuana use and symptoms associated with the disease. It’s possible that cannabis-smoking schizophrenics “might have unpleasant symptoms [that precede full-blown schizophrenia] and are self-medicating” with the psychotropic drug, said Roland Lamarine, a professor of community health at California State University, Chico. “We haven’t seen an increase in schizophrenics, even with a lot more marijuana use.”

In fact, other research suggests that cannabis-using schizophrenics score better on cognitive tests than non-using schizophrenics. Such conflicting reports may be due to the varying concentrations—and varying effects—of cannabinoids in marijuana. In addition to tetrahydrocannabinol (THC), a neurotoxic cannabinoid that is responsible for marijuana’s mind-altering properties, the drug also contains a variety of non-psychoactive cannabinoids, including cannabidiol (CBD), which can protect against neuron damage. Hermann found that the volume of the hippocampus—a brain area important for memory processing—is slightly smaller in cannabis users than in non-users, but more CBD-rich marijuana countered this effect.

A deadly cocktail?
While data supporting the harmful effects of marijuana on its own are weak, some researchers are more worried about the drug in conjunction with other substances, such as tobacco, alcohol, or cocaine. Some studies suggest, for example, that marijuana may increase cravings for other drugs, leading to its infamous tag as a “gateway drug.” A study published earlier this month supported this theory when it found that, at least in rats, THC exposure increases tobacco’s addictive effects. Furthermore, marijuana may not mix well with prescription drugs, as cannabis causes the liver to metabolize drugs more slowly, raising the risk of drug toxicity.

Despite these concerns, however, Lamarine thinks it’s unlikely that the consequences of cannabis use are dire, given the amount of research that has focused on the subject. “We’re not going to wake up tomorrow to the big discovery that marijuana causes major brain damage,” he said. “We would have seen that by now.”

Human Proteome Project Update
Researchers report steady progress in the effort to map all the proteins made by human chromosomes.
By Bob Grant | January 24, 2013
Big science rides again with the announcement that all is well with the Chromosome-centric Human Proteome Project (C-HPP), a 10-year initiative to map all the proteins produced by genes on human chromosomes. The C-HPP was launched last year, and organizers of the effort envision a close to their activities occurring in September of 2022. The current issue of the Journal of Proteome Research is devoted entirely updating the progress of the international teams of scientists involved with the C-HPP. The highlights from the special issue include:
• An update on the effort to characterize the protein-coding genes on male-specific regions of the Y chromosome, including genetic components involved with sex determination and
reversal, spermatogenesis and male infertility, prostate cancer, sex-specific effects on the brain and behavior, and graft-versus-host disease.

- A report from the Biology/Disease-driven Human Proteome Project (B/D-HPP), which aims to identify proteins that play pivotal roles in a variety of diseases.
- Recent findings from a Taiwanese group conducting a pilot study on chromosome 4, which is rich in cancer-associated proteins and could prove useful in biomarker or drug target applications. The study identifies 141 proteins on the chromosome that are “cell-secretable/shedable proteins” and an additional 54 that are classified as cancer-associated proteins.
- A preliminary map of the proteome of chromosome 8, which has a very high mutation rate in humans and therefore could play an important role in tumorigenesis.
- The announcement of a new data integration and analysis software system and browser designed specifically for the C-HPP.

The issue contains many more updates on the progress of several groups working under the auspices of the C-HPP, and the group aims to publish such a special issue for every year of the project.

**Real-time Outbreak Sequencing**

**Sequencing the whole genomes of bacterial pathogens as they spread among hospital patients and health care workers could transform the control of infectious disease.**

By Dan Cossins | December 19, 2012

When an infectious outbreak occurs, hospital investigators combine epidemiological data with bacterial typing to trace the source and path of the pathogen in the hopes of preventing further infections. Current methods are slow and offer limited resolution, meaning they can’t always differentiate between strains originating from the same bacterial clone. But by dramatically increasing the speed and accuracy of strain discrimination, a new generation of rapid, low-cost whole-genome sequencing (WGS) technologies promises to revolutionize outbreak surveillance and investigation.

With full genome sequences, researchers can spot the mutations that accumulate every time a bacterium divides down to the single nucleotide level. This allows them to track the evolution and movement of microbes with unprecedented precision, potentially leading to life-saving interventions and improved infection control strategies.

“I expect whole-genome sequencing will be transformative, in particular in outbreak investigations, within the next few years,” said Kathryn Holt, a microbiologist at the University of Melbourne in Australia. “The key advance is the dramatic increase in resolution, which enables us to be much surer about transmission pathways.”

**Genomic detectives**

Two studies from this year demonstrate the power of this approach. In 2011, the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, experienced an outbreak of a highly resistant form of *Klebsiella pneumoniae*, which causes urinary, respiratory, and blood infections in people with weakened immune systems, and kills more than half of its infected. The doctors knew one patient was carrying the pathogen but she was carefully isolated, so they thought it had been contained. Then, 3 weeks after she was discharged, another patient was diagnosed and more cases followed. In total, 18 patients were infected and 6 died as a direct result.

The conventional method for bacterial typing is pulse-field gel electrophoresis, in which large DNA fragments are separated by an electric field to create genetic fingerprints for each bacterial sample. But the technique “was too coarse to tell us whether our first two cases were two separate introductions or [if] one was transmitted from the other,” said Tara Palmore, an infectious disease physician at the Clinical Center. Doctors and researchers were at a loss to explain the spread—and powerless to stop it.

Once the outbreak was under control, colleagues from the National Human Genome Center sequenced the genomes of the bacteria isolated from affected patients. Genetic similarities between samples revealed that all the strains had come from the first patient (patient 1), which had seemed unlikely from the epidemiological data—because there was no direct contact between that patient and those that were subsequently infected. They also found that patient 1 harbored three genetically distinct versions of *Klebsiella*, and that each had been transmitted on separate occasions to start three different lineages of infection.

Using an evolutionary tree to reconstruct the likely route, the researchers showed that “the dynamics of transmission were far more complex than we first realized,” said Palmore. “It was mostly being spread by asymptptomatically colonized patients,” or “carriers.” For example, the bacteria first jumped from
patient 1 to two patients that remained asymptomatic for some time—and it was those asymptomatic patients that passed the infection on to “patient 2,” the second patient to show signs of infection. Such a counterintuitive path could not have been predicted, and would not have been detected without genetic data.

Over in the United Kingdom, as a strain of methicillin-resistant Staphylococcus aureus (MRSA) spread through a neonatal unit at Rosie’s Hospital in Cambridge, infecting 12 infants over a 6-month period in 2011, researchers also turned to WGS for answers. A team at Cambridge University and the nearby Wellcome Trust Sanger Institute compared full-genome sequences of bacteria from infected infants, and revealed that all the strains were descended from a common source. Then, when another baby was infected 2 months after the previous case, sequencing showed it was part of the same outbreak. That led the team to screen all the staff, which identified one person who was carrying MRSA—and was likely involved spreading it to the babies.

“It’s impossible to prove that this epidemic was stopped by this intervention, but we believe it prevented further transmission,” said Julian Parkhill, a microbiologist at the Sanger Institute and co-author of the study. But either way, he added, it demonstrates the power of whole-genome sequencing for elucidating the movements of pathogens.

Routine practice?
With the latest bench-top machines capable of sequencing a bacterial genome in just a few hours, outbreak analyses can now be performed in real time—with obvious benefits. “It will enable rapid identification of a [real] transmission, and save a lot of time and effort in not having to chase down spurious transmissions,” said Parkhill. And more efficient tracking of transmission allows for much more targeted and effective infection-control measures, Palmore added.

In addition, WGS will help to track antibiotic resistance mutations as they evolve. “It can be quicker than phenotypic testing, which requires growing the bacteria in the presence of a range of antibiotics,” said Holt. “With sequencing, we can quickly see which resistance mechanisms the bug has encoded in its DNA,” which can guide treatments.

Real-time sequencing of hospital pathogens is unlikely to become a routine practice quite yet, however, largely because the interpretation of genetic data requires a level of expertise that lies beyond most clinicians. To overcome that obstacle, the development of analysis tools that can provide clinically relevant information in a manner that infectious-disease physicians can understand is absolutely critical, said Parkhill. “The average clinician in a hospital is not going to be able to do this [analysis], so it has to be automated.” Parkhill’s group is working to develop such a system.

Meanwhile, the UK Health Protection Agency is already exploring whether it is cost-effective to use the approach to supplement existing methods in a select few English hospitals. Indeed, although only a handful of proof-of-principle case studies exist, it’s clear that WGS is going to have a big impact on infection control and public health in the future, said Derrick Crook, a microbiologist at the University of Oxford who worked on a pilot study for tracking MRSA and C. difficile in three UK hospitals. “We’re looking at this being used [in a clinical setting] over the next few years.”

**Universal Flu Vaccines Charge Ahead**

Researchers and biotech companies are bringing a universal flu vaccine closer to reality.

By Sabrina Richards | January 14, 2013

It’s a frustrating fact of life that coming down with influenza one year doesn’t guarantee anyone a flu-free season the next year. Even the flu vaccine doesn’t provide full-proof protection, as it covers only a select few strains of the virus—a selection that’s based on the World Health Organization’s best bet as to which strains around the world will be most prevalent in the coming flu season.

Unfortunately, those predictions are proved wrong about one time out of 20, explained Sarah Gilbert, who leads the Human Influenza Vaccine Programme at the University of Oxford’s Jenner Institute.

However, some researchers are getting closer to creating the ever-elusive universal flu vaccine, which could protect against a number of influenza viruses at once, including pandemic strains. If successful, universal flu vaccines would take the guesswork out of vaccine planning, and only require booster shots every few years.

**One antibody to bind them all**

Influenza is an RNA virus that uses its hemagglutinin (HA) protein like a key to allow it to enter and infect target host cells. In response to infection, or to a typical flu vaccine, the body produces antibodies that bind the head of the HA molecule, preventing free-floating virus from entering and infecting cells.
However, the head is also the part of the HA protein that the virus most frequently changes via mutation, making the antibodies produced against one strain ineffective against another.

The answer to creating a vaccine that protects against many strains lies in forcing the immune system to make antibodies against the portions of the HA molecule that are shared, or genetically conserved, among most influenza viruses, thus creating a more universal vaccine. But, for unknown reasons, most vaccines don’t elicit such antibodies. So researchers are now trying new ways of enticing the immune system into making antibodies that recognize these general targets and neutralize many types of influenza at once.

“Up until about 4 years ago, we didn’t know much about human broadly neutralizing antibodies,” said Ian Wilson, a structural biologist at The Scripps Research Institute. But the last few years, researchers have found individuals who produce antibodies that neutralize a wide variety of both influenza A and B strains, showing that “a universal vaccine is possible if you can elicit the same types of antibodies” in others, said Wilson.

Wilson’s lab helped solve the structure of some of these broadly neutralizing antibodies and the region of HA they target—the conserved stem of HA. More recently, Wilson and his collaborators have shown that because HA’s head region has tiny conserved areas, occasionally even an antibody directed at the HA head can have some cross-reactivity among influenza types.

But most researchers think a stronger antibody can be made against regions in the HA stem. Specifically, some researchers think that a “headless” HA proteins could focus the antibody response on the conserved stem region. Others are looking to design vaccines that contain only small portions of the most important conserved segments of the stem region. Still others are focused on understanding the basic immunology of how antibodies bind and recognize their targets in order to improve vaccines from a different angle, and possibly understand why antibodies aren’t often naturally made to the stalk region, said Wilson.

Several biotech companies are preparing what they hope will become the first universal flu vaccines on the market, though none have been tested as a universal vaccine yet. Most have been tested for safety and ability to stimulate an immune response in healthy volunteers, or boost efficacy of current vaccines with mostly positive results. One strategy being tested combines several conserved regions of flu proteins into one molecule to produce a vaccine that hopefully stimulates an antibody response against a wide variety of strains. This includes the M-001 vaccine from Israel-based BiondVax, which contains regions from HA and two internal virus proteins. When M-001 was combined with the seasonal vaccine, it enhanced immunity to the strains contained in the seasonal vaccine. Other companies are pursuing similar methods, said Gilbert. “They’re all trying to use only very small [conserved] regions, and they all have their own strategies to identify which regions” are the best, as well as ways to produce stronger immune responses, she said.

**Delivery service**

Changing how vaccines are delivered also has the potential to produce more broadly cross neutralizing antibodies. Last year, researchers at the NIH elicited antibodies against the conserved HA stem region by presenting bird flu HA in two different forms. First they primed with a DNA vaccine—a segment of DNA encoding the HA protein, which host cells produce and present to immune cells—and followed this with a protein-based inactivated H5N1 boost. Using this prime-boost method produced neutralizing antibodies targeting the conserved stem region of HA.

John Schrader, an immunologist at the University of British Columbia says that it may be possible to generate broadly neutralizing antibodies using currently available vaccines, if it’s done correctly, he says. Schrader and his colleagues found that infection with, or vaccination against, the pandemic 2009 H1N1 strain (swine flu) produces the elusive broadly cross-neutralizing antibodies that seasonal vaccines do not. This may be because H1N1 is radically different from the other viruses commonly circulating in the human population. That distinctiveness may allow the virus to be recognized by a rare set of memory B cells, Schrader said.

Normally, the seasonal flu virus activates a wide array of B cells, most against the head region, a few against the stalk. Some of each persist after the infection as “memory” cells. When the next seasonal flu virus infects, it has similar head regions to previous viruses, so it’s the memory cells that bind to the head region that are activated, while the rare B cells against the conserved stem region get lost in the shuffle. But a drastically different virus like H1N1 only shares stem regions with previous viruses, so it can activate rare anti-stem memory B cells without also activating the anti-stem memory cells—producing large amounts of broadly neutralizing antibodies, Schrader said.
Therefore, prompting the production of broadly neutralizing antibodies could be as simple as vaccinating with a rare virus strain, and boosting with different rare strains, to ensure that only memory B cells that recognize the stem are activated. It would be key, in Schrader's strategy, to avoid vaccinating someone twice with the same vaccine, so that B cells that recognize the head regions don't also get re-activated.

**A different target**

Rather than trying to find the perfect region or regions of the HA molecule, some researchers are looking to other conserved viral proteins. The M2 protein, which helps the flu virus empty its contents into its target cell, is one of only three viral proteins dotting its surface—and one of the least variable between strains. But M2 presents several challenges for investigators hoping to produce an M2-targeted vaccine, cautioned Sang-Moo Kang, an immunologist at Georgia State University. First, there are many fewer M2 proteins than HA proteins, and secondly, the antibody-targeted region of M2 is about 20 times smaller than HA’s, “so M2 can’t compete in terms of host response,” said Kang. Also, rather than stimulating the generation of antibodies that prevent infection by blocking viral entry into cells, anti-M2 antibodies target infected cells, leading to their lysis. Such a vaccine would likely just contain an infection rather than prevent cells from becoming infected in the first place.

Despite these hurdles, at least one company is targeting M2 in their bid to produce a universal vaccine. VaxInnate, a New Jersey-based biotech company, has performed clinical trials using M2 epitope (M2e) fused to a bacterial protein. Like other vaccines being touted as future universal vaccines, VaxInnate’s method has yet to be shown to be effective against infection with a variety of strains. So far, VaxInnate has used their M2 vaccine to boost immune responses to a current influenza vaccine.

**A new direction**

Although most of the work to date has focused on antibody or B-cell-mediated responses, some researchers think that T cells—which kill virally infected cells—will be an important facet of universal vaccines. Because T cells kill flu-infected cells, they can prevent newly replicated virions from escaping infected cells and thus keep the infection from spreading through the body (sometimes so well that a patient notices no symptoms). Current vaccines don’t do much to activate T cells, which explains why previous infection with seasonal flu can protect against pandemic strains, but previous vaccination does not. T cells react to viral proteins that are chopped up and presented by infected cells, allowing them to recognize regions of conserved internal proteins that B cells—which generally target surface proteins—miss.

