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**Did 'Serial Infector' Spread Hep. C to Thousands?**
Mon, Jul 30 2012

Last week it was believed David Kwiatkowski, the alleged serial infector of hepatitis C, may have infected 30 people with the potentially life threatening disease.

Now, that number has been estimated up—way up. It's now believed that Kwiatkowski may have infected "tens of thousands" of patients in at least 13 hospitals, reports ABC.

Kwiatkowski is alleged to have been a drug addict who was stealing the high power painkiller Fentanyl from the hospitals he worked at. Kwiatkowski had hepatitis C and authorities believe that he injected himself with the painkiller and then replaced the needles with another liquid-like substance.
As a temporary worker, Kwiatkowski traveled from state to state and hospital to hospital working as a lab technician. Throughout his travels, the 32-year-old man had aroused the suspicions of several coworkers and had even been fired by an employer for drug use. Yet, Kwiatkowski kept finding new employment where he could expose patients to hepatitis.

Exeter Hospital in New Hampshire is already being sued by a patient who says he was infected by Kwiatkowski. In that lawsuit, the patient argues that the hospital was negligent in hiring the lab technician.

The hospital says that it conducted a criminal background check and had Kwiatkowski undergo a drug test. Still, given the sensitive position of a lab technician, the argument is that more could have been done. As 6,000 patients at Exeter Hospital alone have been urged to get a hepatitis C test, hospitals could be exposed to hundreds of lawsuits for hiring the serial infector of hepatitis C.

Imprisoned over HIV: One man's story (long)

By Saundra Young, CNN Sr. Medical Producer
updated 11:36 AM EDT, Thu August 2, 2012

(CNN) — The nightmare Nick Rhoades has been living the past four years began after a one-time sexual encounter with another Iowa man, Adam Plendl.

It was June 2008. The 34-year-old Rhoades, who is HIV positive, says he was on antiretroviral medications. His viral load—the amount of virus in his blood—at the time was undetectable and he says he wore a condom. But Plendl contacted the police because Rhoades did not disclose his HIV status.

What happened next, Rhoades says, changed his life forever.

The former hotel administrator was arrested three months later. The official charge: criminal transmission of HIV—a class B felony in Iowa, where the encounter occurred. Other crimes in this category include manslaughter, kidnapping, drug crimes and robbery.

"I was in shock, trying to figure out where this was all going," Rhoades says. "My heart was racing a million miles an hour. I'd never been in trouble."

But Plendl, 22 at the time, says his life was forever changed as well, and that he was severely depressed and suffered panic attacks while waiting to find out if he was infected.

"It was 181 days of pure fear, that six-month window when you don't know," he says.

"Individuals that are HIV positive have a moral and currently legal obligation to inform any of their sexual partners of their positive status. Individuals should have the choice as to whether or not they would engage with someone who is HIV positive when they are not. In this case, that choice—and what I also consider a right—was not afforded to me."

In many countries, intentionally or recklessly infecting another person with HIV is a crime. In the United States, the Center for HIV Law and Policy says 32 states, including Iowa, and two territories—Guam and the U.S. Virgin Islands—have such laws on their books.

In fact, GNP+, the Global Network of People Living with HIV/AIDS, lists the United States at the top of its list of 15 "hot spots" for HIV criminalization.

Now, a debate is under way regarding whether those laws need to be updated or even repealed.

'I felt pretty less than human'

Rhoades ended up pleading guilty. "I entered a guilty plea based on the advice of my attorney," he says. "I really didn't understand the law; I didn't understand it enough to know I shouldn't plead guilty."

So he went to jail, even though Plendl says hospital tests confirmed he was not infected with HIV. His bond was set at $250,000. Unable to post bail, Rhoades spent the next nine months in the Black Hawk County jail.

"I spent six weeks in solitary confinement," he says. "I was in a cell for 23 hours a day with a camera on 24 hours a day. I was allowed just one visit per week. I could not see out a window.

"For nine months I never saw the sun, except for one time on my way to a medical appointment. I was taken to that medical appointment in my orange jumpsuit and my cuffs and shackles. A mother and daughter saw me in the waiting room and got up and moved away from me. I felt pretty less than human."

Save lives: End the HIV stigma

On September 11, 2009, Rhoades was sentenced to 25 years in prison. He was moved to the Clarinda Correctional Facility in Clarinda, Iowa, to begin serving that sentence.

After four months in Clarinda and a successful letter-writing campaign to the judge calling for him to be freed, Rhoades was re-sentenced. His 25 years was reduced to the time he had served, plus five years of
supervised probation. He also had to register as a sex offender, and will continue to do so for the rest of his life.

"When you're a sex offender there's so much stigma and people jump to conclusions," Rhoades says. "My life is forever changed. Do a Google search for my name and some pretty horrific stuff comes up. I have had to change a private medical condition and a private life to public domain.

"That's not to say I can't be happy, find employment, have a satisfying life, but it's never going to just go away."

**Federal, state laws on criminalization**

HIV criminalization laws began in 1990 when the federal Ryan White CARE Act passed. That law mandated that states criminalize intentional transmission of HIV in order to get funding for treatment and prevention programs.

Some states took it a step further than federal law required, defining intentional transmission as failing to disclose positive status to a sexual partner. The second time the act was reauthorized, in 2000, the requirement that states must criminalize intentional transmission was removed.

The criminalization laws were put in place to protect the public—to prevent cases where someone with HIV knowingly exposed others to the virus and did not disclose their HIV status before a sexual encounter.

In 2010, for example, an HIV-positive man was arrested in Indiana for knowingly and intentionally exposing more than 100 women to the virus over five years. Earlier this year, a Michigan man admitted to police that he was trying to infect as many people as possible and told authorities that over the past three years, he had had unprotected sex with thousands of people.

**How to end AIDS**

The laws vary state by state. Some target those who have HIV/AIDS and fail to disclose their status to their partner before an encounter.

According to the Center for HIV Law and Policy, 13 of those states have laws against HIV-positive people spitting or biting someone even though saliva does not transmit HIV. Others address needle sharing or blood, organ or semen donation.

Iowa passed its criminalization law in 1998, 10 years before Rhoades' fateful encounter.

It will be up to legislators in each state to review these laws and decide whether to make changes. This year, Iowa Sen. Matt McCoy, a Democrat, called the laws retaliatory. "This is medieval and it goes back to treating HIV as if it were leprosy and basically we need to repeal these laws," McCoy says. "They are draconian and they are outdated and we know so much more about the disease."

He introduced a bill to repeal and modernize it to include HIV in the contagious disease section of the Iowa code, where penalties for transmission are lower. Currently, the law has a separate section that relates only to HIV.

His bill didn't make it out of subcommittee. He plans to reintroduce another in the legislative session beginning in January.

"Some good questions are being asked about these laws, and I don't believe it hurts for them to be entered in the discussions we will have next session," says Iowa Sen. David Johnson, assistant minority leader for the Senate Republican Caucus.

**Advocate: People with HIV treated as 'dangerous felons'**

At the 19th International AIDS Conference in Washington last week, the Positive Justice Project, launched by the Center for HIV Law and Policy, released a national consensus statement calling on federal and state officials to modernize laws and eliminate HIV-specific statutes.

Catherine Hanssens, executive director of the Center for HIV Law and Policy, says HIV criminalization is unjust, bad public health policy and is a barrier to testing—if a person doesn't know their status, they can't be charged with nondisclosure. She says criminalization is fueling the epidemic rather than reducing it.

"We believe it's necessary to modernize criminal laws to eliminate HIV-specific statutes and ensure that any prosecution on the basis of HIV or any other STIs requires real proof that the person intended to do serious harm, proof that the person engaged in behavior likely to cause that harm, proof that the conduct did in fact result in the harm intended, and punishment that is proportionate to the actual harm caused," Hanssens said.

"In Tennessee, for example, HIV criminal law allows up to a 15-year sentence and lifetime sex offender registration for a single exposure offense, while reckless endangerment with a deadly weapon has a maximum penalty of six years," she says.
"In Ohio, so-called HIV exposure results in a far harsher sentence than vehicular homicide or manslaughter. You will find similar disparities in a number of other states, from Georgia to California."

But those are not Hanssens' only concerns. She says available data shows that HIV criminalization disproportionately affects people of color, in particular African-American men.

"The availability of the criminal law to pursue so-called HIV exposure and failure to disclose cases can serve as a proxy for pursuing people on the basis of race, sexual orientation—society's outlaws," Hanssens says.

"...It is just not appropriate—even in those relatively rare cases when HIV transmission actually occurs—to treat people with HIV as dangerous felons, sex offenders and murderers who deserve decades in prison for a disease that all of us can and must be empowered to protect ourselves against," she says.

Experts address HIV problem among African-American men

However, Scott Burns, executive director of the National District Attorneys Association, says these laws should not be repealed.

"I think I speak for most prosecutors in stating that in certain circumstances, there certainly should be a criminal statute where people should be punished for knowingly, intentionally infecting someone with the HIV virus," Burns said.

"Certainly the law should catch up with the science and people ought not to be held responsible for acts that would not infect someone with HIV. You can be held guilty of assault for biting someone or spitting in someone's face, but there ought to be laws where someone intentionally or intends to intentionally infect somebody.

"For example, if someone with HIV has unprotected sex with somebody who does not, and doesn't reveal that or doesn't disclose that and the other person becomes HIV-positive, I think that's unconscionable."

Rep. Barbara Lee, D-California, took advantage of the international focus on the disease last week by raising the issue of criminalization during the conference's opening ceremony: "We can and we must repeal laws and politically motivated policies that violate human rights."

Lee has been a leader in the fight against HIV/AIDS and has for years fought to repeal laws she calls unfair and discriminatory. Last year, she introduced a bill that creates incentives for states to reform their criminalization policies.

"Laws that place an additional burden on HIV-positive individuals because of their HIV status lag far behind the medical advances and scientific discoveries in the fight against the epidemic," says Lee. "Instead of progress against the disease and protection for people living with HIV/AIDS, criminalization laws breed fear, discrimination, distrust and hatred."

Although the country has made significant advances in the global fight against the disease, there is still a lot of work to do here at home, she says.

AIDS survivor: Epidemic isn't over yet

"The decriminalization of HIV/AIDS is one way we can reduce stigma in our communities, while fighting the epidemic in a rational, holistic and truly rights-based fashion."

Rhoades' case: Where it's headed

In Iowa, Rhoades is fighting to have his conviction thrown out. His new lawyer, Scott Schoettes with Lambda Legal, has appealed his conviction to the Iowa Supreme Court.

Schoettes says the conviction should be overturned because Rhoades wore a condom. Schoettes also says Rhoades' former attorney never explained to him that the statute requires proof that an HIV-positive person intentionally tried to infect the victim.

"What drives these laws is ignorance regarding the real routes and risks of transmission," Schoettes said. "It's much harder to transmit than people think, and I think the sentences are driven by the misunderstanding of the current-day consequences of living with HIV."

The laws, Schoettes says, are being used to stigmatize and marginalize people with HIV.

"We treat people who are being prosecuted under these laws as if they are violent sex offenders, when most of them have engaged in a consensual act with another adult," he says. "If you engage in safe sex, you have not committed a crime. If you put on a condom, you have engaged in safe sex. However, this is not the way the law was applied, certainly not in Nick's case."

Pendl, however, disagrees. "The argument that since a condom was used there was no intent to transmit is a false statement," he says.

"While I realize that medical research reflects a significantly low number of HIV transmissions occur through oral exposure, in any event prior to the sexual intercourse with the defendant in this case, there was oral exposure to seminal fluid, which does contain and can transmit the HIV virus."
Plendl believes some state laws need to be modified with regards to maximum sentencing, but should not be repealed under any circumstances.

"I do believe that the statutory maximum sentence of 25 years in prison under Iowa law probably is too harsh," Plendl says. "However, the defendant in this case is not serving a 25-year sentence any longer. Furthermore, to have no consequences for this type of crime and irresponsible behavior seems completely illogical."

The Black Hawk County prosecutor in Rhoades’ case did not return multiple calls from CNN.

Talk of 'cure' at historic AIDS conference
A hearing in Rhoades’ case has been scheduled for August 15. Schoettes expects the new trial to begin late this year or in early 2013.

"It is our fervent hope and belief that this conviction should be overturned, and that's what we're working for on Nick's behalf," he says.

"If the Iowa Supreme Court does a careful review of the law, it should see that no crime was committed here. We hope to take away some of the worse consequences of this prosecution for Nick. But as long as the law is on the books, this can happen to someone else."

Still, for Rhoades, life has been irrevocably changed.

"I have to undergo a polygraph test every six months," he says. "My house is subject to search and seizure at the whim of the probation officer."