Gilbert at the Jenner Institute and her colleagues **created a vaccine made of two conserved internal influenza proteins attached to a live vaccinia virus that is rendered unable to replicate.** When patients were exposed to a strain of flu they had not encountered before, only 2 out of 11 patients who’d been vaccinated with Gilbert’s vaccine contracted the flu compared to 5 out of 11 unvaccinated controls. Despite the promising results, “I wouldn’t want to sell a vaccine that only targets T cells,” noted Gilbert, who is currently working on combining her T cell vaccine with proteins to stimulate neutralizing antibodies as well.

Even if researchers do create vaccines that protect against all influenza viruses, we’ll still need to get vaccinated regularly—just not every year, said Gilbert. Unlike some other viruses, the flu doesn’t stimulate strong enough immune memory to keep us protected for life, even using a more universal vaccine. Gilbert estimates that future vaccines may stretch our yearly needle jabs to once every 5 years or so.

**Non-coding Mutations May Drive Cancer**

**The majority of human melanomas contain mutations in a gene promoter, suggesting mutations in regulatory regions may spur some cancers.**

By Dan Cossins | January 24, 2013

Mutations in the regulatory, or non-coding, regions of the telomerase reverse transcriptase (TERT) gene—a cancer-associated gene that encodes a component of telomerase, an enzyme known to help protect the ends of chromosomes and support cell longevity—may be at the root of most melanomas, according to two papers published today (January 24) in *Science*.

In both studies, researchers identified mutations that created new binding sites in the TERT promoter for particular transcription factors and resulted in increased transcriptional activity at the TERT promoter, which may in turn lead to increased expression of the gene and the endless cell division characteristic of cancer cells. The findings suggest that mutations in regulatory parts of the genome, in
addition to those in protein-coding sequences, may be a key mechanism causing the growth of certain types of cancer.

“I am excited by the finding that regulatory mutations can apparently act as drivers of carcinogenesis,” Elaine Mardis, a cancer geneticist and co-director of the Genome Institute at Washington University, Missouri, who was not involved in the research, said in an email. “This is great news for labs like ours that have always emphasized the importance of whole genome sequencing over exome or targeted sequencing.”

Until recently, sequencing efforts focused almost exclusively on the protein encoding regions of cancer genomes, due to the high cost of whole genome sequencing and the fact that it’s easier to identify effects of mutations in protein-coding genes. As a result, scientists have identified many recurrent mutations in protein-coding regions that contribute to cancer development, but very few in non-coding regions.

To see if tumor genomes also harbor mutations in these under-explored regulatory regions, Franklin Huang and Eran Hodis of Harvard Medical School and colleagues took a closer look at whole genome sequences of malignant melanomas published last May. Sure enough, they found two somatic mutations, which they called C228T and C250T, in the TERT promoter region in 71 percent of the tumors they analysed—making them more common than the known melanoma mutations in the coding regions of the genes BRAF and RNAs.

“The fact that these mutations occur so frequently near what is a very important gene in cancer development was unexpected, but it was staring us in the face,” said Hodis.

Intriguingly, both mutations generated an identical DNA sequence containing a transcription factor binding site, increasing the transcription of reporter genes linked to the TERT promoter by 2- to 4-fold. This led the researchers to propose that these promoter mutations may be driving melanoma development by increasing TERT expression, which is tightly regulated in normal cells. When TERT is over-expressed, cells produce elevated levels of telomerase, prompting the regeneration of chromosome-capping telomeres and resulting in cells that can divide limitless. Mutations that increase TERT expression could thus be expected to promote cancerous growth.

“The fact that these mutations create a transcription factor binding site, although we haven’t shown it actually binds a transcription factor, is a clue that this could be one mechanism for how it increases activation of TERT,” said Hodis.

In a separate study, Susanne Horn of the German Cancer Research Center in Heidelberg and colleagues compared the whole genome sequences of tumors from a melanoma-prone family who did not carry two known germline mutations linked to melanoma, and identified a germline mutation in the TERT promoter in individuals with the cancer. Once again, the sequence change created a new binding pattern for certain transcription factors and increased transcription activity.

 “[We think] the binding of transcription factors up-regulates the telomerase gene in the developing tumors,” Horn said. “High levels of telomerase may then lead to cells that can divide more often.”

Horn and her colleagues also screened the TERT promoter in 168 cell lines derived from metastatic melanomas from the general population, and found recurrent somatic mutations in 74 percent of them. The majority of those mutations generated new transcription factor binding sites.

Together, the studies show that “although our focus has been on the 1 percent of the genome that codes for proteins, there are potentially important discoveries in the rest of the genome,” said Huang. Indeed, Mardis added, if researchers continue to focus on exome or targeted sequencing of cancer genomes, “we are going to miss the clues available from analysis of the whole genome that may . . . ‘matter’ to driving the cancer growth.”


Bottle-Feeding Urged for U.S. Moms with HIV
By Crystal Phend, Senior Staff Writer, MedPage Today
Published: January 28, 2013
Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco and Dorothy Caputo, MA, BSN, RN, Nurse Planner

**Action Points**
- American women with HIV shouldn’t breastfeed their babies, regardless of low levels of the virus and antiviral treatment, according to the American Academy of Pediatrics (AAP).
• Note that this recommendation differs from World Health Organization recommendations for poor regions of the world, where infant formula feeding typically isn't feasible and malnutrition and infectious disease are bigger threats.

• American women with HIV shouldn’t breastfeed their babies, regardless of low levels of the virus and antiviral treatment, the American Academy of Pediatrics (AAP) cautioned.

The only way to completely prevent HIV transmission through human milk is not to breastfeed, a policy statement from the group pointed out in the February issue of Pediatrics.

This guideline breaks from the strong AAP stance in favor of breastfeeding for women without HIV infection.

It also differs from World Health Organization recommendations for poor regions of the world, where infant formula feeding typically isn't feasible and malnutrition and infectious disease are bigger threats.

That guideline recommends exclusive breastfeeding through age 6 months, then breastfeeding with complimentary foods through 12 months, together with antiretroviral prophylaxis for mother or child to reduce HIV transmission risk.

Without prophylaxis, the risk of infection for the baby is around 1% per week in the first 4 to 6 weeks of life, then about 0.2% per week for the duration of breastfeeding, translating to a cumulative transmission risk of 14% in one study.

With 6 months of antiretroviral prophylaxis, the risk dropped to 1% to 5% in studies of African mothers.

Although a low risk, "transmission can occur despite undetectable maternal plasma RNA concentrations," noted Lynne Mofenson, MD, of the National Institute of Child Health and Human Development in Rockville, Md., and colleagues in the AAP statement.

For families with access to clean water and affordable infant formula, any transmission risk outweighs the benefits of breastfeeding in this setting, it argued.

The transmission risk is higher with acute maternal infection, mastitis or other breast abnormalities; high viral load levels or low CD4 cell counts in the mother; and mixed formula and breast feeding.

Women suspected to have an acute HIV infection shouldn't breastfeed their child until HIV infection is ruled out. Pumping and discarding the milk meanwhile may help maintain its supply.

If an HIV-infected woman with repeatedly undetectable HIV viral loads on antiretroviral therapy chooses to breastfeed despite intensive counseling, she wouldn’t automatically qualify for a referral to Child Protective Services.

In such a case, the document recommended that the pediatrician consult and coordinate with the mother's HIV specialist to carefully monitor her viral levels and treatment adherence.

Antimicrobial agents should be given promptly if the woman develops clinical mastitis. The baby should also be monitored for HIV status through 6 months after weaning.

Flash heating breast milk to pasteurize it doesn't eradicate HIV cells. Pre-chewing food for infants has also been associated with transmission of the infection in some cases.

If women are worried about affording infant formula, pediatricians should help them find financial support, such as the Special Supplemental Nutrition Program for Women, Infants, and Children.

"In the United States, where there is access to clean water and affordable replacement feeding, the AAP continues to recommend complete avoidance of breastfeeding as the best and safest infant feeding option for HIV-infected mothers, regardless of maternal viral load and antiretroviral therapy," the statement concluded.

**Pitt Team Finds "Achilles Heel" of Key HIV Replication Protein**

*HealthNewsDigest.com*, (01.24.2013)

University of Pittsburgh School of Medicine researchers report they have developed a way to track—and perhaps block—the activity of Nef, an HIV protein that is critical to HIV replication. According to researcher Thomas Smithgall, Ph.D., the team reasoned it might be possible to stop HIV replication by preventing Nef’s “usual interactions with other proteins.”

The researchers linked Nef to Hck—an enzyme activated in HIV-infected cells—and screened close to 250,000 compounds for a compound that would block Nef’s role in replication. The automated screening procedure identified a promising compound, B9, which interrupts Nef’s role in HIV replication by preventing two Nef molecules from forming “dimers,” an essential step in the HIV replication process.

The team believes their discovery of the point where B9 binds to Nef could lead to the invention of new drugs that could prevent HIV from developing into AIDS. Smithgall says test-tube and cell culture
experiments confirm this spot is an HIV “Achilles heel” that could be a target for drugs that stop the virus from replicating. The University of Pittsburgh Drug Discovery Institute is working to find a formula similar to B9 that can be tested with animals. The full report, “Effector Kinase Coupling Enables High-Throughput Screens for Direct HIV-1 Nef Antagonists with Antiretroviral Activity,” was published online in the journal Chemistry & Biology (2013; 20(1):82–91).

**Focus Water, Sanitation Investments On Cholera Risk Zones, Aid Groups Say**
"Aid groups are urging donors to invest in water and sanitation in areas known as hotbeds for cholera," saying "while such projects might directly affect a relatively small population, the indirect impact in terms of cholera reduction could be immense," IRIN reports. "The call comes as [non-governmental organizations (NGOs)], donors, and governments study lessons learned from one of the severest cholera outbreaks in years—a Guinea-Sierra Leone cross-border epidemic which broke out in coastal areas, where there is no access to clean water, then exploded in the capitals," the news service continues. The article includes comments from representatives of the European Union aid agency ECHO, the group Action Against Hunger (ACF), and the U.K.’s Department for International Development (DFID), as well as a local medical officer in Sierra Leone. Christophe Valingot of ECHO said, "The identification of risk zones allows us to say, OK, we’ve got to invest here if we want to have an impact on cholera," according to IRIN (1/25).

**Polio Eradication Must Fit Into Larger Public Health, Development Goals**
"The tragic murders of nine anti-polio workers in Pakistan last month, followed by the New Year’s Day killing of seven more local community development workers, was both a wake-up call to the global polio eradication effort in its current form, and a 'canary in the mine' regarding the deteriorating state of development and security in the country," Heidi Larson, a senior lecturer and principal investigator at the London School of Hygiene & Tropical Medicine, writes in a SciDev.Net opinion piece. "The past month of public reporting and private discussions on what happened, why and what happens next have revealed a complex web of governance failings, inadequate development structures and a landscape of multiple security threats, both locally and internationally," she states, describing possible factors and challenges that led to the killings.

"[E]fforts at [polio] eradication should not be pushed as the priority above all others in Pakistan," Larson writes, adding, "Instead, efforts to eradicate polio need to engage with activities addressing other local priorities—not by temporarily adding other services to polio campaigns, but instead by supporting measures that contribute to long-term, sustainable development." She continues, "Polio eradication is indeed a priority for global health and, for Pakistan’s leaders, failing to eliminate it would certainly compromise the country’s already fragile regional and global positioning." Larson concludes, "The last leg of eradication cannot be business as usual. Each step will need to carefully consider the local political, cultural and operational dynamics—and not the dynamics of the past year, but of the current week, and even each new day they operate in" (1/25).

**Tuesday, January 22, 2013**

**Penicillin, not the pill, may have launched the sexual revolution**
The 1950s were not as prudish as they seemed on the surface, says economist Andrew Francis.
By Carol Clark
The rise in risky, non-traditional sexual relations that marked the swinging ’60s actually began as much as a decade earlier, during the conformist ’50s, suggests an analysis recently published by the Archives of Sexual Behavior.

“It’s a common assumption that the sexual revolution began with the permissive attitudes of the 1960s and the development of contraceptives like the birth control pill,” notes Emory University economist Andrew Francis, who conducted the analysis. “The evidence, however, strongly indicates that the widespread use of penicillin, leading to a rapid decline in syphilis during the 1950s, is what launched the modern sexual era.”

As penicillin drove down the cost of having risky sex, the population started having more of it, Francis says, comparing the phenomena to the economic law of demand: When the cost of a good falls, people buy more of the good.

“People don’t generally think of sexual behavior in economic terms,” he says, “but it’s important to do so because sexual behavior, just like other behaviors, responds to incentives.”

Syphilis reached its peak in the United States in 1939, when it killed 20,000 people. “It was the AIDS of the late 1930s and early 1940s,” Francis says. “Fear of catching syphilis and dying of it loomed large.”

Penicillin was discovered in 1928, but it was not put into clinical use until 1941. As World War II escalated, and sexually transmitted diseases threatened the troops overseas, penicillin was found to be an effective treatment against syphilis.

“The military wanted to rid the troops of STDs and all kinds of infections, so that they could keep fighting,” Francis says. “That really sped up the development of penicillin as an antibiotic.”

Right after the war, penicillin became a clinical staple for the general population as well. In the United States, syphilis went from a chronic, debilitating and potentially fatal disease to one that could be cured with a single dose of medicine.
From 1947 to 1957, the syphilis death rate fell by 75 percent and the syphilis incidence rate fell by 95 percent. “That’s a huge drop in syphilis. It’s essentially a collapse,” Francis says.

In order to test his theory that risky sex increased as the cost of syphilis dropped, Francis analyzed data from the 1930s through the 1970s from state and federal health agencies. Some of the data was only available on paper documents, but the Centers for Disease Control and Prevention (CDC) digitized it at the request of Francis.

For his study, Francis chose three measures of sexual behavior: The illegitimate birth ratio; the teen birth share; and the incidence of gonorrhea, a highly contagious sexually transmitted disease that tends to spread quickly.

“As soon as syphilis bottoms out, in the mid- to late-1950s, you start to see dramatic increases in all three measures of risky sexual behavior,” Francis says.

While many factors likely continued to fuel the sexual revolution during the 1960s and 1970s, Francis says the 1950s and the role of penicillin have been largely overlooked. “The 1950s are associated with prudish, more traditional sexual behaviors,” he notes. “That may have been true for many adults, but not necessarily for young adults. It’s important to recognize how reducing the fear of syphilis affected sexual behaviors.”

A few physicians sounded moralistic warnings during the 1950s about the potential for penicillin to affect behavior. Spanish physician Eduardo Martinez Alonso referenced Romans 6:23, and the notion that God uses diseases to punish people, when he wrote: “The wages of sin are now negligible. One can almost sin with impunity, since the sting of sinning has been removed.”

Such moralistic approaches, equating disease with sin, are counterproductive, Francis says, stressing that interventions need to focus on how individuals may respond to the cost of disease.

He found that the historical data of the syphilis epidemic parallels the contemporary AIDS epidemic. “Some studies have indicated that the development of highly active antiretroviral therapy for treating HIV may have caused some men who have sex with men to be less concerned about contracting and transmitting HIV, and more likely to engage in risky sexual behaviors,” Francis says.

“Policy makers need to take into consideration behavioral responses to changes in the cost of disease, and implement strategies that are holistic and longsighted,” he concludes. “To focus exclusively on the defeat of one disease can set the stage for the onset of another if preemptive measures are not taken.”