"I am not allowed to have an e-mail account, instant messaging, not allowed on any social networking sites. I have to register all vehicles I drive with the local sheriff's department ... I have a midnight curfew."

He’s working as a hotel front desk clerk and also for the Center for HIV Law and Policy, but finding employment has been difficult. He has found it hard to shake the past and move forward amid uncertainty concerning his case.

What’s the worst consequence of all?

"I am really close to my nieces and nephews. I have six of them," Rhoades said. "I am not allowed to be alone with a niece or nephew or any child. My brother could be charged with a felony if he left me in the room alone with my niece or nephew."

"I so fear a violation of my probation—I still spend time with my niece and nephew, but not to the degree that I used to because I am afraid."

On 25th anniversary, a quilt displays an American tragedy

Digital pills make their way to market
30 Jul 2012 | 21:31 BST | Posted by Amy Maxmen
Digestible microchips embedded in drugs may soon tell doctors whether a patient is taking their medications as prescribed. These sensors are the first ingestible devices approved by the US Food and Drug Administration (FDA). To some, they signify the beginning of an era in digital medicine.

"About half of all people don’t take medications like they’re supposed to," says Eric Topol, director of the Scripps Translational Science Institute in La Jolla, California. "This device could be a solution to that problem, so that doctors can know when to rev up a patient’s medication adherence." Topol is not affiliated with the company that manufactures the device, Proteus Digital Health in Redwood City, California, but he embraces the sensor’s futuristic appeal, saying, "It’s like big brother watching you take your medicine."

The sand-particle sized sensor consists of a minute silicon chip containing trace amounts of magnesium and copper. When swallowed, it generates a slight voltage in response to digestive juices, which conveys a signal to the surface of a person’s skin where a patch then relays the information to a mobile phone belonging to a healthcare-provider.

Currently, the FDA, and the analogous regulatory agency in Europe have only approved the device based on studies showing its safety and efficacy when implanted in placebo pills. But Proteus hopes to have the device approved within other drugs in the near future. Medicines that must be taken for years, such as those for drug resistant tuberculosis, diabetes, and for the elderly with chronic diseases, are top candidates, says George Savage, co-founder and chief medical officer at the company.

"The point is not for doctors to castigate people, but to understand how people are responding to their treatments," Savage says. "This way doctors can prescribe a different dose or a different medicine if they learn that it’s not being taken appropriately."
Proponents of digital medical devices predict that they will provide alternatives to doctor visits, blood
tests, MRIs and CAT scans. Other gadgets in the pipeline include implantable devices that wirelessly inject
drugs at pre-specified times, and sensors that deliver a person’s electrocardiogram to their smartphone.
In his book published in January, *The Creative Destruction of Medicine*, Topol says that the 2010s
will be known as the era of digital medical devices. “There are so many of these new technologies coming
along,” Topol says, “it’s going to be a new frontier for rendering care.”

**Young African Women Risk HIV Infections from Older Men**

*Agence France Presse*, (07.23.2012)

Cross-generational sex, particularly between older men and younger women, is a main reason females
account for 60 percent of southern Africa’s HIV cases, according to experts.

“It’s one of the means for HIV transmission, especially men that have their spouses but they go out
with these younger ladies,” said Linda Chongo, of Mozambique’s National Network of AIDS Service
Organizations. “As money rules, the person with the money will be the one who will impose the rules to be
taken. It is quite difficult to negotiate safe sex when you are already in a lower position.”

Even young women who are aware of the HIV risks often become involved with older men, said Stuart
Chuka, a Malawi AIDS treatment program coordinator. “One of the reasons is that the young women do
not have the capacity, more especially because of finances,” to provide for themselves, he said.

But Chongo said poverty only partly explains the phenomenon. “If you look into Africa you will see
that poverty has always been there, but our grandmothers and mothers didn’t behave the way we are
behaving now,” she noted.

Zimbabwe officials are developing campaigns discouraging what are known as “small houses”—long-
term extra-marital affairs between older men and young women, as compared to the “big house” where a
man’s wife resides. “As part of our ongoing campaign to prevent new infections, we are designing posters
to discourage age-mixing in relationships,” said Beauty Nyamwanza, a National AIDS Council program
officer.

After South Africa’s KwaZulu-Natal province recorded an increase in teenage pregnancies linked to
sex with older men, it put up 89 billboards highlighting the dangers of cross-generational sex and created
support groups to help young women resist such relationships.

**Gilead HIV Drug as Good as Merck’s Isentress: Study**

*Reuters*, (07.24.2012) Bill Berkrot

Gilead Sciences Inc. said elvitegravir, a component in its four-drug HIV treatment Quad, showed similar
efficacy and tolerability compared to Merck & Co.’s Isentress in a two-year trial.

The results of the study in previously treated HIV patients were presented at the 19th International
AIDS Conference. In the late-stage clinical trial, elvitegravir met the primary clinical goal of being non-
inferior to Isentress, the researchers said.

“As patients are living with HIV longer, there is a continued need for new treatment options,
particularly those that are effective against strains of the virus that have developed resistance to currently
available therapies,” said Dr. Richard Elion, lead investigator.

US and European health regulators are reviewing elvitegravir for approval. The US Food and Drug
Administration is expected to make an approval decision on Quad in August.

Both once-daily elvitegravir and twice-daily Isentress (raltegravir) are integrase inhibitors: They
interfere with HIV’s replication by thwarting its ability to integrate into the genetic material of human
cells.

Both treatment groups had similar rates of adverse side effects, side effect-related discontinuations,
and drug resistance development; however, reports of diarrhea were more common among study subjects
taking elvitegravir (13 percent vs. 8 percent).

**Rodent Study Shows Potential For Development Of More Virulent Malaria If 'Leaky'
Vaccine Used**

Using a rodent model to examine the long-term effects of a potential malaria vaccine, a new study
published in *PLoS Biology* by researchers at Penn State University shows that the vaccine could lead to
the development of more virulent forms of malaria, the *PLoS* blog "*Biologue*” reports (Gross, 7/31). "Vicki
Barclay, the study’s lead author, said it shows a need to track the long-term impact of any malaria vaccine,
especially since any such vaccine is expected to be ‘leaky’—meaning it won’t offer complete protection, and
the disease will continue to spread, albeit at a slower rate," CNN's "The Chart" writes. "Researchers working with the leading candidate vaccine immediately questioned [the study], saying they've seen no sign of dangerous changes as a result of their work," the blog continues (Hellerman, 8/1).