1/28/13

Some Health Benefits Of Berries May Not Make It Past Your Mouth
COLUMBUS, Ohio – Research has suggested that compounds that give colorful fruits their rich hues, especially berries, promote health and might even prevent cancer. But for the first time, scientists have exposed extracts from numerous berries high in those pigments to human saliva to see just what kinds of health-promoting substances are likely to survive and be produced in the mouth.

It’s too early to name the best berry for health promotion based on this initial work. But the researchers have discovered that two families of pigments that provide berries with their colors, called anthocyanins, are more susceptible to degradation in the mouth than are the other four classes of these pigments.

The Ohio State University study also showed that bacteria living in the mouth are responsible for most of the breakdown of these compounds that occurs in saliva. Researchers are investigating whether it’s the berry pigments themselves, or instead the products of their degradation, that actually promote health.

Scientists say that these early findings will contribute to the further development of confectionaries, gums and other delivery devices for the prevention and possibly the treatment of conditions such as periodontal disease and oral cancers.

The researchers exposed extracts of anthocyanin pigments from blueberries, chokeberries, black raspberries, red grapes and strawberries to the saliva collected from 14 people. Black raspberries, in particular, have been shown in numerous previous studies to have chemopreventive effects on tumors in the mouth, esophagus and colon, mostly in animal studies. Their high anthocyanin content has been linked to those benefits.

“All fruits are unique because their chemical composition, or fingerprint, varies,” said Mark Failla, professor of human nutrition at Ohio State and interim chair of the Department of Human Sciences.

“There are many different edible berries. Some might be better for providing health-promoting effects
within the oral cavity, whereas others may be more beneficial for colonic health. We simply do not know at this time.

“Increased intake of fruits and vegetables is associated with decreased risk of some chronic diseases. An understanding of the metabolism of these compounds, and the relative activities of the compounds in the consumed fruit and their metabolic products, is needed to make scientifically sound dietary recommendations and to develop effective delivery vehicles for the mouth,” Failla said.

The research is published in a recent issue of the journal *Food Chemistry*.

Failla and colleagues asked 14 healthy individuals between the ages of 21 and 55 years to collect saliva in the morning before they had eaten breakfast or brushed their teeth. Research participants later collected additional saliva samples before and after they had rinsed their mouths with an antibacterial liquid.

The five fruits selected for study allowed the scientists to test the six distinct families of the anthocyanin pigments. Researchers purified the anthocyanins from each berry type and added the extracts to saliva.

The extent of the pigment degradation in saliva was primarily a function of the chemical structure of a given anthocyanin, said Failla, also an investigator in Ohio State’s Comprehensive Cancer Center and Food Innovation Center.

Two families of anthocyanins consistently degraded when exposed to saliva: delphinidin and petunidin. Four other families were more stable: cyanidin, pelargonidin, peonidin and malvidin.

“Our observations suggest that the bacteria within one’s oral cavity are a primary mediator of pigment metabolism. The bacteria are converting compounds that are present in the foods into metabolites,” Failla said. “One area of great interest is whether the health-promoting benefits associated with eating anthocyanin-rich fruits like berries are provided by the pigment itself, the natural combinations of the pigments in the fruit, or the metabolites produced by bacteria in the mouth and other regions of the gastrointestinal tract.”

There is context for this study that further complicates the understanding of anthocyanins’ benefits. Multiple studies have led to the conclusion that anthocyanins themselves are very poorly absorbed by the body.

“If anthocyanins are the actual health-promoting compound, you would want to design food products, confectionaries and gels containing mixtures of anthocyanins that are stable in the mouth. If, on the other hand, the metabolites produced by the metabolism of anthocyanins are the actual health-promoting compounds, there will be greater interest in fruits that contain anthocyanins that are less stable in the oral cavity,” Failla said. “We lack such insights at this time.”

The extent to which the anthocyanins were degraded varied among the 14 people whose saliva was used in the study. However, two families of anthocyanins consistently degraded the most in all volunteers. Failla said the observed variation among individuals is likely related to differences in the microbial community that resides in each person’s mouth.

This research group is continuing the work, examining which bacteria are most involved in the metabolism of anthocyanins and testing the stability of the pigments in berry juices in the mouths of human volunteers rather than in test tubes containing their saliva.

**A safer way to vaccinate**

Polymer film that gradually releases DNA coding for viral proteins could offer a better alternative to traditional vaccines.

Anne Trafton, MIT News Office

January 27, 2013

Vaccines usually consist of inactivated viruses that prompt the immune system to remember the invader and launch a strong defense if it later encounters the real thing. However, this approach can be too risky with certain viruses, including HIV.

In recent years, many scientists have been exploring DNA as a potential alternative vaccine. About 20 years ago, DNA coding for viral proteins was found to induce strong immune responses in rodents, but so far, tests in humans have failed to duplicate that success.

In a paper appearing in the Jan. 27 online issue of *Nature Materials*, MIT researchers describe a new type of vaccine-delivery film that holds promise for improving the effectiveness of DNA vaccines. If such vaccines could be successfully delivered to humans, they could overcome not only the safety risks of using
viruses to vaccinate against diseases such as HIV, but they would also be more stable, making it possible to ship and store them at room temperature.

This type of vaccine delivery would also eliminate the need to inject vaccines by syringe, says Darrell Irvine, an MIT professor of biological engineering and materials science and engineering. “You just apply the patch for a few minutes, take it off and it leaves behind these thin polymer films embedded in the skin,” he says.

Irvine and Paula Hammond, the David H. Koch Professor in Engineering, are the senior authors of the Nature Materials paper. Both are members of MIT’s David H. Koch Institute for Integrative Cancer Research. The lead author of the paper is Peter DeMuth, a graduate student in biological engineering.

**Gradual vaccine delivery**

Scientists have had some recent success delivering DNA vaccines to human patients using a technique called electroporation. This method requires first injecting the DNA under the skin, then using electrodes to create an electric field that opens small pores in the membranes of cells in the skin, allowing DNA to get inside. However, the process can be painful and give varying results, Irvine says.

“It’s showing some promise but it’s certainly not ideal and it’s not something you could imagine in a global prophylactic vaccine setting, especially in resource-poor countries,” he says.

Irvine and Hammond took a different approach to delivering DNA to the skin, creating a patch made of many layers of polymers embedded with the DNA vaccine. These polymer films are implanted under the skin using microneedles that penetrate about half a millimeter into the skin — deep enough to deliver the DNA to immune cells in the epidermis, but not deep enough to cause pain in the nerve endings of the dermis.

Once under the skin, the films degrade as they come in contact with water, releasing the vaccine over days or weeks. As the film breaks apart, the DNA strands become tangled up with pieces of the polymer, which protect the DNA and help it get inside cells.

The researchers can control how much DNA gets delivered by tuning the number of polymer layers. They can also control the rate of delivery by altering how hydrophobic (water-fearing) the film is. DNA injected on its own is usually broken down very quickly, before the immune system can generate a memory response. When the DNA is released over time, the immune system has more time to interact with it, boosting the vaccine’s effectiveness.

The polymer film also includes an adjuvant — a molecule that helps to boost the immune response. In this case, the adjuvant consists of strands of RNA that resemble viral RNA, which provokes inflammation and recruits immune cells to the area.

The ability to provoke inflammation is one of the key advantages of the new delivery system, says Michele Kutzler, an assistant professor at Drexel University College of Medicine. Other benefits include targeting the wealth of immune cells in the skin, the use of a biodegradable delivery material, and the possibility of pain-free vaccine delivery, she says.

“It’s an interesting approach that can be applied not just to delivery of DNA-based vaccine antigens, but other small molecules,” says Kutzler, who was not part of the research team.

**Eliciting immune responses**

In tests with mice, the researchers found that the immune response induced by the DNA-delivering film was as good as or better than that achieved with electroporation.

To test whether the vaccine might provoke a response in primates, the researchers applied a polymer film carrying DNA that codes for proteins that resemble viral RNA, which provokes inflammation and recruits immune cells in the epidermis. DNA treated with the film, DNA was easily detectable, while DNA injected alone was quickly broken down.

“The hope is that that’s an indication that this will translate to large animals and hopefully humans,” Irvine says.

The researchers now plan to perform further tests in non-human primates before undertaking possible tests in humans. If successful, the vaccine-delivering patch could potentially be used to deliver vaccines for many different diseases, because the DNA sequence can be easily swapped out depending on the disease being targeted.

“If you’re making a protein vaccine, every protein has its little quirks, and there are manufacturing issues that have to be solved to scale it up to humans. If you had a DNA platform, the DNA is going to behave the same no matter what antigen it’s encoding,” Irvine says.
Bugs in the Atmosphere: Significant Microorganism Populations Found in Middle and Upper Troposphere

Jan. 28, 2013 — In what is believed to be the first study of its kind, researchers used genomic techniques to document the presence of significant numbers of living microorganisms—principally bacteria—in the middle and upper troposphere, that section of the atmosphere approximately four to six miles above Earth’s surface.

Whether the microorganisms routinely inhabit this portion of the atmosphere—perhaps living on carbon compounds also found there—or whether they were simply lofted there from Earth’s surface isn’t yet known. The finding is of interest to atmospheric scientists, because the microorganisms could play a role in forming ice that may impact weather and climate. Long-distance transport of the bacteria could also be of interest for disease transmission models.

The microorganisms were documented in air samples taken as part of NASA’s Genesis and Rapid Intensification Processes (GRIP) program to study low- and high-altitude air masses associated with tropical storms. The sampling was done from a DC-8 aircraft over both land and ocean, including the Caribbean Sea and portions of the Atlantic Ocean. The sampling took place before, during and after two major tropical hurricanes—Earl and Karl—in 2010.

The research, which has been supported by NASA and the National Science Foundation, was scheduled to be published online January 28th by the journal Proceedings of the National Academy of Sciences.

"We did not expect to find so many microorganisms in the troposphere, which is considered a difficult environment for life," said Kostas Konstantinidis, an assistant professor in the School of Civil and Environmental Engineering at the Georgia Institute of Technology. "There seems to be quite a diversity of species, but not all bacteria make it into the upper troposphere."

Aboard the aircraft, a filter system designed by the research team collected particles—including the microorganisms—from outside air entering the aircraft’s sampling probes. The filters were analyzed using genomic techniques including polymerase chain reaction (PCR) and gene sequencing, which allowed the researchers to detect the microorganisms and estimate their quantities without using conventional cell-culture techniques.

When the air masses studied originated over the ocean, the sampling found mostly marine bacteria. Air masses that originated over land had mostly terrestrial bacteria. The researchers also saw strong evidence that the hurricanes had a significant impact on the distribution and dynamics of microorganism populations.

The study showed that viable bacterial cells represented, on average, around 20 percent of the total particles detected in the size range of 0.25 to 1 microns in diameter. By at least one order of magnitude, bacteria outnumbered fungi in the samples, and the researchers detected 17 different bacteria taxa—including some that are capable of metabolizing the carbon compounds that are ubiquitous in the atmosphere—such as oxalic acid.

The microorganisms could have a previously-unknown impact on cloud formation by supplementing (or replacing) the abiotic particles that normally serve as nuclei for forming ice crystals, said Athanasios Nenes, a professor in the Georgia Tech School of Earth and Atmospheric Sciences and School of Chemical and Biomolecular Engineering.

"In the absence of dust or other materials that could provide a good nucleus for ice formation, just having a small number of these microorganisms around could facilitate the formation of ice at these altitudes and attract surrounding moisture," Nenes said. "If they are the right size for forming ice, they could affect the clouds around them."

The microorganisms likely reach the troposphere through the same processes that launch dust and sea salt skyward. "When sea spray is generated, it can carry bacteria because there are a lot of bacteria and organic materials on the surface of the ocean," Nenes said.

The research brought together microbiologists, atmospheric modelers and environmental researchers using the latest technologies for studying DNA. For the future, the researchers would like to know if certain types of bacteria are more suited than others for surviving at these altitudes. The researchers also want to understand the role played by the microorganisms—and determine whether or not they are carrying on metabolic functions in the troposphere.

"For these organisms, perhaps, the conditions may not be that harsh," said Konstantinidis. "I wouldn’t be surprised if there is active life and growth in clouds, but this is something we cannot say for sure now."
Other researchers have gathered biological samples from atop mountains or from snow samples, but gathering biological material from a jet aircraft required a novel experimental setup. The researchers also had to optimize protocols for extracting DNA from levels of biomass far lower than what they typically study in soils or lakes. "We have demonstrated that our technique works, and that we can get some interesting information," Nenes said. "A big fraction of the atmospheric particles that traditionally would have been expected to be dust or sea salt may actually be bacteria. At this point we are just seeing what’s up there, so this is just the beginning of what we hope to do."

**Journal Reference:**

**More Severe Flu Seasons Predicted Due to Climate Change**

Jan. 28, 2013 — The American public can expect to add earlier and more severe flu seasons to the fallout from climate change, according to a research study published online Jan. 28 in *PLOS Currents: Influenza*.

A team of scientists led by Sherry Towers, research professor in the Mathematical, Computational and Modeling Sciences Center at Arizona State University, studied waves of influenza and climate patterns in the U.S. from the 1997-1998 season to the present.

The team’s analysis, which used Centers for Disease Control data, indicates a pattern for both A and B strains: warm winters are usually followed by heavy flu seasons.

"It appears that fewer people contract influenza during warm winters, and this causes a major portion of the population to remain vulnerable into the next season, causing an early and strong emergence," says Towers. "And when a flu season begins exceptionally early, much of the population has not had a chance to get vaccinated, potentially making that flu season even worse."

The current flu season, which is still in high gear in parts of the nation, began early and fiercely. It followed a relatively light 2011-2012 season, which saw the lowest peak of flu since tracking efforts went into effect, and coincided with the fourth warmest winter on record. According to previous studies, flu transmission decreases in warm or humid conditions.

If global warming continues, warm winters will become more common, and the impact of flu will likely be more heavily felt, say the study’s authors.

Mathematical epidemiologist Gerardo Chowell-Puente, an associate professor in the School of Human Evolution and Social Change in the College of Liberal Arts and Sciences, adds that the findings could inform preparedness efforts following mild winters: "The expedited manufacture and distribution of vaccines and aggressive vaccination programs could significantly diminish the severity of future influenza epidemics."

The goal of the overarching study is to better grasp the character and trajectory of influenza in all its forms.

**Journal Reference:**
Sherry Towers, Gerardo Chowell, Rasheed Hameed, Matthew Jastrebski, Maryam Khan, Jonathan Meeks, Anuj Mubayi, George Harris. Climate change and influenza: the likelihood of early and severe influenza seasons following warmer than average winters. *PLoS Currents*, 2013; DOI: [10.1371/currents.flu.3679b56a3a531d7e043fb944c6f5b3](https://doi.org/10.1371/currents.flu.3679b56a3a531d7e043fb944c6f5b3)
Skin, Soft Tissue Infections Succumb to Blue Light

Jan. 28, 2013 — Blue light can selectively eradicate *Pseudomonas aeruginosa* infections of the skin and soft tissues, while preserving the outermost layer of skin, according to a proof-of-principle study led by Michael R. Hamblin of the Massachusetts General Hospital, and the Harvard Medical School, Boston.

The research is published online ahead of print in the journal *Antimicrobial Agents and Chemotherapy*.

"Blue light is a potential non-toxic, non-antibiotic approach for treating skin and soft tissue infections, especially those caused by antibiotic resistant pathogens," says Hamblin.

In the study, animal models were infected with *P. aeruginosa*. All of the animals in the group treated with blue light survived, while in the control, 82 percent (9 out of 11) of the animals died.

Skin and soft tissue infections are the second most common bacterial infections encountered in clinical practice, and represent the most common infection presentation—more than 3 percent—in patients visiting emergency departments, says Hamblin. The prevalence of skin and soft tissue infections among hospitalized patients is 10 percent, with approximately 14.2 million ambulatory care visits every year and an annual associated medical cost of almost $24 billion (equivalent to $76 for every American), says Hamblin.