**Partners In Health Reports On Efforts To Curb Haiti’s Cholera Epidemic Using Oral Vaccinations**

"In April, Partners In Health [PIH] responded to Haiti’s cholera epidemic by providing oral vaccinations to 45,000 people living in the country's Artibonite region—specifically, to two rice-farming communities hit hard by cholera," Louise Ivers, senior health and policy adviser at PIH, reports in an article on the organization's webpage. "In partnership with Haiti’s Ministry of Health, hundreds of community health workers fanned out across the rural, flood-prone area, delivering two doses to each person by the end of May," she writes, and discusses the impact of the campaign (8/1).

**Bacteria-immune system 'fight' can lead to chronic diseases, study suggests**

ATLANTA – Results from a study conducted at Georgia State University suggest that a "fight" between bacteria normally living in the intestines and the immune system, kicked off by another type of bacteria, may be linked to two types of chronic disease.

The study suggests that the "fight" continues after the instigator bacteria have been cleared by the body, according to Andrew Gewirtz, professor of biology at the GSU Center for Inflammation, Immunity and Infection. That fight can result in metabolic syndrome, an important factor in obesity, or inflammatory bowel disease (IBD).

The results were published in the journal *Cell Host & Microbe*.

"The implication at present is that it is very important to control the early environment," Gewirtz said. "We need to examine how this can be achieved – perhaps via breastfeeding, a more diverse diet, probiotics are possibilities."

The study's results are important as instances of chronic diseases like metabolic syndrome and IBD are increasing rapidly among humans, he explained.

Metabolic syndrome involves risk factors, including obesity, which can lead to cardiovascular disease, diabetes and stroke. According to the American Heart Association, about 35 percent of adults are affected by this syndrome.

IBD, which includes Crohn’s disease and ulcerative colitis, happens when the intestines become inflamed, leading to abdominal cramps and pain, diarrhea, weight loss and bleeding.

More than 600,000 Americans annually have some kind of inflammatory bowel disease, according to the American Academy of Family Physicians.

Bacteria normally live in the gut of humans, with the average human having about 4 pounds of bacteria living there.

"It is increasingly apparent that bacteria are playing a role in healthy development, and need to be properly managed by the mucosal immune system to avoid inflammatory diseases" Gewirtz explained.

**Equatorial Regions in Brazil Less Affected by 2009 Influenza Pandemic**

ScienceDaily (Aug. 1, 2012) — The death toll of the 2009 influenza pandemic in equatorial climates may have been much lower than originally thought, according to a study supported by the National Institutes of Health's Fogarty International Center. The paper challenges the idea that the pandemic was deadlier in the tropics, which harbor nearly half of the world’s population and which have the highest burden of infectious disease.

The study may have a direct bearing on global estimates of pandemic burden and on the assessment of immunological, socioeconomic and environmental drivers of the outbreak, according to Fogarty researcher Dr. Wladimir J. Alonso, who led the study. The authors stressed that comparing disease burden as reliably as possible is critical in areas with competing health priorities and limited resources, as is the case for Brazil and other countries in the equatorial region.

Alonso's group of epidemiologists found evidence of far milder and delayed influenza pandemic mortality towards areas of Brazil closer to the equator. "We found that respiratory mortality was substantially higher during the pandemic in the southern and richer half of Brazil, where its circulation coincided with the colder winter months," said Alonso. "But even more puzzling, little or no difference from pre-pandemic mortality levels was identified in equatorial regions."
To arrive at these estimates, the researchers investigated laboratory-confirmed pandemic deaths in each Brazilian state and estimated the mortality burden caused by the pandemic that was above what would be expected in an average year. The analytical approach they employed determined baseline mortality in pre-pandemic years by considering the usual variability—including that of seasonal epidemics—in each location, and let them compare the impact of the pandemic across areas with different climatic and epidemiological profiles.

The observed difference in pandemic mortality spanned more than 2,700 miles and was independent of social and demographic factors, with lower-income states being less affected by the pandemic. The findings also suggested that, similar to seasonal influenza, climate played a key role in the dynamics of the outbreak.

The researchers included data going back to 1996, using mortality statistics from two independent sources maintained by the Brazilian government. "Brazil represents a unique opportunity, as it has a large population dispersed across climate zones and yet also exposed to uniform immunization and mitigation efforts," said Dr. Cynthia Schuck-Paim, director of Origem Scientifica Ltd. Data Analysis in Sao Paulo, Brazil, and the lead author of the article.

According to Alonso, the study is the first to generate such results. "The finding that the severity and timing of circulation of this pandemic strongly depended on latitude does not imply that future pandemics will behave similarly," Alonso said. "Research on other past pandemics, such as the flu that swept the globe in 1918 and killed an estimated 50 million people, is also crucial for the elaboration of better preparedness plans."

**HIV-Infected T Cells Help Transport the Virus Throughout the Body**

ScienceDaily (Aug. 1, 2012) — A new study has discovered one more way the human immunodeficiency virus (HIV) exploits the immune system. Not only does HIV infect and destroy CD4-positive helper T cells—which normally direct and support the infection-fighting activities of other immune cells—the virus also appears to use those cells to travel through the body and infect other CD4 T cells. The study from Massachusetts General Hospital (MGH) investigators, which will appear in the journal Nature and has received advance online release, is the first to visualize the behavior of HIV-infected human T cells within a lymph node of a live animal, using a recently developed "humanized" mouse model of HIV infection.

"We have found that HIV disseminates in the body of an infected individual by 'hitching a ride' on the T cells it infects," says Thorsten Mempel, MD, PhD, of the MGH Center for Immunology and Inflammatory Diseases, who led the study. "Infected T cells continue doing what they usually do, migrating within and between tissues such as lymph nodes, and in doing so they carry HIV to remote locations that free virus could not reach as easily. There are drugs that can manipulate the migration of T cells that potentially could be used to help control the spread of virus within a patient."

When HIV is introduced into blood or tissues, the virus binds to CD4 molecules on the surface of helper T cells, injecting its contents into cells and setting off a process that leads to the assembly and release of new virus particles. It has long been assumed that these free virus travel by diffusion through tissue fluids to encounter new cells that can be infected. But recent studies have suggested that HIV can also pass directly from cell to cell when structures called virological synapses form during long-lasting interactions between T cells. Since CD4 T cells usually migrate quickly and form only transient contacts with other cells, the current study was designed to examine whether HIV alters the migration of infected T cells, allowing the kind of persistent contact that facilitates the spread of infection.