Treatment of skin and soft tissue infections has been significantly complicated by the explosion of antibiotic resistance, which may bring an end to what medical scientists refer to as the antibiotic era, says Hamblin. "Microbes replicate very rapidly, and a mutation that helps a microbe survive in the presence of an antibiotic drug will quickly predominate throughout the microbial population. Recently, a dangerous new enzyme, NDM-1, that makes some bacteria resistant to almost all antibiotics available has been found in the United States. Many physicians are concerned that several infections soon may be untreatable."

Besides harming public health, antibiotic resistance boosts health care costs. "Treating resistant skin and soft tissue infections often requires the use of more expensive, or more toxic drugs, and can result in longer hospital stays for infected patients," says Hamblin.

Journal Reference:

Slow-Release 'Jelly' Delivers Drugs Better

Jan. 28, 2013 — Duke University biomedical engineers have developed a new delivery system that overcomes the shortcomings of a promising class of peptide drugs—very small proteins—for treating diseases such as diabetes and cancer.

There are more than 40 peptide drugs approved for use in humans and more than 650 are being tested in clinical studies. One example is the hormone insulin, a peptide that regulates the metabolism of carbohydrates in the body and is used as a drug to treat diabetes.

Despite their effectiveness, peptide drugs cannot achieve their full potential for a number of reasons. They are rapidly degraded in the blood stream and they are cleared rapidly from the body, which requires multiple, frequent injections. Because of this, peptide concentrations in the blood can rise precipitously just after injection and fall dramatically soon thereafter, causing unwanted side effects for patients.

One popular method to solve this problem involves loading peptide drugs into polymer microspheres that are injected under the skin and slowly degrade to release the peptide drug. Microsphere-release technology has proven useful, but has many issues related to its manufacture and ease of patient use, the researchers said.

"We wanted to know if we could create a system that does what the polymer microspheres do, but gets rid of the microspheres and is more patient-friendly," said Ashutosh Chilkoti, Theo Pilkington professor of biomedical engineering in Duke’s Pratt School of Engineering.

The new approach involves making a "fusion protein" that consists of multiple copies of a peptide drug fused to a polymer which is sensitive to body heat. The fusion molecule is a liquid in a syringe but transforms into a "jelly" when injected under the skin. Enzymes in the skin then attack the injected drug depot and liberate copies of the peptide, providing a constant and controllable release of the drug over time.

Miriam Amiram, former Chilkoti graduate student and first author on the paper, dubbed the new delivery system POD, for protease-operated depot.
In the latest experiments, published on-line in the journal *Proceedings of the National Academy of Sciences*, the researchers fused glucagon-like peptide-1 (GLP-1), a hormone that regulates the release of insulin, with a genetically engineered heat-sensitive polymer to create the POD.

"Remarkably, a single injection of the GLP-1 POD was able to reduce blood glucose levels in mice for up to five days, which is 120 times longer than an injection of the peptide alone," Chilkoti said. "For a patient with type 2 diabetes, it would be much more desirable to inject such a drug once a week or once a month rather than once or twice a day.

"Additionally, this approach avoids the peaks and valleys of drug concentrations that these patients often experience," Chilkoti said.

Unlike peptide-loaded microspheres, PODs are also easy to manufacture, because the peptide drug and the heat-sensitive polymer are all made of amino acids. They can be built as one long stretch of amino acids by engineered bacteria.

"This new delivery system provides the first entirely genetically encoded alternative to peptide drug encapsulation for sustained delivery of peptide drugs," Chilkoti said.

**Journal Reference:**
Miriam Amiram, Kelli M. Lugtenbuhl, Xinghai Li, Mark N. Feinglos, and Ashutosh Chilkoti. *Injectable protease-operated depots of glucagon-like peptide-1 provide extended and tunable glucose control*. PNAS, January 28, 2013 DOI: 10.1073/pnas.1214518110

**New Technique Sheds Light On RNA**
Jan. 28, 2013 — When researchers sequence the RNA of cancer cells, they can compare it to normal cells and see where there is more RNA. That can help lead them to the gene or protein that might be triggering the cancer.

But other than spotting a few known instigators, what does it mean? Is there more RNA because it’s synthesizing too quickly or because it’s not degrading fast enough? What part of the biological equilibrium is off?

After more than a decade of work, researchers at the University of Michigan Comprehensive Cancer Center have developed a technique to help answer those questions.

The method involves a compound called bromouridine, which can be used to tag or label newly created RNA. Researchers apply the bromouridine for 30 minutes then isolate the RNA to see where the new RNA was made. They call this process Bru-Seq.

On the other hand, the researchers can follow up the bromouridine labeling with a rinse with the chemical uridine for different periods of time. They call this BruChase-Seq because the uridine chases away the newly made RNA so they can look at how the RNA ages over the course of one hour, two hours or six hours. In other words, is the RNA degrading like it’s supposed to?

"We can see the whole pattern of all the RNA that’s synthesized and all the RNA that’s stable vs. degrading. We can sort it out in terms of synthesis and stability and see if a particular RNA is more stable in the cancer cell than the normal cell or if it is taking longer to degrade in the cancer cell than in the normal cell," says study author Mats Ljungman, Ph.D., associate professor of radiation oncology at the U-M Medical School.

"With our technique, we’re adding 10-fold more depth to the picture of how genes are expressed," he adds.

Ljungman is part of the Cancer Center’s new Translational Oncology Program, which brings together cancer researchers from across the University of Michigan to speed the translation of basic science into clinical trials and new treatment opportunities for patients.

The Cancer Center is currently using gene sequencing techniques to help match advanced cancer patients with potential clinical trial opportunities based on the make-up of their tumor.

In addition to helping with cancer sequencing, Ljungman sees potential for this new technique to help with identifying diseases such as diabetes or inflammation. In the paper describing the technique, published online in Proceedings of the National Academy of Sciences, the researchers describe how they used it to understand an inflammatory response in cells. The researchers have also used the technique to test blood samples.

With a great deal more investigation, Ljungman envisions that one day the test could potentially be offered to people visiting their doctor as a way to monitor changes in the RNA.

"If something is significantly changed from one test to the next, it could be a red flag or an early warning sign of disease. That would be the broadest use of this technology," Ljungman says.

**Journal Reference:**
What Holds Chromosomes Together? Structure of DNA-Packaging Proteins Described
Jan. 28, 2013 — To ensure that the genetic material is equally and accurately distributed to the two daughter cells during cell division, the DNA fibers must have an ordered structure and be closely packed. At the Max Planck Institute of Biochemistry in Martinsried near Munich scientists have now elucidated the structure of a ring-shaped protein complex (SMC-kleisin), which ensures order in this packaging process. Together with their cooperation partners at the Korea Advanced Institute of Science and Technology, they studied these proteins in bacteria and found structural analogies to the human complex.

The findings have now been published in the journal *Nature Structural & Molecular Biology*.

In each cell about two meters of DNA must fit into a cell nucleus that has a diameter of only a few thousandths of a millimeter. There the DNA is organized in individual chromosomes in the form of very long filaments. If they are not equally and accurately distributed to the daughter cells during cell division, this can result in cancer or genetic defects such as trisomy 21. Therefore, to ensure safe transport of DNA during cell division the long and coiled DNA fibers must be tightly packed.

Scientists have only a sketchy understanding of this step. The SMC-kleisin protein complexes play a key role in this process. They consist of two arms (SMC) and a bridge (kleisin). The arms wrap around the DNA like a ring and thus can connect duplicated chromosomes or two distant parts of the same chromosome with each other.

Learning from bacteria Simple organisms like bacteria also use this method of DNA packaging. The scientists, in collaboration with colleagues from South Korea, have now elucidated the structure of a precursor of human SMC-kleisin complexes of the bacterium *Bacillus subtilis*. The researchers showed that the bacterial SMC-kleisin complex has two arms made of identical SMC proteins that form a ring. The arms differ in their function only through the different ends of the kleisin protein with which they are connected.

In humans the DNA packaging machinery is similarly organized. "We suspect that this asymmetric structure plays an important role in the opening and closing of the ring around the DNA," explains Frank Bürmann, PhD student in the research group 'Chromosome Organization and Dynamics' of Stephan Gruber. In addition, the scientists discovered how the ends of the kleisin can distinguish between correct and wrong binding sites on one pair of arms.

The cohesion of chromosomes is of critical importance for reproduction as well. In human eggs this cohesion must be maintained for decades to ensure error-free meiosis of the egg cell. Failure of cohesion is a likely cause for decreased fertility due to age or the occurrence of
genetic defects such as trisomy 21. “The elucidation of the structure of SMC-kleisin protein complexes is an important milestone in understanding the intricate organization of chromosomes,” says group leader Stephan Gruber.

**Journal Reference:**

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**Immune Cell Suicide Alarm Helps Destroy Escaping Bacteria**

Shown in red are bacteria that have invaded host cells and escaped into the interior cytosolic compartment of the cell. (Credit: Miao lab, UNC School of Medicine)

Jan. 24, 2013 — Cells in the immune system called macrophages normally engulf and kill intruding bacteria, holding them inside a membrane-bound bag called a vacuole, where they kill and digest them.

Some bacteria thwart this effort by ripping the bag open and then escaping into the macrophage’s nutrient-rich cytosol compartment, where they divide and could eventually go on to invade other cells.

But research from the University of North Carolina School of Medicine shows that macrophages have a suicide alarm system, a signaling pathway to detect this escape into the cytosol. The pathway activates an enzyme, called caspase-11, that triggers a program in the macrophage to destroy itself.
"It's almost like a thief sneaking into the house not knowing an alarm will go off to knock down the walls and expose him to capture by the police," says study senior and corresponding author Edward Miao, PhD, assistant professor of microbiology and immunology at UNC. "In the macrophage, this cell death, called pyroptosis, expels the bacterium from the cell, exposing it to other immune defense mechanisms."

A report of the research appears online in the journal Science on January 24, 2013.

Miao, also a member of the UNC Lineberger Comprehensive Cancer Center, says the new findings show that having this detection pathway protects mice from lethal infection with the type of vacuole-escaping Burkholderia species: B. thailandensis and B. pseudomallei.

Both are close relatives. But they differ in lethality. B. pseudomallei is potentially a biological weapon. Used in a spray, it could potentially infect people via aerosol route, causing sickness and death. Moreover, it also could fall into a latent phase, "essentially turning into a 'sleeper' inside the lungs and hiding there for decades," Miao explains. In contrast, B. thailandensis, which shares many properties with its species counterpart, is not normally able to cause any disease or infection.

These environmental bacteria are ubiquitous throughout S.E. Asia, and were it not for the caspase-11 pathway defense system, that part of the world could be uninhabitable, Miao points out.

This grim possibility clearly emerged in the study. Mice that lack the caspase-11 detection pathway succumb to infection not only by B. pseudomallei, but also to the normally benign B. thailandensis. "Thus caspase-11 is critical for surviving exposure to ubiquitous environmental pathogens," the authors conclude.

Miao points to research elsewhere showing that the pathway's abnormal activation in people with septic shock, overwhelming bacterial infection of the blood, is associated with death. "We discovered what the pathway is supposed to do, which may help find ways to tone it down in people with that critical condition."

As to bioterrorism, the researcher says it may be possible to use certain drugs already on the market that safely induce the caspase-11 pathway. "Since this pathway requires pre-stimulation with interferon cytokines, it is conceivable that pre-treating people with interferon drugs could ameliorate a bioterror incident. This could be quite important in the case of Burkholderia, since these bacteria are naturally resistant to numerous antibiotics.

"But first we have to find out if they would work in animal models, and consider the logistics of interferon stockpiling, which are currently cost prohibitive."

**Journal Reference:**

**HIV-Like Viruses in Non-Human Primates Have Existed Much Longer Than Previously Thought**
Jan. 24, 2013 — Viruses similar to those that cause AIDS in humans were present in non-human primates in Africa at least 5 million years ago and perhaps up to 12 million years ago, according to study published January 24 in the Open Access journal *PLOS Pathogens* by scientists at Fred Hutchinson Cancer Research Center. Until now, researchers have hypothesized that such viruses originated much more recently.

HIV-1, the virus responsible for AIDS, infiltrated the human population in the early 20th century following multiple transmissions of a similar chimpanzee virus known as SIVcpz. Previous work to determine the age of HIV-like viruses, called lentiviruses, by comparing their genetic blueprints has calculated their origin to be tens of thousands of years ago.

However, other researchers have suspected this time frame to be much too recent. Michael Emerman, Ph.D., a virologist and member of the Human Biology Division at Fred Hutchinson Cancer Research Center, and Alex Compton, a graduate student in the Emerman Lab, describe the use of a technique to estimate the extent to which primates and lentiviruses have coexisted by tracking the changes in a host immunity gene called APOBEC3G that were induced by ancient viral challenges.

They report that this host immunity factor is evolving in tandem with a viral gene that defends the virus against APOBEC3G, which allowed them to determine the minimum age for the association between primates and lentiviruses to be around 5 or 6 million years ago, and possibly up to 12 million years ago.

These findings suggest that HIV-like infections in primates are much older than previously thought, and they have driven selective changes in antiviral genes that have incited an evolutionary arms race that continues to this day. The study also confirms that viruses similar to HIV that are present in various
monkey species today are the descendants of ancient pathogens in primates that have shaped how the immune system fights infections.

"More than 40 non-human primate species in sub-Saharan Africa are infected with strains of HIV-related viruses," Emerman said. "Since some of these viruses may have the potential to infect humans as well, it is important to know their origins."

**Journal Reference:**

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**War a Money-Spinner for Rank-And-File Soldiers in Late Middle Ages**

Jan. 24, 2013 — Research by a University of Southampton historian has found that the practice of ransom was widespread among all soldiers during the Hundred Years War (1337—1453) and not, as generally thought, just the preserve of kings, knights and higher orders.

Dr Rémy Ambühl has found that ransom in war provided a valuable source of income for all classes in the Late Middle Ages, including those in the lower orders. He says: "There is widespread evidence to suggest that during the 15th century the practice of ransom is increasingly extended to commoners, not just Kings or chivalrous Knights."

Dr Ambühl’s research has led him to examine a large number of historical sources which support this, including; court records, financial documents, receipts, ordinances of war, petitions, biographical texts and even poetry. He has concluded that contracts which drew-up the terms and conditions of ransom were commonplace between individual soldiers or small groups on opposing sides. This involved captors and captives of all ranks and the practice was an accepted way of making profit out of war. This is supported by an apparent increase in the size of the rank-and-file sections of the French and English armies during this period.

Dr Ambühl explains: "Patriotism was not the driving force to encourage enrollment and ordinary men would have been reluctant to join armies willingly if they faced death upon capture. However, under the terms of ransom, prisoners were less likely to be harmed and additionally the practice provided them with an opportunity to make money — another incentive to enlist."

"Over the course of the Hundred Years War, more and more rank-and-file soldiers captured more and more rank-and-file prisoners giving rise to a form of social recognition between equals — the principle of reciprocity meant good treatment on one side would induce good treatment on the other. It can also be argued that materialism had started to penetrate the whole of society and even a small profit gained from the ransom of commoner prisoners was thought to be worthwhile."

From the moment of capture, prisoners became the individual responsibility of their masters who were expected to secure an appropriate place and conditions for them to be held in. The Master had to work out the appropriate value of their prisoners and enter negotiations with them, their family and friends. In turn, prisoners, or their connections, would work to raise funds or arrange an exchange for their release.

Dr Ambühl comments, "Negotiations were crucial in this process and a dialogue was kept open between masters and prisoners at all stages. The ransom culture was essentially contractual and so firmly rooted that it could even supersede or invalidate arguments from the 'law of arms'."