The team's experiments used the humanized BLT mouse model, which has what is essentially a human immune system and is the only non-primate that can be infected with HIV. After first confirming that human T cells enter and normally migrate within the animals' lymph nodes—known to be important sites of HIV replication—the researchers injected the animals with HIV engineered to express green fluorescent protein (GFP), allowing them to track the movement of infected cells within living animals using a method called intravital microscopy. They first observed that, within two days, infected T cells continued to migrate and were uniformly distributed within lymph nodes but remained in nodes closest to the site of injection.

While the HIV-infected cells actively moved within lymph nodes, they did not move as quickly as comparable but uninfected T cells. In addition, 10 to 20 percent of the HIV-infected T cells formed abnormally long and thin extensions that appeared to trail behind moving cells, often exhibiting branches. The researchers hypothesized that the HIV envelope protein, which is expressed on the surface of infected T cells before they release new virus particles, might cause infected cells to form tethering contacts with
uninfected cells, producing these extensions. A series of experiments verified that the elongated shape of some infected cells requires the presence of the envelope protein and that many of the elongated cells contained multiple nuclei, suggesting they had been formed by the fusion of several cells.

To test the role of T cell migration in HIV infection, the researchers injected another group of BLT mice with HIV and at the same time treated them with an agent that prevents T cells from leaving lymph nodes. Two months later, levels of HIV in the bloodstream and in lymph nodes distant from the site of injection were much lower than in untreated HIV-infected animals, supporting the importance of T cell migration to carry virus throughout the body. Treatment with the migration-suppressing agent, however, did not reduce viral levels in animals with already established HIV infection.

"While our observation of tethering interactions between infected and uninfected CD4-expressing cells suggest that HIV may be transmitted between T cells by direct contact, we will have to clearly show this in future studies and explore how important it is relative to the transmission by free virus," explains Mempel, an assistant professor of Medicine at Harvard Medical School. He adds that the availability of the BLT mouse was instrumental in their ability to carry out this study. "This approach provides a new vantage point to investigate previously unexplored aspects of HIV pathogenesis."

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Posted: Tue, Aug. 7, 2012, 3:01 AM

**The Milton Hershey School apologizes to HIV-positive student**

By Kathy Boccella, Inquirer Staff Writer

The president of the Milton Hershey School has apologized to an HIV-positive student who was denied admission because of his condition and said he was welcome to attend the residential school in the fall if he still wanted to.

President Anthony Colistra said in a statement that he made the offer in a July 12 letter to the boy and his mother. The school originally said that its residential setting and the risk of sexual activity made the teen too much of a "threat."

The change of heart comes months after a lawsuit filed by the AIDS Law Project on behalf of the boy in November in U.S. District Court in Philadelphia, alleging that the school violated the Americans With Disabilities Act, which includes HIV.

The student, who is now 14 and lives in Delaware County where he attends public school, is considering the offer but is also looking at other options, said his lawyer, Ronda Goldfein.

"They said he was a threat to everybody. ... He has to do a lot of thinking about that," she said, adding that she was "delighted" the school reversed course but that they were pressing ahead with the case.

"We told them what the law was and they ignored it," Goldfein said. "They made some pretty negative comments about our client."

School spokeswoman Connie McNamara previously told ABC News that the school was worried the boy would have sex at some point at the school. Students live together in campus housing in groups of 10 to 12.

The school was founded by the chocolate magnate in 1909 for white male orphans and is now the nation's biggest and wealthiest boarding school for needy children of both sexes and all races.

Colistra said Hershey will no longer refuse admission to any qualified student who has HIV, and is issuing an equal opportunity policy to that effect. It is also developing training for staff and students on HIV issues, he said.

The president denied that the school did anything wrong by turning down the boy, noting that the "application of federal law to our unique residential setting was a novel and difficult issue."

The U.S. Department of Justice did not see it that way and advised the school that it "disagrees with how we evaluated the risks and applied the law," Colistra said.

"Our mission is to help children in need. It's who we are as members of the Milton Hershey School community. And it's what we have been doing for more than 100 years," said Colistra, a graduate of the school.

The school has been beset by a string of sexual scandals, including the sentencing last October of William Charney Jr., a married father of two who was responsible for residential life at the school and was a former house parent, for possessing almost 700 images and 40 videos of child pornography.

In 2010 the school settled the claims of five former students who said they had been sexually abused by a serial molester who gained access to the campus through his mother, a part-time house parent. And in 2007 and 2006, two teachers, one male and one female, were prosecuted in separate cases for having sexual relations with students.
A 2011 federal lawsuit described student sexual activity during a school-sponsored vacation to an amusement park in 2004. The then-vice president for residential life was said to have joked about the situation during a school social event.

**Safe sex? Indonesia’s conservatives would rather ‘sinners’ and sex-workers got Aids**

Katherine Butler reports from Jakarta, where religious intolerance is undermining the fight against Asia’s fastest-growing HIV epidemic

Katherine Butler
Tuesday, 7 August 2012

Her name may or may not be Rizki. In any case, it’s what the 29 year old with long sleek black hair calls herself for work. In her T shirt with a cartoon character on the front, cropped jeans and sensible sandals she looks as if she could be on her way to a job in one of the factories in Bekasi, an industrial sprawl east of Jakarta that’s home to big international manufacturing giants like Converse and Samsung.

But Rizki works in a bar in a Bekasi shantytown called Tenda Biru, where every night from 6pm to 3am, she dances with the long distance truck drivers and factory workers who come here to drink and relax after their shifts. If they want sex, she sells that to them too.

“It’s a long story. But I don’t want to go into it”. Rizki says about why she left her village in West Java four years ago to work in a sex and karaoke strip off the main highway to Jakarta. Entering prostitution after a failed teenage marriage is a common story for poor young women in Indonesia.

She “enjoys” her work here, she says, although it would be hard to imagine anyone choosing a job in this labyrinth of narrow, muddy, dimly-lit lanes packed with shacks offering bottled Bali Hai beer, dancing and young women if they didn’t have to. On a hot and humid Tuesday night recently the lanes were thronged with drinkers by 11pm and every bar was pumping out a different pop song, generating a deafening cacophony. A child of about eight, wearing a hijab to cover her modesty, darting in and out of the bars, made the most incongruous sight.

From her two to three customers a night, up to five on weekends, Rizki earns enough, around $50 a week, to pay off a “Mammy” or pimp. Both Rizki and her friend Melli, 25, say they protect themselves against Aids. “If he won’t use a condom I can walk away”, says Melli.

But both women are single mothers, so turning down customers isn’t a light choice. Little wonder that some 25 of the 250 of the women who work here are HIV positive.

Indonesia’s Aids epidemic is among the fastest-growing in Asia. From small pockets at the turn of the century it has spread to all parts of the country. At just under 0.2 percent the infection rate is still low compared to parts of Africa. But new infections have tripled in the last six years, and alarmingly, risky sexual behaviour has taken over from intravenous drug use as the main route for its spread. In the words of the plain-speaking new health minister Dr Nafsiah Mboi, the epidemic is driven by “the four Ms: macho men with money and mobility”.

In Tenda Biru, free condoms are available from a shack operated by an NGO which receives funding from the Global Fund to combat Aids, TB and Malaria. The charity also provides three-monthly HIV testing via a mobile clinic. But culturally, condoms are a problem. Men won’t use them and women are typically too powerless to demand that they do. Three quarters of HIV infections in Indonesia come from unprotected sex. According to one estimate, 19 million Indonesians could be at risk of contracting the disease because of unsafe sexual conduct.

If ignorance or reckless sexual behaviour weren’t problematic enough, the country is now also in the grip of a moral battle over condoms led by Islamic pressure groups arguing that they encourage promiscuity. Their stance mirrors the Catholic church’s preaching against condom use among the faithful in Aids-ravaged parts of Africa, complete with arguments over whether the virus is too small to be stopped by the pores in the latex.

Dr Mboi, former head of the National Aids Commission was plunged into a firestorm on joining government in June, after launching a campaign to promote safe sex among 15 to 24 year olds. The former paediatrician was denounced as “obscene” by the Islamic Defenders Front or FPI—the group that led protests forcing Lady Gaga to cancel her Jakarta concerts in the spring—and excoriated in a Twitter campaign.

The 70 year old released a YouTube video denying that she ever intended to distribute free condoms to high schools, but warning that unprotected sex was affecting people of all ages, including children. She was summoned to parliament to explain herself where she faced a protest organised by the radical Islamist movement Hizbut Tahrir, accusing her of peddling “free sex”.

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Tuti Alawiyah, a former Women’s minister, reacted to the health minister’s initiative by telling the Jakarta Post that condoms would just encourage pre-marital sex. “Keep the disease away with preventative action by improving the nation’s morality. There are positive ways to prevent HIV transmission, ways that do not follow the Western style”.

There is nothing “Western style” about the commercial sex on offer in Bekasi. The clients are all Indonesians and despite the conservatives’ preoccupation with “crimes against decency” which is sometimes interpreted to include prostitution, a similar sex trade is booming (and widely tolerated) all over Indonesia. “There isn’t a bus terminal in the country that doesn’t have prostitutes”, one official told me.

Aldo Saragi, who runs an advocacy group campaigning for the rights of sex workers blames hypocrisy among conservative law makers for driving the sex industry underground making it more difficult to educate people about safe sex and treatment. Nationally, only around 30% of sex workers are believed to be using condoms and only 10% of men who visit prostitutes use them.

“The religious groups try to use HIV as an excuse to criminalise prostitution. But prostitution will go on because there is so much demand for it. The problem when they break up regulated prostitution zones is that then we can’t check every hotel or carpark, so it becomes even more dangerous for the spread of HIV/AIDS”.

The poverty that drives single mothers like Rizki and Melli to the sex trade is the neglected underbelly of Asia’s biggest recent economic success story. In ten years Indonesia has gone from tanks on the streets, bankruptcy and total economic collapse, to democratic rule and an annual growth rate averaging 6% even as the rest of the industrialised world is mired in recession.

The optimism of new money is on show in downtown areas of Jakarta, with its shiny megamalls and high rise business hotels filled with international investors from the Asia-Pacific region. No wonder Barack Obama didn’t recognise much when he returned here for the first time since the years of his childhood spent in the city.

But the rise in religious intolerance, illustrated by the Lady Gaga episode, is becoming a potential threat to investors’ confidence in a moderate strain of Islam that sits easily with the rule of law. In recent months Christian churches and some Muslim minorities have been targeted by sectarian violence, women in some cities have been ordered by local authorities to cover up, and last month there was outcry after an atheist civil servant was jailed for posting the slogan “God does not exist” on Facebook. At the same time, the government is fostering a new atmosphere of economic nationalism, making life tougher for foreign-owned businesses.

While mainstream Muslim groups are fully involved with the Government’s anti-Aids campaign, the disease is increasingly a battleground for hardliners because it requires official acknowledgement of the extent of prostitution and sexual promiscuity. “HIV/AIDS is a disease of sinners as far as the conservatives are concerned so why spend public money on them is the attitude”, Dr Mboi says.

Vast sums of money from international donors have poured into Indonesia’s anti-Aids campaign; nearly $500m from the Geneva-based Global Fund to combat Aids, TB and Malaria alone, since 2002. This has subsidised free life-saving Anti-Retroviral drugs which would otherwise cost about $80 a month, unaffordable to Indonesians surviving on or under the average monthly income of $200.

But this effort is thwarted by having to constantly play down Aids prevention to avoid antagonising religious extremists. “We have to package our broadcasts about condoms on community radio so that they are not too vulgar or explicit” says Tri Irwanda Maulana, spokesman for the West Java division of the National Aids Commission. Despite that, he laments: “We are still struggling with condom use. The religious leaders refuse to allow it. Even though the provincial vice-governor publicly supported condoms in the campaign against Aids”.

In West Java, which has a population of 43million, the incidence of sexually transmitted HIV is higher than anywhere else in Indonesia.

Asep Gufron a local authority official in an area of Bandung, West Java’s capital, where impressive work is being done by Muslim voluntary groups to lower the stigma around TB (TB and HIV usually go hand in hand) denies that there is a problem advocating the use of condoms – for married people. “It is not a taboo, we use condoms for family planning purposes but tackling Aids needs to be about safe behaviour and that means abstinence and delaying the first sexual intercourse for young people”.

The devastating flaw in this message becomes obvious during a visit to the Hasan Sadikin hospital in Bandung. Doctors at the hospital’s HIV clinic explain that married women are increasingly testing positive at a rate that is rising more quickly than for sex workers.
“Housewives are being infected by their partners. It used to be drug users, but after 2009 heterosexual infection rates soared” says Dr Nirmala Kesumah the head of the clinic.