Records show that the earliest evidence of a set scale of ransom payments for the bottom of the social hierarchy dates from the battle of Agincourt (Friday, 25 October 1415). Dr Ambühl concludes this may reflect an evolution of the ransom system in the first decades of the 15th century.

By the 16th century, scales of ransom payments were based on the wages of soldiers and throughout this period and into the 17th century there was increasing control from the state. Eventually a practice which had been shaped by combatants over the centuries ended up being tightly controlled by authorities. Dr Rémy Ambühl’s full research on this subject can be found in his recently published book, Prisoners of War in the Hundred Years War: Ransom Culture in the Late Middle Ages.
Plague Outbreak in Libya, 2009, Unrelated to Plague in Algeria
Nicolas Cabanel, Alexandre Leclercq, Viviane Chenal-Francisque, Badereddin Annajar, Minoarisoa Rajerison, Souad Bekkhoucha, Eric Bertherat, and Elisabeth Carniel

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Suggested citation for this article

Abstract
After 25 years of no cases of plague, this disease recurred near Tobruk, Libya, in 2009. An epidemiologic investigation identified 5 confirmed cases. We determined ribotypes, NotI restriction profiles, and IS100 and IS1541 hybridization patterns of strains isolated during this outbreak. We also analyzed strains isolated during the 2003 plague epidemic in Algeria to determine whether there were epidemiologic links between the 2 events. Our results demonstrate unambiguously that neighboring but independent plague foci coexist in Algeria and Libya. They also indicate that these outbreaks were most likely caused by reactivation of organisms in local or regional foci believed to be dormant (Libya) or extinct (Algeria) for decades, rather than by recent importation of Yersinia pestis from distant foci. Environmental factors favorable for plague reemergence might exist in this area and lead to reactivation of organisms in other ancient foci.

Plague is a zoonosis caused by the bacillus Yersinia pestis. Rodents are the reservoir and fleas are the vector of this organism. Humans most often become infected by an infectious fleabite, which leads to development of a bubonic form of plague (1). If the bacillus reaches the lungs, the patient will expel the bacteria while coughing, causing another clinical form: pneumonic plague, which is directly transmissible from person to person. Without prompt and efficient treatment, the case-fatality rate is 40%–70% for bubonic plague and ≈100% for pneumonic plague (1).

The plague bacillus is believed to have originated <20,000 years ago in central Asia (2), from which it has spread on multiple occasions and caused 3 well-documented pandemics (1). The first pandemic, known as Justinian’s plague, reached Africa and then Europe during the sixth century. The second pandemic struck the countries surrounding the Mediterranean in 1348 and then spread rapidly throughout Europe. The third pandemic started in Hong Kong in 1894 and reached previously unscathed territories worldwide. These 3 pandemics were extremely devastating and killed millions of persons. Because of identification of the causative agent (3), the reservoir, and the vector of the disease at the end of the 19th century (4) and then the availability of effective antimicrobial drugs, human illness and death caused by plague have been considerably reduced since the middle of the 20th century.
Figure 1. Locations of plague outbreaks in Oran, Algeria, and Tobruk, Libya. Upper panels show regions around Oran and Tobruk where plague cases were found.

However, the disease has not been eradicated. Plague-endemic foci persist in Africa (the most affected continent), Asia, South America, and North America (5). Moreover, since the beginning of the 1990s, plague outbreaks have recurred in countries where no cases were reported for decades, and where the disease was believed to have been eliminated. Among the most conspicuous examples is that of India, which experienced a large outbreak of pneumonic plague in 1994 after 30 years with no reports of plague cases (6). Another striking example of plague reemergence is that of Algeria, where the most recent cases were reported in the 1940s. After an absence of >50 years, the disease reappeared in 2003 in a village south of Oran (7,8); and then in 2008, in the Laghouat area (9) (Figure 1). Whether these outbreaks were caused by reimportation of the disease from other countries or by reactivation of organisms in a local quiescent plague focus could not be formally established.

Neighboring Libya experienced several plague outbreaks during 1913–1920, the largest of which resulted in 1,449 deaths in Benghazi in 1917 (10). Other plague epidemics of lower amplitude occurred in 1972, 1976, 1977, and 1984. After an apparent absence of 25 years, plague cases recurred in June 2009 near Tobruk, Libya, close to the border with Egypt (Figure 1). A total of 5 plague cases were confirmed, 3 of which occurred in 1 family and the other 2 in patients living in the same district (11,12). An even more recent plague epidemic that had >21 suspected cases was reported in May 2011 in the city of Tobruk (12). An investigation of this epidemic did not confirm the plague etiology, but the political troubles resulting from the onset of the revolution in February made this investigation difficult.

The purpose of this study was to obtain insights into the origin of the outbreak that occurred near Tobruk in 2009. We analyzed Y. pestis strains that were isolated from patients during this epidemic and determined whether links exist to the recent resurgence of plague in Algeria.

Materials and Methods
Bacterial Strains Isolation and Characterization
The Y. pestis strains used in this study are shown in the Table. Y. pestis strains were isolated from biological specimens after streaking them on cefsulodin-irgasan-novobiocin plates (Merck, Schaffhausen, Switzerland) and injection of bacteria into mice. Phenotypic characterization of strains was determined by biochemical reactions on API 20E and API 50CH strips (bioMérieux, Marcy l’Etoile, France) incubated at
28°C, lysis by a *Y. pestis*–specific bacteriophage, reduction of nitrates, and glycerol fermentation. For further analyses, bacteria were grown in Luria-Bertani broth or on Luria-Bertani agar plates containing 0.002% hemin for 24–48 h at 28°C.

**Molecular Typing**

Total genomic DNA was extracted by using a Gentra Puregene Cell Kit (QIAGEN, Hilden, Germany) according to the manufacturer’s instructions. Ribotyping was performed as described (12) after digestion of genomic DNA with *EcoRI* or *EcoRV* restriction enzymes for 30 min at 37°C. Each profile was classified according to the scheme of Guiyoule et al. (13).

Insertion sequence–restriction fragment length polymorphism (IS-RFLP) analysis was performed as described (14). DNA samples were digested with *EcoRI* (IS100-RFLP) or *HindIII* (IS1541-RFLP) for 30 min at 37°C before being loaded onto 0.8% agarose gels and subjected to electrophoresis for 24 h. The IS fingerprints were analyzed by using BioNumerics software version 6.6 (Applied Maths, Kortrijk, Belgium) as described (14). Two IS profiles were considered identical when their percent similarity was >98%.

For pulsed-field gel electrophoresis (PFGE), bacterial genomic DNA was prepared in agarose plugs as described (15) and digested with 50 U of *NotI* endonuclease in 200 µL of the corresponding buffer for 3 h at 37°C. Electrophoresis was performed as described (16), except that the pulse time ranged from 4 s to 8 s over 42 h in a buffer maintained at 14°C.

**Results**

**Plague Outbreak in Libya**

On June 9, 2009, three patients 14, 13, and 4 years of age were admitted to Tobruk Central Hospital because of a severe infectious syndrome. All 3 persons were members of the same family of nomads leaving in Eltarsha, 30 km south of Tobruk. The 13-year-old patient (patient 1) had a septicemic syndrome 2 days after admission and died on June 11 despite intensive care. His 14-year-old brother (patient 2) had a tender left cervical lymph node and a fever of 39.5°C. He received ciprofloxacin and doxycycline before being transferred to Benghazi Hospital on June 11, and he recovered. His 4-year-old sister (patient 3) had signs of severe infection with no visible bubo. She received cefotaxime and metronidazole and then gentamicin before being transferred to Benghazi Hospital, and she recovered. Their father reported having axillary lymphadenitis and indicated that 2 or 3 sudden deaths had occurred in the previous 2 months in the region.

On the basis of clinical manifestations and previous plague cases in the Tobruk area, these 3 patients were considered to have contracted plague. All patients from this area with an infectious syndrome were reported as having suspected cases of plague. All but 1 of these patients received gentamicin at Tobruk Hospital and no additional deaths occurred. On June 13, the Libyan authorities reported 13 cases of plague to the World Health Organization (WHO) and requested technical assistance.

A joint investigation of the outbreak led by WHO and the Libyan National Center for Infectious Disease Prevention and Control concluded that the number of plague cases was overestimated, but it identified 2 additional probable cases. These cases were in a 20-year-old woman (patient 4) and a 24-year-old woman (patient 5) who had an infectious syndrome and a painful inguinal lymph node and were admitted to the Tobruk Hospital on June 16 and 18, respectively. Patient 4 lived in Beer Alashahab and patient 5 lived in Zafrana (Figure 1), ≈60 and 30 km from Eltarsha, respectively. Control measures (chemoprophylaxis of contact persons, insecticide treatment, and rodent control) were implemented, and no additional cases were reported.

**Bacteriologic Findings**

In Benghazi, blood samples collected from patients 3, 4, and 5 contained gram-negative bacteria resembling *Yersinia* spp. These blood samples and serum samples from all 5 patients and a bubo aspirate from patient 4 were sent to the WHO Collaborating Center at the Institut Pasteur in Antananarivo, Madagascar, for further analyses. F1 dipstick test (17) results were positive for samples from all 5 patients. A *Y. pestis* strain was isolated from the blood of patients 3 and 5 and from the bubo aspirate of patient 4, thus confirming the etiology of this outbreak. These 3 strains were then sent to the WHO Collaborating Center at the Institut Pasteur in Paris, France, for further characterization. On the basis of glycerol fermentation and nitrate reduction, the 3 strains were assigned to *Y. pestis* biovar Medievalis (18).
Molecular Characteristics of Strains from Libya

Figure 2. *Nod* pulse-field gel electrophoresis patterns of *Yersinia pestis* strains of biovar Medievalis obtained during plague outbreak in Libya, 2009. A)
The 3 strains exhibited identical NotI PFGE profiles (Figure 2, panel A), and all had ribotype O (EcoRI4 + EcoRV.5) according to Guiyoule et al. (13) and identical IS100 and IS1541 hybridization patterns (Figure 3). These results are consistent with a single Y. pestis strain as the origin of the cases that occurred in distinct places in the Tobruk area.

Figure 4
Figure 4. IS\textsubscript{100} and IS\textsubscript{1541} restriction fragment length polymorphism patterns of 70 \textit{Yersinia pestis} isolates of worldwide origin. A) Medievalis branch. B), ancient strain from Algeria (IP1867); C) other strains from Algeria and various isolates from Africa. The dendrogram was constructed by using the unweighted pair group method with arithmetic mean clustering analysis and a position tolerance of 1.8%. Biovar is shown on the right. UN, unknown; ND, not determined.

Ribotype O is commonly associated with biovar Medievalis strains (13). When the IS\textsubscript{100} and IS\textsubscript{1541} profiles were combined (2IS-RFLP), the isolates from Libya clustered with other biovar Medievalis strains (Figure 4) in our database (14). Moreover, the chromosomal location of some IS\textsubscript{100} sequences determined by PCR was typical of this biovar (19). Therefore, our results demonstrate unambiguously that
the Y. pestis strain that caused the plague outbreak in Libya in 2009 belongs to the biovar Medievalis lineage, a lineage typical for strains that originated in central Asia.

The 2IS-RFLP dendrogram suggested that strains from Libya were closely related but different from those from Kurdistan and more distantly related to the biovar Medievalis strain from Turkey (Figure 4). A comparison of the NotI PFGE profile of an isolate from Libya with those of 5 other biovar Medievalis strains confirmed this observation: all isolates had similar but different profiles (Figure 2, panel B), and the similarity was more pronounced with strains from Kurdistan than with the strain from Turkey. Thus, strains from the 2009 outbreak in Libya are genetically close to those isolated in the Iranian part of Kurdistan.

**Y. pestis Strains that Caused the Plague Outbreak in Algeria in 2003**

Because Y. pestis strains were isolated from patients during the outbreak that occurred in the region of Oran in 2003 (7) (Figure 1), we performed the same analyses on these strains and compared them with isolates from Libya. Biochemical characterization of the 5 strains from Algeria indicated that they belonged to biovar Orientalis. They were of ribotype B (EcoRI.1 + EcoRV.2), which is found only in biovar Orientalis strains (13). Their IS100 + IS1541 profiles also included them in the biovar Orientalis group (Figure 4). Therefore, the strains that caused the 2003 plague outbreak in Algeria belong to the biovar Orientalis lineage.

Four of these strains had identical IS100 + IS1541 profiles, but the IS1541 profile of the strain from Hamoul (IP1862) displayed 1 additional band. The NotI PFGE patterns of the 5 strains from Algeria were highly similar but differed by a few bands (Figure 5). The 2 strains from Ain Temouchent (IP1863 and IP1864) had an identical NotI pattern, which was different from that of the strain from Hamoul (IP1862), which also slightly differed from the NotI profile of the strains from Kehailia (IP1860) and Hama Ali (IP1861). Thus, these results suggest that the 2003 outbreak in Algeria was caused by closely related, but not identical, strains.

Two Y. pestis strains isolated in Oran in 1944 and 1945 from bubonic plague patients were available in our collection and were used for comparison with the 2003 strains. These 2 more ancient isolates also belonged to biovar Orientalis. However, the strain isolated in 1945 (IP1867) had ribotype E, a ribotype found in strains from Saigon, Vietnam. This strain also clustered with an isolate from Saigon (IP532) in the 2IS-RFLP dendrogram (Figure 4), which suggested an epidemiologic link between these 2 foci. In contrast, the strain isolated in 1944 (IP1866) had ribotype B and was found in the same cluster in the 2IS-RFLP dendrogram as that containing the 2003 strains from Algeria (Figure 4). This cluster grouped all other strains from northern Africa (Morocco and Senegal). These data support a local or regional origin of the strains that caused the 2003 plague outbreak in Algeria.

**Discussion**

After decades of no plague cases, human plague cases have recently recurred in countries surrounding the Mediterranean Sea. New cases occurred in Saudi Arabia in 1994 (20) where no human cases of plague had been reported for 240 years, in Jordan in 1997 (21), where no cases had been reported during the past 70 years, in Algeria in 2003, where no cases had been reported for 50 years (7), and more recently in Libya in 2009, where the last plague case was reported 25 years ago. Recent reappearance of plague cases in this area could have been caused by regional spread of organisms from a single focus, reimportation of strains from distant areas by land or sea transportation, or reactivation of the organism in local foci that had been apparently dormant for years.
Analysis of the 3 strains isolated in Libya in 2009 showed that they were identical by 2IS-RFLP and PFGE, which suggested that a single strain caused this outbreak and that a single focus was the source of infection for different human patients. Phenotypic and genetic analyses indicated that this strain belongs to the biovar Medievalis lineage. Thus, as for other strains of this lineage, the strain from Libya most likely originated in central Asia. To our knowledge, no biovar Medievalis strains have been reported in Africa. However, this finding might reflect a lack of reporting rather than a true absence of these strains in countries in Africa near Asia.

Camel caravans travel through central Asia and the Middle East and consumption of infected camel meat were shown to be responsible for human plague cases in Libya in 1976 (22), in Saudi Arabia in 1994 (20), in Jordan in 1997 (21), and in Afghanistan in 2007 (23). Thus, infected camels could have been a means of importing new Y. pestis strains into Libya. However, because camels are highly susceptible to plague, it is unlikely that sick animals could travel long distances. Furthermore, dead rats were found in the vicinity of a sick camel in Libya (22). Y. pestis strains were isolated from rodents and fleas in the corral where a camel died of plague in Saudi Arabia (20), and dogs had antibodies against the plague bacillus in Jordan (21). These observations suggest that plague was already present in these countries and that camels were not the mode of transport.