The Global Fund pays for caesarean sections for pregnant HIV positive women to minimise the risk of transmission from mother to child. But they still have more than 100 babies and children registered at the clinic, aged 1 to 14. “We have no experience of how to disclose to a child that they are HIV positive” says Dr Rudi Wisaksana. It is an enormous burden, they want to know why they have it, and they find it hard to accept that they have to be on medication for the rest of their lives”.

Even without religious tensions, Aids would be a massive challenge for Indonesia. Its population of 230 million people is geographically spread over 17000 islands and there are hundreds of different cultures and languages. It takes eight hours to fly from Aceh at one tip of the country to West Papua at the other. This doesn’t hinder the mobility of the citizens: at the domestic terminal at Jakarta’s Soekarno-Hatta airport, low budget flights to all parts of the archipelago take off and land every few minutes. But the dispersal makes risky behaviour easier, and poses a massive challenge to a coherent implementation of a national anti-Aids strategy.

Local laws often run counter to national policy, in particular when dealing with prostitutes and other high-risk groups. When democracy arrived in Indonesia after the overthrow of the dictator Suharto in 1998, the 33 provinces gained more control over their affairs, and some are more conservative than others. In semi-autonomous Aceh, sharia law is in force and sex outside of marriage is criminalised. Adultery is an offence punishable by stoning and homosexuality (although legal in Indonesia) by public floggings and steep prison sentences. Women are regularly stopped for such transgressions as wearing tights and shorts.

“Decentralisation is one of the biggest problems” says Aldo Saragi of the sex workers’ collective. “Aceh is the only part of Indonesia that has sharia law, but others are following their lead”.

For the government in Jakarta to either keep up with what’s going on in far-flung areas, or to challenge by laws that are unconstitutional, seems to be a political high wire act it’s unwilling to take on. The President, Susilo Bambang Yudhoyono, has been criticised for pandering to hardliners for political gain.

Sex worker Aldo Saragi argues that foreign donors bankrolling Indonesia’s Aids programme could do more to safeguard the rights of minorities like gays, lesbians and the transgender community. “Look, if Lady Gaga was rejected by the religious leaders, they have the power. So there is no choice but to work with them. But right now, we in the civil society groups are almost being driven underground, we are scared of these religious groups”.

Meanwhile, austerity in donor countries is raising the spectre of the flow of money to foreign aid programmes, including for HIV/AIDS, being scaled down. The Global Fund subsidisation of Aids drug treatment has been transformative in helping to reduce the stigma of Aids Dr Mboi says. “We have been able to say to people, look if you test positive, then you will get free treatment, and that has been hugely important”.

Although she insists that Indonesia is a “lower middle” income country, not a “middle income” one, she believes it will maintain public spending on Aids prevention and treatment even if foreign cash runs dry. “Our dignity as a nation means we should provide the funding when the Global Fund is gone”. But she admits that if Aids programmes revert to a decentralised control, the impact would be unpredictable, even disastrous, in certain areas. “Who knows what would happen to the epidemic?”

Meanwhile, under an illustrated poster showing couples how to avoid HIV infection, Dhafik Rizki, 26, in skinny jeans, and a hoodie waits in a queue to see doctors at the HIV clinic in Bandung. His sleeping toddler, Merrijane is stretched out in his arms. Dhafik’s wife died last year of Aids. Merrijane, 2, inherited HIV from her mother. “I didn’t know anything about this disease until she became ill” Dhafik says. “The government is telling us every day on the radio and TV about Aids, but people don’t listen”. How will he tell his daughter that she has the disease? “If we continue to get the right medication, then it’s ok, we will cope”.

Uganda and Malawi Offer Opposite Lessons for AIDS

Washington Post, (08.06.2012) Anne Gearan

HIV prevention and treatment efforts in small, poor Malawi offer a model for other African nations and a contrast to the cautionary tale of Uganda, a large and relatively prosperous county struggling with an alarming rise in infections.
During her eight-nation tour of Africa, Secretary of State Hillary Rodham Clinton visited both Uganda and Malawi. Speaking at an HIV/AIDS clinic in the Ugandan capital of Kampala, she said, “I am here because I am worried. Uganda is now the only country in sub-Saharan Africa where the rate is going up instead of down,” referring to the country’s doubling of HIV cases between 2004 and 2011.

Uganda has been widely praised for its AIDS-fighting efforts, which focused on prevention and treatment. More than $1.6 billion in US assistance during the past six years has helped even very poor Ugandans access antiretroviral drugs and live normal lives. But the unintended consequences have resulted in a reduced perception of risk and made a positive diagnosis a route to access badly needed general medical care, say AIDS advocates.

Another explanation is a more socially and religiously conservative approach taken by President Yoweri Museveni’s government. A proposed bill further criminalizing homosexuality would stall HIV prevention efforts by driving risky gay sex underground, advocates say.

In Malawi, where the per capita income is around $900, US officials estimate one in 10 people have HIV/AIDS. However, the rate has dropped from 13 percent over five years. Innovative prevention and treatment programs are found throughout the country and have the support of President Joyce Banda. Malawi has cut mother-to-child HIV transmission; condom use is widely accepted; and a male circumcision program, once thought to be incompatible with traditional culture, is currently overwhelmed by requests.

**Prevention: Less Sleep May Affect Response to Vaccine**

*New York Times*, (08.07.2012) Nicholas Bakalar

People who sleep less may be less likely to benefit from a vaccine, new research suggests.

In the observational study, 125 healthy adults underwent vaccination against hepatitis B virus: two doses one month apart, followed six months later by a booster. During the seven-day period surrounding each injection, participants wore devices to monitor their sleep and kept sleep diaries. After the second and third shots, scientists measured the levels of HBV antibodies in the subjects’ blood.

After adjusting for other factors that affect antibody response, the team found that sleep duration, as measured by the monitoring devices, predicted the blood level of HBV antibodies following the second injection. Sleep duration also predicted the likelihood of sufficient HBV antibody levels for clinical protection after the booster.

The effect was modest, said lead author Aric A. Prather, a University of California-San Francisco clinical health psychologist. “The vaccine works for almost everyone, irrespective of their sleep, and there’s no evidence that changing your sleep pattern improves vaccination response,” he said. “What was most surprising to us was that shorter sleep duration predicted a person’s likelihood of being protected six months later.”