Resurgence of plague in Libya in 2009 could most likely be attributed to reactivation of established and permanent local plague foci resulting from ancient importation from central Asia. Strengthening this hypothesis are the numerous plague outbreaks that occurred in Libya during the 20th century. In the Tobruk area, human cases were reported in 1976–1977 and in 1984 (24). This finding and the fact that the recent epidemic involved persons living 30–60 km from each other are highly evocative of reactivation of organisms in a local plague focus in 2009. Comparison of strains from past epidemics in Libya with the strain from 2009 would have helped answer this question, but such strains were not available in our collection.

The sudden resurgence of plague cases in the Tobruk region >2 decades after the last reported case might be linked to unusual climatic conditions. The outbreak was preceded by a particularly humid winter, which favored flea proliferation, and exceptionally good harvests, which supported rodent multiplication. The effect of climatic changes on human plague has been documented (25,26) and further emphasizes the need to take into consideration the effect of global warming on infectious diseases that have a nonhuman reservoir.

Although Libya and Algeria have a common border, our results demonstrate that the plague outbreaks that occurred recently in Algeria were not caused by spread of organisms from the focus in Libya. Phenotypic and genetic analyses of 5 strains isolated from patients in Algeria in 2003 demonstrated that they belong to biovar Orientalis. Similarly, the strains that caused the plague episode in Laghouat (550 km south of Algiers) in 2008 had a multispacer sequence type typical for biovar Orientalis strains (9). This lineage is distinct from the biovar Medievalis lineage of strains from Libya. Thus, the plague foci in Algeria and Libya are not linked.

Several plague outbreaks in Oran have been attributed to importation of infected rodents or fleas by marine shipping, e.g., during World War II military operations (27). Ribotyping and 2IS-RFLP analyses of the Y. pestis strain isolated from a bubonic plague patient in the Oran area in 1945 fully support this point and suggest that this strain was imported from southern Vietnam (Saigon). In contrast, Y. pestis isolates from 1944 and from 2003 in Oran cluster together by 2IS-RFLP. They also cluster with the other strains from northern Africa (Morocco and Senegal) isolated in the 1940s. These results are consistent with reactivation of organisms in a local or regional plague focus and argue against importation of infected materials or animals from a distant plague-infected region.

Also arguing for existence of an active local reservoir was detection of Y. pestis DNA in fleas collected near Oran 1–2 years after the 2003 outbreak (8) and in native rodents trapped in the Laghouat area a few months after the 2008 plague cases (9). The fact that 3 similar but distinct NotI patterns were observed among the 5 Y. pestis strains isolated in Oran in 2003 also argues against importation of a foreign strain and suggests emergence of variants from a local common ancestor. If true, this suggestion would also imply that it was not organisms in 1 focus but organisms in several adjacent foci that were reactivated at the same time in the Oran region. Climatic and environmental factors may have played a critical role in this resurgence because they have been shown to be predictors of human risk for exposure to plague in other foci in Africa (28).

Our results indicate that adjacent but independent plague foci coexist in Algeria and Libya. Plague outbreaks that occurred in these 2 countries are most likely the result of reactivation of organisms in local foci that were believed to be dormant (Libya) or extinct (Algeria). Recent reemergence of these...
independent foci suggests that climatic and environmental changes in northern Africa may be favorable for the *Y. pestis* epidemiologic cycle. Thus, other countries in northern Africa that have had plague foci may also be at risk for plague outbreaks in the near future.

Mr Cabanel is a research technician in the Yersinia Research Unit at the Institut Pasteur in Paris, France. His research interests are strain characterization and molecular typing of *Y. pestis*.

References


Figures

- **Figure 1.** Locations of plague outbreaks in Oran, Algeria, and Tobruk, Libya. Upper panels show regions around Oran and Tobruk where plague cases were found.
- **Figure 2.** *NotI* pulsed-field gel electrophoresis patterns of *Yersinia pestis* strains of biovar Medievalis obtained during plague outbreak in Libya, 2009. A) Pattern of three 2009 isolates from Libya, Lane...
Figure 3. Insertion sequence–restriction fragment length polymorphism profiles of 3 *Yersinia pestis* strains obtained during plague outbreak in Libya, 2009. Genomic DNA of strains IP1973 (lane 1), IP1974 (lane 2),...

Figure 4. IS100 and IS1541 restriction fragment length polymorphism patterns of 70 *Yersinia pestis* isolates of worldwide origin. A) Medievalis branch. B), ancient strain from Algeria (IP1867); C) other strains...

Figure 5. NotI pulsed-field gel electrophoresis patterns of *Yersinia pestis* isolates from plague outbreak in Algeria, 2009. Lane M, low-range DNA marker (New England Biolabs, Ipswich, MA, USA); lane 1,...

Table

Fifteen strains of *Yersinia pestis* used for analysis of plague outbreaks in Libya, 2009, and Algeria, 2003

<table>
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Table. Fifteen strains of *Yersinia pestis* used for analysis of plague outbreaks in Libya, 2009, and Algeria, 2003

**Tenofovir impairs enzyme that stops cells ageing**

Gus Cairns  
Published: 31 January 2013  
A team of Australian researchers has found that tenofovir and, to a lesser extent, other drugs from the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) class, impairs an enzyme that slows down or stops ageing processes in immune cells in the test tube.

They also found that, in people living with HIV, a marker of cell age called telomere length showed that both older age and duration of treatment with NRTI drugs were significantly associated with signs of the senescence (biological ageing) and approaching death of immune system cells, and that the enzyme that protected cells against this process was less active.

**Background**

The observation that AIDS resembles accelerated aging, and that some manifestations of this – ranging from raised cardiovascular disease and cancer risk to neurocognitive impairment – did not go away when HIV treatment was introduced, has spurred research into a possible cause. While recent studies have tended to suggest that lifestyle issues such as higher rates of smoking may be the primary cause of diseases associated with age in people with HIV, HIV infection itself and also the side-effects of HIV drugs cannot yet be ruled out and are the subject of ongoing research.

In this case the researchers wanted to see if HIV and specifically NRTI drugs had an effect on telomeres.

Telomeres are lengths of DNA, consisting of a single repeated pattern, that do not code for genes and which sit at the ends of each one of the 23 pairs of chromosomes that make up the sum total of each cell’s genetic material. There they act exactly like aglets, the plastic or metal ends of shoelaces that stop their ends fraying.

Every time a cell divides, its chromosomes lose approximately 100 base pairs (the ‘letters’ that spell out the genetic code). Even the smallest human chromosome has 25 million base pairs, but even so
repeated cell division would lead rather quickly to gene degradation and loss of cell function, were it not that the telomeres provide expendable ‘junk’ DNA that can be lost without harm.

Nonetheless with age, the telomeres eventually do wear away, especially in frequently dividing cells, and the cells then die. This has been suggested as one of the root causes of ageing.

Cells, also, however, have a telomere-repair kit in the shape of the enzyme telomerase. This is able to add new base pairs to DNA and repair the telomere. Cells with highly active telomerase are essentially immortal, and this is a property of cancer cells: telomerase inhibitors are currently being investigated as possible anti-cancer drugs.

One of the most important subunits of telomerase is telomerase reverse transcriptase (TeRT), a protein which, as its name suggests, has a similar mode of action and structure to HIV reverse transcriptase. The question the researchers wanted to ask, therefore, was whether the NRTI drugs that inhibit the HIV enzyme also inhibited TeRT and whether this affected telomerase activity.

The study
The study was conducted by researchers at Monash University in Melbourne, Australia under the direction of Sharon Lewin, a pioneer in HIV cure research.

They did three separate experiments. Firstly, they cultured immune-system white blood cells (so-called peripheral blood mononuclear cells or PBMCs), taken from HIV-positive and HIV-negative donors, in the test-tube, stimulated them to divide, and then exposed them to different levels of the NRTI drugs tenofovir, lamivudine (3TC), emtricitabine (FTC), abacavir, zidovudine (AZT) and tenofovir and 3TC combined.

Secondly, they assessed telomere length and telomerase activity in the PBMCs, and the CD4 and CD8 subsets of PBMCs, in 29 HIV-negative men who had taken post-exposure prophylaxis (PEP) containing tenofovir+FTC (Truvada) or, in two cases, AZT+3TC (Combivir) for four weeks.

Thirdly, they also looked at telomere length and telomerase activity in 39 people with HIV who were on NRTI-containing antiretroviral therapy (ART) and compared them to the same measurements in 42 HIV-negative people. They then also compared telomere length in the 39 HIV-positive people to that in 11 HIV-positive people who were on ART regimens not containing NRTIs.

Results
In the first experiment, it was found that adding NRTIs in the test tube did inhibit telomerase activity, but that the effect of tenofovir was considerably greater than other NRTIs and only tenofovir inhibited telomerase at the levels one would see in a patient taking it for HIV treatment. Telomerase activity was cut by two-thirds with 0.3 micromols of tenofovir, whereas was only cut by a third at 100 times this concentration (over 30 micromols) of FTC and abacavir, and at 333 times this concentration (100 micromols) of AZT. 3TC also inhibited telomerase, but precise concentrations could not be determined. This experiment did not measure whether CD4 or CD8 cells were particularly affected.

In the second experiment, four weeks of PEP did not inhibit TeRT activity and telomerase length either during or after taking the PEP regimen, though there was a tendency for TERT activity to be lower in CD4 and CD8 cells than other cell types. This experiment appears to show that short-term tenofovir use does not impact on telomerase.

In the third experiment, telomerase activity was significantly lower in people with HIV taking NRTI drugs than in HIV-negative people (p = 0.011) and there was a trend, which didn’t quite reach statistical significance, towards having shorter telomeres (p=0.061). It is perhaps notable that telomere length was significantly shorter in older HIV-positive people, but wasn’t shorter in the older HIV-negative ones, suggesting that NRTIs might indeed be inhibiting the compensatory repairs telomerase is making in ageing cells.

When comparing people on NRTI and non-NRTI-containing ART, telomerase activity was significantly lower in people on NRTIs (p = <0.001) but telomere length was no different. They were also able to compare telomerase activity in six patients when they were taking NRTIs and also after they were switched to non-NRTI regimens, but found no difference.

In a univariate analysis, looking at telomere length in all people with HIV, shorter telomere length was associated both with older age and with being on NRTI drugs. But in a multivariate analysis that also controlled for gender, current and lowest-ever CD4 count, and duration on tenofovir and AZT as well as on all NRTIs, the association was no longer significant.

Conclusions
It’s important to have a sense of what this study does not tell us. It doesn’t prove that there is a link between the greater affinity of tenofovir for telomerase reverse transcriptase in the test tube, and shorter telomere length in people who take NRTI drugs. In addition, shorter telomere length wasn’t specifically
tied to tenofovir use. It also doesn’t show that there’s any link between shorter telomere length and reduced telomere activity and diseases of age or shorter lifespan in people with HIV – which, as we said above, may also be caused by lifestyle or by the effects of HIV itself.

What it does do is let us know that NRTI drugs, already known for causing the damage to mitochondrial DNA that leads to peripheral neuropathy, fat loss and some other side-effects, also exert an effect on cellular DNA, and that in this case tenofovir may be the drug to keep an eye on.

Telomerase shortening is, by definition, a side-effect that won’t start causing symptoms for many years, and the study does provide a cautionary note in discussions about the possibility of very long-term side-effects associated with the use of tenofovir, both in HIV treatment and in pre-exposure prophylaxis.

Reference

**Michael Palm HIV Basic Science, Vaccines, and Prevention Project Weblog**

By Richard Jefferys, Project Coordinator at Treatment Action Group (TAG)

« David Baltimore and Vectored Immunoprophylaxis | Main | Revitalizing T Cells by Blocking PD-L1 »

**Australian AIDS Cure Claim Leads to a Maelstrom of Hype and Misinformation**

On January 16, a scientist named David Harrich and his institution, the Queensland Institute for Medical Research (QIMR) in Brisbane, Australia, issued a press release invoking the word cure in an effort to publicize a scientific paper containing in vitro (lab dish) study results of uncertain significance at best. The release spawned a maelstrom of misleading media coverage that has continued to swirl for weeks afterward.

Several factors seem to have contributed to the story’s gaining traction. Harrich’s work involves a modified version of an HIV protein (Tat) that can inhibit HIV replication; this was presented as a strategy that “turns HIV on itself.” Although this sounds potentially exciting and new (and clearly was appealing to the media), Harrich’s paper explains that, going as far back as the late 1980s, several other HIV proteins have been altered in ways that inhibit viral replication. This type of inhibition involves a well-described phenomenon wherein a modified protein (described as a dominant negative protein) can inhibit the function of the unmodified counterpart. The novel claim Harrich makes for his modified Tat protein, named Nullbasic, is that it appears to be able to inhibit several different steps in the HIV life cycle. This claim has yet to be independently verified but, more importantly, inhibiting HIV replication is not the major challenge in attempting to achieve a cure: as Harrich’s paper also notes, there is an array of proteins than can inhibit HIV. Furthermore, there are proteins that can completely block HIV from entering target cells (a strategy with many advantages compared to those like Harrich’s which attempt to block replication after the virus has entered a cell). The major problem in cure research is delivering these inhibitors to the cells where they are needed, and Harrich’s study does not help address this issue at all.

In addition to the notion of turning HIV on itself, news stories glommed onto several egregious irresponsible and unjustified quotes in the press release:

*If this research continues down its strong path, and bear in mind there are many hurdles to clear, we’re looking at a cure for AIDS.*

The use of the word *if* and the attempted caveat in the middle of this sentence do not compensate for the wild-eyed claim at the end. Like any other human disease, AIDS cannot be cured in a laboratory dish, and it is impossible to know if you are looking at a cure based on in vitro results.

*You would still be infected with HIV, it’s not a cure for the virus. But the virus would stay latent, it wouldn’t wake up, so it wouldn’t develop into AIDS. With a treatment like this, you would maintain a healthy immune system.*

Perhaps unintentionally, this quote sounds like an early misunderstanding of HIV pathogenesis that was debunked by the early 1990s. In the original erroneous model, HIV was thought to be latent during the asymptomatic phase of the infection before somehow awakening to cause AIDS. It was subsequently shown that HIV replicates throughout the course of infection, causing a persistent activation of the immune system that leads to a gradual attrition of immune-system resources, ultimately resulting in AIDS. Many media outlets failed to notice this misstatement, and instead just repeated the claim that Harrich’s protein could prevent the development of AIDS. Harrich’s in vitro results do not even show that Nullbasic causes HIV to "stay latent" in infected cells; rather they report a roughly eight- to tenfold reduction in viral replication.

In case this all sounds like pessimistic naysaying, the good news is that there are several gene therapy approaches that are already in human trials, including approaches that aim to completely protect...
ABSTRACT

Here we show potent inhibition of HIV-1 replication in a human T cell line and primary human CD4+ cells by expressing a single antiviral protein. Nullbasic is a mutant form of the HIV-1 Tat protein that was previously shown to strongly inhibit HIV-1 replication in non-hematopoietic cell lines by targeting three steps of HIV-1 replication: reverse transcription, transport of viral mRNA and transactivation of HIV-1 gene expression. Here we investigated gene delivery of Nullbasic using lentiviral and retroviral vectors. While Nullbasic could be delivered by lentiviral vectors to target cells, transduction efficiencies were sharply reduced primarily due to negative effects on reverse transcription mediated by Nullbasic. However Nullbasic did not inhibit transduction of HEK293T cells by an MLV-based retroviral vector. Therefore, MLV-based VLPs were used to transduce and express Nullbasic-EGFP or EGFP in Jurkat cells, a human leukaemia T cell line, and Nullbasic-ZsGreen1 or ZsGreen1 in primary human CD4+ cells. HIV-1 replication kinetics was similar in parental Jurkat and Jurkat-EGFP cells, but was strongly attenuated in Jurkat-Nullbasic-EGFP cells. Similarly, virus replication in primary CD4+ cells expressing a Nullbasic-ZsGreen1 fusion protein was inhibited by approximately 8 to 10-fold. These experiments demonstrate the potential of Nullbasic, which has unique inhibitory activity, as an antiviral agent against HIV-1 infection.

Effort to enforce HIV 'health threat' law raises questions January 31, 2013 in HIV & AIDS

(Medical Xpress)—Michigan health officials are using HIV surveillance technologies to assist in enforcing a "health threat" law that makes it illegal for HIV-positive people to have sex without disclosing their status.


A new University of Michigan study reveals that health officials employ the state’s names reporting database, alongside partner services referrals, for law enforcement purposes. However, this is bad social policy for a variety of reasons, says Trevor Hoppe, the study's author and a doctoral candidate in sociology and women's studies. When clients visit publicly funded health clinics in Michigan to be tested for HIV, they can expect more than just a finger prick or blood draw. Counselors also ask clients extensive
questions about their sexual practices and partners. If the client tests positive for HIV or other sexually transmitted diseases, the counselor will provide treatment referrals. They are also legally mandated to ask clients to report the names of sexual partners, which health officials attempt to contact to recommend that they be tested. Hoppe found that some health officials also ask their clients if any of their partners reported to them that they were HIV-positive. Officials then attempt to cross-reference the reported name against the state's database of everyone in the state who has been diagnosed as HIV-positive. If an individual reported as a partner is identified by the state as HIV-positive and the client did not report that they disclosed, an investigation would be launched that could have legal ramifications. At least 24 states have laws making it a misdemeanor or felony for HIV-positive people to have sex without first disclosing their status. In Michigan, failing to disclose is a felony punishable by up to four years in prison—whether or not the person was ever at risk of contracting the disease from their partner. "The evidence is mounting that these laws are bad public policy and certainly bad public health policy, yet Michigan health officials are helping to enforce them," Hoppe said. At the minimum, there is little transparency in how health officials use epidemiological data for law enforcement purposes, he says. "Health officials in some local jurisdictions are using data they collect for public health purposes to help enforce the law, but they're not telling their clients how their personal information could be used," Hoppe said. From an ethical perspective, the question is whether it is reasonable for health officials to use confidential medical information to enforce the law. Hoppe interviewed 25 local health officials who manage "health threat" cases from 14 jurisdictions across Michigan. His research also reveals that how local health officials interpret what qualifies as a "health threat" varies. In some cases, local officials suggested that an HIV-positive woman who became pregnant or contracted another STI might be labeled a "health threat." "These systems were not intended for legal surveillance, yet data collected by them are susceptible to being used for criminal proceedings," Hoppe said. Whether this practice should be continued must be discussed among policymakers, advocates and stakeholders, including those in the HIV-positive and –negative community, he said. The findings appear in the February issue of the journal Social Problems.

HIV Patients At Two-Fold Higher Risk For Non-Melanoma Skin Cancers
Article Date: 31 Jan 2013 – 1:00 PST

HIV-positive patients have a higher incidence of non-melanoma skin cancers, according to a Kaiser Permanente study that appears in the current online issue of the Journal of the National Cancer Institute. Specifically, basal cell and squamous cell carcinomas occur more than twice as often among HIV-positive individuals compared to those who are HIV-negative.

The study cohort of 6,560 HIV-positive and almost 37,000 HIV-negative subjects was drawn from members of Kaiser Permanente Northern California from 1996 to 2008.

Overall, HIV-positive subjects had a 2.1-fold higher risk for basal cell carcinomas and a 2.6-fold higher risk for squamous cell carcinomas, compared to HIV-negative subjects. In addition, squamous cell carcinomas were associated with lower CD4 counts, a measure of immunodeficiency. Prior antiretroviral therapy was not found to be associated with the incidence of either squamous cell carcinomas or basal cell carcinomas.

"These findings represent unique data on non-melanoma skin cancers in HIV patients. Most cancer registries, on which previous studies relied, do not record these types of cancers," said lead author Michael J. Silverberg, PhD, MPH, of the Kaiser Permanente Division of Research.

"This should be of interest to several fields, including HIV, dermatology and cancer. Given the increasing longevity for HIV-positive individuals, the burden of many age-related, non-AIDS-defining cancers, including NMSCs, will only continue to increase. Based on our studies, non-melanoma skin cancers are by far the most common cancer this population experiences."

Non-melanoma skin cancers are the most common cancers in the United States, with more than 3.5 million new cases diagnosed each year. Although most non-melanoma skin cancers are easily cured, many become locally invasive and destructive.

"In the general population, we see one case of squamous cell carcinoma for every four cases of basal cell carcinoma," said senior author Maryam M. Asgari, MD, MPH, a Kaiser Permanente dermatologist and investigator at the Division of Research. "It was notable in this study that for HIV-positive subjects with high CD4 counts, this ratio was similar to HIV-negative subjects. But for HIV-positive subjects with low CD4 counts, there was one case of squamous cell carcinoma for every two cases of basal cell carcinoma."

The increased incidence rate of non-melanoma skin cancers in HIV-positive subjects is consistent with the growing evidence about this population's increased risk for a broad range of cancers, according to
the study authors. They cited a large meta-analysis in which both HIV/AIDS and organ-transplant populations exhibited increased incidence for many types of cancer. The increased cancer risk is likely due to immunodeficiency, the main risk factor these populations have in common. This conclusion was reinforced by a recent large, population-based study of U.S. transplant recipients.

Until now, however, limited data existed about the association between HIV/AIDS and the risk of non-melanoma skin cancer, specifically with regard to the risks for basal cell carcinomas and squamous cell carcinomas. Several studies that have used linked data from HIV/AIDS and cancer registries have reported standardized incidence ratios for other non-epithelial skin cancers that range from 1.8 to 6.5, whereas other studies have indicated no statistically significant associations with HIV infection. However, most cancer registries exclude basal cell carcinomas and squamous cell carcinomas, which are not reportable malignancies.

While non-melanoma skin cancers are harder to detect, Kaiser Permanente’s comprehensive and integrated approach to care allows clinicians to identify these cancers sooner and get members the care they need.

"The clinical implications for these findings include increased vigilance in skin-cancer screening for HIV-positive individuals, especially for squamous cell carcinomas and particularly for those who are not on antiretroviral therapy or who were diagnosed late and have more advanced HIV/AIDS," said Dr. Asgari. "HIV-positive individuals should also be advised to reduce behaviors that may further increase non-melanoma skin cancer incidence, such as excessive sun exposure. In addition, given the observed association of immunodeficiency and squamous cell carcinomas, earlier initiation of antiretroviral therapy to maintain higher CD4 counts may also help reduce the burden of this cancer."

A 'neurosteroid' found to prevent brain injury caused by HIV/AIDS

New research in The FASEB Journal suggests that a network of steroid molecules found in the brain is disrupted during HIV infection, and treatment with the steroid DHEA-S prevents brain damage

Bethesda, MD—A team of scientists from Canada, Thailand and Morocco have found that DHEA-S may prevent neurocognitive impairment that affects a significant percentage of AIDS patients. In a report appearing in the February 2013 issue of The FASEB Journal, they describe how a network of steroid molecules found in the brain, termed "neurosteroids," is disrupted during HIV infection leading to brain damage. This suggests that treatment with one of these steroid molecules, called DHEA-S, may offset the disruption caused by the virus to prevent or reduce brain damage.

"From these studies, we have gained a better understanding of how HIV injures the brain during AIDS, together with developing a new treatment approach for the resulting neurological disabilities arising from HIV/AIDS," said Christopher Power, M.D., co-author of this study from the Department of Medicine at the Medical Research Centre at the University of Alberta in Edmonton, Canada.

To make their discovery, Power and colleagues initially found that neurosteroid enzyme levels were suppressed in the brains of people with HIV/AIDS and that a neurosteroid molecule, DHEA-S, prevented damage to cultured brain cells (neurons) caused by HIV. Then, using an animal model of AIDS, they showed that treatment with DHEA-S prevented neuronal damage in the brain by reducing the adverse effects of HIV. Neurosteroids have already been proposed as treatments for epilepsy, head injury, post-traumatic stress disorder and depression, and these findings extend the potential treatment applications for neurosteroid-related molecules.

"Most people know that AIDS wrecks total havoc on our immune systems," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal, "but far fewer people know that the disease can also lead to noticeable brain damage. This research study offers an explanation why this occurs as well as a possible solution for preventing it. The next steps, of course, involve looking into whether or not people will benefit from some form of DHEA-S treatment."


Latent TB Germs Can Hide in Marrow Cells, Study Says

Boston Globe (01.31.2013) Carolyn Y. Johnson

A Forsyth Institute research team found latent TB bacteria concealed in “bone and cartilage-forming stem cells in bone marrow” where the bacteria can evade immune system activity and antibiotics that would
normally kill them. This ability to hide from treatment by lying dormant in bone marrow stem cells could explain how TB is able to persist for years and recur, according to the Forsyth team, which is composed of stem cell specialists and infectious disease researchers from Stanford University School of Medicine, Cambridge University, and India.

The study first demonstrated that it was possible to infect bone marrow stem cells with TB in the laboratory. The researchers then infected mice with TB bacteria engineered to stay dormant until activated by a drug. When they tested the mice, the team found dormant TB bacteria in both the lungs and bone marrow stem cells. The team was also able to grow TB bacteria from bone marrow stem cells harvested from nine people—thought to be long cured of TB—in a remote village in India.

The Forsyth study does not provide definitive proof that the bone marrow stem cells are the TB bacteria's hiding place. Other theories suggest TB bacteria can persist in a “zombie-like” state that enables the bacteria to resist treatment and then reactivate later. However, the study does contribute to researchers’ understanding of TB’s latent phase and could point to how new treatments might target TB bacteria hiding in the safe harbor of the bone marrow stem cells. Latent infections comprise 90 percent of the world’s 2.2 billion TB cases.

The full report, “CD271+ Bone Marrow Mesenchymal Stem Cells May Provide a Niche for Dormant Mycobacterium Tuberculosis,” was published online in the journal Science Translational Medicine: Integrating Medicine and Science (2013; doi: 10.1126/scitranslmed.3004912).

### African Programme for Onchocerciasis Control 1995–2015: Model-estimated health impact and cost

**Fight against river blindness is successful and inexpensive**

A relatively inexpensive program set up to combat river blindness, an infectious disease, has resulted in major health improvements in Africa, shows a study conducted by Erasmus University Medical Center researchers. The study, due to be published January 31 in *PLOS Neglected Tropical Diseases*, shows that US$250 million helped cure or prevent blindness, skin disease, severe itching, and other symptoms in millions of people. In collaboration with the Management of the African Programme for Onchocerciasis Control (APOC), the researchers calculated the health impact of APOC.

Onchocerciasis, also known as river blindness, is an infectious parasitic disease transmitted by flies that live near fast-flowing rivers. The worm that causes the disease lives in subcutaneous nodules. The bite of the fly passes the worm’s larvae from human to human. During their lifetime, people in endemic regions often contract several infections, which accumulate and can lead to blindness. Infected people may suffer from severe itching, leading to insomnia and inability to concentrate. This makes working or going to school difficult. 'This means people are less able to provide for themselves, especially in developing countries,' says Erasmus MC researcher Luc Coffeng. 'It is for a reason that in images of river blindness you often see a blind person moving around holding the end of a stick accompanied by a child holding the other end.'

In 1995, the WHO launched the African Programme for Onchocerciasis Control (APOC) to combat river blindness. APOC has geographically mapped the disease, and has started annual mass treatment with the drug ivermectin in sixteen African countries. Ivermectin kills the larvae in the human and thus prevents transmission of the infection and development of irreversible symptoms, such as blindness. Manufacturer Merck helps by providing ivermectin for as long as needed, free of charge. APOC distributes the drug in an efficient and inexpensive manner through a community-directed approach. Specially trained volunteers operate at the local level; they find out which people are eligible for treatment, and ensure that these people get the drug. This saves time for health professionals, and makes it easier to continue mass treatment in situations of political instability.

In fifteen years’ time, APOC has had a major health impact at relatively low cost, according to the researchers. The percentage of people infected with the parasite decreased from 45 to 31 percent among a population of 104 million people. 'Blindness and visual impairment now occur much less frequently in the APOC countries. And the percentage of people suffering from severe itching decreased from 14 to 6 percent,' said Coffeng. The researchers express the impact of the programme in terms of years of healthy life gained: 'This metric expresses our preference for people to live their life in good health rather than in disease. For instance, for every year lived in blindness, we consider 0.6 years of healthy life lost.' The program has already saved a total of eight million healthy years of life, at a cost of about US$250 million. 'Peanuts compared to what we in the Western world are spending on healthcare,' commented Coffeng.
'APOC costs 30 dollars for every year of healthy life gained, while in the Western world we are willing to spend tens of thousands of dollars to achieve this.'

The fight against river blindness is not yet over. The percentage of people carrying infection is expected to decline further, to about 18% in 2015. 'APOC has made tremendous efforts to implement mass treatment in all countries in need. The last countries joined the program only in 2010. Treatment must continue for many years, because the drugs only kill the larvae and not the adult worms, which can live inside humans for over 10 years,' observes Coffeng. In other words: it is very important that APOC continues its activities, which requires continued support from drug-donating pharmaceutical companies and donor countries, and continued commitment from national governments of the African countries in question and local volunteers. 'The eventual goal of APOC is to completely eradicate river blindness, and this seems to be possible if all stakeholders commit to that goal.'


**Target 'super-spreaders' to stop hepatitis C**

Each intravenous drug user contracting Hepatitis C is likely to infect around 20 other people with the virus, half of these transmissions occurring in the first two years after the user is first infected, a new study estimates.

The work, led by researchers from Oxford University, suggests that early diagnosis and treatment of Hepatitis C in intravenous drug users could prevent many transmissions by limiting the impact of these 'super-spreaders' (a highly infectious person who spreads a disease to many other people).

Working out 'who has infected who' in fast-spreading diseases such as influenza is often relatively straightforward, but in slow-spreading diseases such as Hepatitis C and HIV, where instances of transmission are spread over months or years, it is extremely difficult. The new approach, developed by a team from Oxford University, University of Athens and Imperial College, combines epidemiological surveillance and molecular data to describe in detail, for the first time, how Hepatitis C spreads in a population.

A report of the research appears in this week's *PLOS Computational Biology*.

'For the first time we show that super-spreaders in Hepatitis C is led by intravenous drug users early in their infection,' said Dr Gkikas Magiorkinis of Oxford University's Department of Zoology, lead author of the study. 'Using this information we can hopefully soon make a solid argument to support the scaling-up of early diagnosis and antiviral treatment in drug users. Helping these people and stopping the spread of Hepatitis C is our ultimate target.'

The World Health Organisation has identified Hepatitis C as a major public health problem: up to 180 million people worldwide live with the virus, most are unaware that they have been infected and remain undiagnosed for more than 10 years. 20% of those infected will develop cancer or liver scarring (cirrhosis) after 20 years of infection, at which point the only treatment is liver transplantation, which costs around £100,000 ($160,000) for each patient.

Unlike other forms of Hepatitis there is currently no vaccine available for Hepatitis C, although there are effective treatments. The virus mainly transmits through contaminated blood and before 1990 the major transmission route was blood transfusions and blood products. Since screening for blood transfusions was introduced, after the discovery of the virus in 1989, the only significant transmission route for Hepatitis C is now intravenous drug use – users are at risk through the sharing and re-use of syringes.

'Working out how many people are likely to be infected by each 'super-spreader' of Hepatitis C, as well as how soon they will be infected, has been a puzzle for over 20 years,' said Dr Magiorkinis. 'Our research has resolved this issue and paves the way for a modelling study to show what kind of public health interventions could really make a difference. Our approach should also be very useful to those studying HIV.'

The research draws on data from four Hepatitis C epidemics in Greece, using information on 943 patients in treatment studies between 1995 and 2000, and around 100 genetic sequences representative of the epidemic taken from frozen plasma samples collected between 1996 and 2006. The team then used a mathematical model to estimate the variance of secondary infection and how long it takes for such infection to occur.
Assault by deadly disease may get expanded definition in state's criminal laws
By Zoey Palmer
Bonney Lake-Sumner Courier-Herald Reporter
JANUARY 26, 2013 · 9:11 PM
A Washington state law that criminalizes intentionally infecting other persons with HIV without their consent may be expanded to include any disease that is dangerous or deadly.

House Bill 1018, sponsored by Rep. Jim Moeller (D-49th District, Vancouver), amends existing state laws defining assault, replacing the language singling out HIV with a more general definition of communicable disease.

Moeller, who is the bill’s sole sponsor, says the original language of the law, which took effect in 1988, reflected attitudes about HIV (the virus that can cause AIDS) that are no longer relevant.

"A lot has changed over the years regarding HIV," he said during a public hearing at a House Public Safety Committee meeting Jan. 17. "There was a great deal of fear – unreasonable fear – around HIV. This bill simply removes that stigma," he said.

Other states have already made similar changes to their laws to reflect a modern understanding of HIV, said Moeller, who is one of six openly gay members of the Legislature.

Along with eliminating language specifying HIV, the bill changes the legal definition of poison to include fluids infected with a dangerous disease, regardless of how it is transmitted. The amended law would include any illness – including HIV – that, if left untreated, normally results in serious harm or death.

"What we've learned is that there are other diseases out there that are equally if not more dangerous than HIV," said Moeller.

Washington Association of Prosecuting Attorneys executive secretary Tom McBride said during the hearing that, despite the much broader language, he doesn't expect a large increase in first-degree assault cases because the law requires that there is intent to cause serious harm or death.

"There's no point to single out a disease here," said McBride, whose organization supports the bill.

There have only been three successfully prosecuted first-degree assault cases under the current law since it went into effect, he said. "Getting into somebody's head and being able to prove specifically what they intend" is extremely difficult, said McBride.

First-degree assault is a Class A felony, which can carry a maximum sentence of life in prison.

The bill also removes an exception for HIV from a law that criminalizes knowingly infecting another person with an STD without his or her consent, a gross misdemeanor that can result in up to one year in prison.

Carey Morris, a lobbyist for Lifelong AIDS Alliance, a Seattle-based non-profit, testified in support of the bill at last week's hearing. The American Civil Liberties Union has also expressed support.

Moeller says that, because of support from state prosecutors, unions and social-justice groups, he doesn't expect any major difficulties passing the bill in the House.

The bill has not yet been scheduled for a committee vote.

Number of HIV cases in ČR highest since 1985
ČTK | 31 January 2013
Prague, Jan 30 (CTK)—The number of HIV positive cases registered in the 10.5-million Czech Republic in 2012 has been the highest in the Czech Republic since 1985 when the HIV testing was launched in the country, National Reference Laboratory head Vratislav Nemecek has said.

The laboratory has confirmed 212 new HIV cases of Czech citizens and foreigners with long-term residence, Nemecek added.

Consequently, the Czech Republic cannot be considered a country with the lowest HIV incidence in Europe any longer as the limit of two cases per 100,000 inhabitants has been exceeded.

"It has been confirmed that the trend of HIV incidence in the Czech Republic has long been considerably accruing," Nemecek said.

Compared to 2010, the number of HIV incidence cases increased by 32 in 2012, and by 59, compared to 2011.

In 1985-2012, 1887 HIV positive case were registered in the Czech Republic. AIDS developed in 366 cases and 266 died of it.

Last year, 185 men and 27 women were among the HIV positive cases.
The decrease in the number of HIV-infected women, which started in 2004, stopped last year. The share of women rose from 8.5 percent in 2011 to 12.7 percent last year.

The average age of HIV-infected men and women was 34 and 33 years, respectively. The HIV-infected men were aged from six to 56 and women from four to 63 years.

When tested positive, 156 people had no health troubles, 27 suffered from acute infections, in 14 cases the infection was diagnosed late and in 15 cases the disease has developed.

The highest number of the newly registered HIV-positive people had their usual residence in Prague. The highest number of the HIV-infected per 100,000 inhabitants is in the capital, too.

Out of 212 new HIV cases, 61 were foreigners with long-term residence: 18 from Slovakia, ten from Ukraine, five from Russia and Vietnam each, four from Moldova and three from Latvia, Poland and Serbia each.

The share of foreigners among the HIV positive has been rising in the long run and is approaching 30 percent in the country.

The HIV infection is in most cases transferred by sexual intercourse (90.6 percent), while 153 cases (72.2 percent) were men who got infected via homosexual intercourse.

The HIV infection transfer via intravenous drug application has long been low in the Czech Republic. Last year it was diagnosed in two men and three women.

Moreover, two HIV positive children were registered in 2012. They are siblings of a family of foreigners living in the Czech Republic on the basis of long-term residence permit. Both parents are HIV-positive.

HIV positive women gave birth to nine babies in the Czech Republic in 2012. Six mothers knew they were HIV positive when they got pregnant and three cases were revealed during screening. One of the babies was born abroad.

In Michigan, Effort To Enforce HIV "Health Threat" Law Raises Questions
A University of Michigan study reports that public health officials in 14 Michigan jurisdictions are using information from the HIV surveillance names reporting database to find and prosecute HIV- or STD-infected people who are legally considered a “health threat.” In addition to asking a newly diagnosed client for the name of the client’s sexual partner(s), the public health officials are inquiring whether the sexual partner disclosed HIV status before having sex.

It is a felony or misdemeanor in 24 states for an HIV-infected person to have sex without first disclosing HIV status to a partner. In Michigan, failure to disclose HIV status prior to having sex is a felony punishable by up to four years in prison, even if the sexual partner was never at risk for HIV. People who oppose the use of data from the names reporting database for legal action urge transparency in the use of epidemiological data and recommend public health officials use the confidential medical information only for treatment referral and partner counseling.

Trevor Hoppe, author of the study, stated he also found inconsistency across the state in health officials’ definition of “health threat.” Some officials described HIV-infected women who became pregnant or infected with another STD as health threats.


AHF Challenges Gilead over AIDS Drug Price Gouging of U.S. Gov't Programs on Strivid
Rock Hill Herald Online (Rock Hill, S.C.), (01.29.2013)
The AIDS Healthcare Foundation (AHF) reported that Gilead Sciences, Inc. charges US HIV patients $28,500 per year for the new HIV drug Strivid, in comparison to $16,600 per patient per year in Canada and European countries with price controls. AHF president Michael Weinstein questioned why Gilead was willing to charge US government programs like ADAP and US HIV patients 42 percent more per patient, per year than price-controlled countries with stronger economies.

When the FDA approved Strivid, a drug that combines four HIV medicines in one pill, in September 2012, Gilead immediately set the U.S. Wholesale Acquisition Cost (WAC) at $28,500. Strivid costs 35 percent more per patient, per year than Atripla, Gilead’s best selling three-in-one combination drug.
The WAC for other Gilead drugs also went up in 2013: Atripla increased 6 percent to $1,878.23 per month; Complera went up 5.8 percent to $1,936.53; Emtriva rose by 5.5 percent to $478.45; and Viread increased 6 percent to $771.39.

Weinstein stated AHF challenged Gilead’s pricing strategy to educate people in the United States about the cost of HIV medicines and to pressure Gilead into changing its US pricing policies.

Researchers Await Clinical Trial Results Of Potential TB Vaccine, Expected Early Next Week
"After nearly 100 years, researchers could be on the verge of finding a vaccine that would eradicate tuberculosis [TB] infections," Reuters reports, noting, "Global health experts are eagerly awaiting clinical trial results, expected early next week, of the first new vaccine in 90 years designed to prevent tuberculosis infections." The news service writes, "While it might not prove effective, it will bring scientists much closer to creating a new generation of TB vaccines," adding, "A lot is riding on the trial’s results, which will give the first solid clues about whether scientists are on the right track to create a new generation of TB vaccines."

"Known as MVA85A, the vaccine is the farthest along of more than a dozen candidates being developed globally to stop the transmission of mycobacterium tuberculosis, which is quickly outsmarting the best antibiotic weapons used against it," according to Reuters. "MVA85A is being developed by researchers at Britain’s Oxford University with support from Aeras, the Wellcome Trust, the European Commission and the Oxford-Emergent Tuberculosis Consortium, a joint venture between Oxford and Emergent Biosolutions Inc. created to make the vaccine," the news service notes, adding, "It is one of 16 vaccines being studied in human clinical trials and the study results will inform the design of more than 50 vaccines being tested in preclinical trials in animals" (Steenhuysen, 2/1).

Two New Studies Examine Causes, Treatment Of Severe Malnutrition
"Two studies of malnourished children offer the first major new scientific findings in a decade about the causes and treatment of severe malnutrition, which affects more than 20 million children around the world and contributes to the deaths of more than a million a year," the New York Times reports. "Merely giving children a cheap antibiotic along with the usual nutritional treatment could save tens of thousands of lives a year, researchers found," the newspaper notes, adding, "The studies, [conducted] in Malawi [and] led by scientists from Washington University in St. Louis, reveal that severe malnutrition often involves more than a lack of food, and that feeding alone may not cure it" (Grady, 1/30).

In one study, published Thursday in the New England Journal of Medicine, researchers "followed the treatment of more than 2,700 Malawian children, six months to five years old, all diagnosed with severe malnutrition," Agence France-Presse reports. The children were given a peanut-based nutrient-dense food supplement and "were also randomly assigned to receive a seven-day course of one of two antibiotics—amoxicillin or cefdinir—or just a placebo," AFP writes, noting "the success rate was noticeably higher ... among the children treated with either antibiotic" (1/31). "Another study, published Wednesday in the U.S. journal Science, showed that insufficient—or insufficiently nutritious—diets may not be the only reason some children develop severe malnutrition," according to AFP/Dawn.com, which adds that the study "suggested that differences in the microbes found in the intestines contribute to why some children suffer more acutely from hunger than others" (2/1).

WHO Issues New Guidance On Sodium Intake
"The World Health Organization (WHO) has for the first time recommended limits on children’s daily consumption of sodium which it hoped would help in the global fight against diet-related diseases becoming chronic among all populations," Reuters reports, adding, "The guidelines vary depending on the child’s size, age and energy needs, and apply to children over the age of two." The news service adds, "The WHO also somewhat revised its recommendations for adults, down to less than 2,000 mg of sodium intake per day, from the current 2,000 mg, in addition to a recommendation of at least 3,510 mg of potassium a day" (Nebehay, 1/31). "The guidelines are an important tool for public health experts and policymakers as they work in their specific country situations to address non-communicable diseases such as heart disease, stroke, diabetes, cancer and chronic respiratory diseases," a WHO press release states (1/31).
Autism speaks through gene expression
Philadelphia, Pa. — Autism spectrum disorders affect nearly 1 in 88 children, with symptoms ranging from mild personality traits to severe intellectual disability and seizures. Understanding the altered genetic pathways is critical for diagnosis and treatment. New work to examine which genes are responsible for autism disorders will be presented at the 57th Annual Meeting of the Biophysical Society (BPS), held Feb. 2-6, 2013, in Philadelphia, Pa.

"Autism is the most inheritable of neurodevelopmental disorders," explains Rajini Rao of Johns Hopkins University in Baltimore, Md., "but identifying the underlying genes is difficult since no single gene contributes more than a tiny fraction of autism cases." Rather, she continues, "mutations in many different genes variably affect a few common pathways."

A team of scientists at Johns Hopkins and Tel Aviv University in Israel looked at genetic variations in DNA sequence in the ion transporter NHE9 and found that autism-associated variants in NHE9 result in a profound loss of transporter function. "Altering levels of this transporter at the synapse may modulate critical proteins on the cell surface that bring in nutrients or neurotransmitters such as glutamate," says Rao. "Elevated glutamate levels are known to trigger seizures, possibly explaining why autistic patients with mutations in these ion transporters also have seizures."

A unique aspect of the team’s approach was that they exploited decades of basic research done in bacteria and yeast to study a complex human neurological disorder. First, the group at Tel Aviv University, led by Nir Ben-Tal, built structural models of NHE9 using a bacterial relative as a template, allowing the Rao laboratory at Johns Hopkins to use the simple baker’s yeast for screening the mutations. In the future, as genomic information becomes readily available for everyone, such easy, inexpensive, and rapid screening methods will be essential to evaluate rare genetic variants in autism and other disorders.

Rao and her team are optimistic about the potential benefits of their latest findings. "Although the research is still at an early stage, drugs that target the cellular pathways regulated by NHE9 could compensate for its loss of function and lead to potential therapy in the future," Rao says. "These findings add a new candidate for genetic screening of at-risk patients that may lead to better diagnosis or treatment of autism."

Presentation #118-Plat, "Functional evaluation of autism associated mutations in SLC9A9 (NHE9)," will take place at 9:15 a.m. on Sunday, Feb. 3, 2013, in the Pennsylvania Convention Center, Room 113C. ABSTRACT: http://tinyurl.com/apjmm7a

Propping open the door to the blood brain barrier
New approach to delivering therapeutics could lead to better treatment of central nervous system disorders
Philadelphia, Pa. — The treatment of central nervous system (CNS) diseases can be particularly challenging because many of the therapeutic agents such as recombinant proteins and gene medicines are not easily transported across the blood-brain barrier (BBB). Focused ultrasound can be used to "open the door" of the blood brain barrier. However, finding a way to "prop the door open" to allow therapeutics to reach diseased tissue without damaging normal brain tissue is the focus of a new study by a team of researchers at the Institute of Biomedical Engineering at National Taiwan University presenting at the 57th Annual Meeting of the Biophysical Society (BPS), held Feb. 2-6, 2013, in Philadelphia, Pa.

The group is investigating the feasibility of using heparin, a common anticoagulant, to enhance the delivery of therapeutic macromolecules using ultrasound into the brain. Heparin could be employed to increase treatment efficacy in patients with different types of CNS diseases under the guidance of medical imaging system providing new hope in these challenging cases. Initial results show that heparin does have the potential to optimize therapeutic delivery with ultrasound, acting as a "doorstop," allowing drugs to better permeate the BBB and enhancing treatment success.

"A higher acoustic pressure and longer sonication, and/or a higher dose of microbubbles may increase the delivery of drugs or tracers into the sonicated brain tissue," explains Kuo-Wei Lu, a member of the research team, "but side-effects, such as microhemorrhage, can also increase dramatically. The results of this study indicate that heparin may offer a safer way can to enhance the delivery of therapeutics to patients with CNS diseases."

With these encouraging results, the next step for the team is to develop a focused ultrasound system with Magnetic Resonance Imaging (MRI) guidance to establish suitable parameters needed for patient clinical trials. "Focused ultrasound sonication is a noninvasive technology capable of localized and transient BBB opening for the delivery of CNS therapeutics," Lu states. "We hope by developing suitable parameters and using chemical enhancers like heparin, this can be a valuable tool in the treatment of patients with CNS diseases, opening the door to better patient outcomes."
Presentation #3539-Pos, "Impact of initial vascular permeability and recovery speed of disrupted blood-brain barrier on nanodrug delivery into the brain tissue," will take place at 10:30 a.m. on Wednesday, Feb. 6, 2013, in the Pennsylvania Convention Center, Hall C. ABSTRACT: http://tinyurl.com/adycds6