PNU editor’s note: The authors wrote in their conclusion, “Short sleep duration in the natural environment may negatively affect in vivo antibody responses to novel antigens, providing a possible explanation for observed associations of poor sleep with increased susceptibility to infectious disease.”


**Drug Companies Developing Novel Treatments For MDR-TB**

With incentives to find new antibiotics signed into U.S. law last month, "multiple players are vying for the lead in the [multi-drug resistant tuberculosis (MDR-TB)] drug development niche," *Nature Medicine* reports. "The fifth reauthorization of the U.S. Prescription Drug User Fee Act (PDUFA), signed into law on 9 July, includes a subsection called the Generating Antibiotic Incentives Now (GAIN) Act that aims to spur development of antibiotics for drug-resistant bacteria, including MDR-TB," the news service writes, noting, "Drug makers that ask for approval of medicines to treat these pathogens will receive priority review, as well as five additional years of market exclusivity and fast-track status." Currently, MDR-TB treatment "involves a bevvy of regular tuberculosis medicines that, in many cases, must be administered for as long as two years or more ... [and] don't always work," *Nature Medicine* states, adding, "The hope is that new medicines will shorten treatment times and improve cure rates." The article discusses several medicines that are in different phases of research (Willyard, 8/6).
White Blood Cells Mediate Insulin Resistance: Neutrophils’ Role Is a Surprise and a Potential New Target for Treating Diabetes

ScienceDaily (Aug. 5, 2012) — Researchers at the University of California, San Diego School of Medicine say neutrophils, an abundant type of white blood cell typically tasked with attacking bacteria and other foreign invaders, also plays an unexpected role in mediating insulin resistance—the central characteristic of type 2 diabetes, which afflicts an estimated 26 million Americans.

The findings are published in the August 5, 2012 Advance Online Publication of Nature Medicine.

Neutrophils are the first immune cells to respond to tissue inflammation, and can promote chronic inflammation by summoning other white blood cells called macrophages. Chronic low-grade inflammation—common in adipose or fat tissue—is an important cause of systemic insulin resistance.

Using liver and fat cells from mice and humans and live mouse models, a team led by Jerrold M. Olefsky, MD, associate dean for scientific affairs at UC San Diego Health Sciences and professor of medicine, discovered that an enzyme secreted by neutrophils called neutrophil elastase (NE) impairs insulin signaling and boosts resistance. Conversely, deletion of NE in obese mice fed a high-fat diet improved insulin sensitivity.

"These results are largely unexpected," said Da Young Oh, an assistant project scientist in Olefsky’s lab and study co-author. "Although several immune cells have been established in the etiology of insulin resistance, the role of neutrophils in this process has remained unclear until now."

Oh said neutrophils were considered to be "transient infiltrates," temporary cells (average lifespan: 5 days) that were incapable of sustaining chronic, low-grade inflammation. "Our studies now suggest neutrophils possess powerful immune modulatory effects," Oh said.

Specifically, neutrophils use NE to activate a signaling pathway which triggers pathogen-eating macrophages to secrete proinflammatory molecules called cytokines. NE degrades IRS1, a key protein in the insulin signaling pathway in both liver and fat cells. Although NE has been shown to degrade this protein in lung cancer cells, the scientists said, the effect on insulin target tissues such as liver and adipose is striking.

The insulin-mediating role of neutrophils makes them a new target for developing treatments of insulin resistance in particular and diabetes in general. "Given that NE mediates insulin resistance, one could, in theory, take an NE activity inhibitory approach to reverse or improve insulin resistance," Oh said, noting that NE inhibitors are already used for treatment of emphysema in Japan and are being tested in the United States, both for emphysema and type 1 diabetes.

Journal Reference:
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Small Protease Sensitive Oligomers of PrPSc in Distinct Human Prions Determine Conversion Rate of PrPSc

Chae Kim1,2, Tracy Haldiman1,2, Krystyna Surewicz2, Yvonne Cohen1,2, Wei Chen1,2, Janis Blevins1,2, Man-Sun Sy4, Mark Cohen1,2, Qingzhong Kong1,2, Glenn C. Telling4, Witold K. Surewicz2, Jiri G. Safari2.

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The mammalian prions replicate by converting cellular prion protein (PrPc) into pathogenic conformational isoform (PrPsC). Variations in prions, which cause different disease phenotypes, are referred to as strains. The mechanism of high-fidelity replication of prion strains in the absence of nucleic acid remains unsolved. We investigated the impact of different conformational characteristics of PrPsC on conversion of PrPc in vitro using PrPsC seeds from the most frequent human prion disease worldwide, the Creutzfeldt-Jakob disease (sCJD). The conversion potency of a broad spectrum of distinct sCJD prions was governed by the level, conformation, and stability of small oligomers of the protease-sensitive (s) PrPsC. The smallest most potent prions present in sCJD brains were composed only of~20 monomers of PrPsC. The tight correlation between conversion potency of small oligomers of human sPrPsC observed in vitro and duration of the disease suggests that sPrPsC conformers are an important determinant of prion strain characteristics that control the progression rate of the disease.

Author Summary Top

Mammalian prion diseases were originally characterized by accumulation of protease-resistant prion protein (PrPsC), often forming large amyloid deposits and fibrils. However, the apparent absence of protease-resistant PrPsC or amyloid fibrils in growing number of prion diseases raised several fundamental questions; specifically, whether presumably protease-sensitive forms of PrPsC exist as
distinct conformers; and whether they comprise the initial steps in prion replication or are related to the alternative misfolding pathway generating noninfectious aggregates. We investigated the conformational characteristics of protease sensitive conformers of PrP\textsuperscript{Sc} and their role in the pathogenesis of sporadic Creutzfeldt-Jakob disease (sCJD). Using two different in vitro prion protein (PrP\textsuperscript{C}) conversion techniques in tandem with biophysical methods, we identified small oligomers of protease sensitive PrP\textsuperscript{Sc} present in sCJD brains as the most potent initiators of PrP\textsuperscript{C} conversion. Their concentration and conformational stability determine the distinctly different replication potency of PrP\textsuperscript{Sc} in individual isolates of sCJD and each of these characteristics correlates tightly with duration of the disease. These features argue for a broad range of distinct prion strains causing the sCJD and imply that small oligomers of protease sensitive conformers of pathogenic prion protein are encoding incubation time and progression rate of the disease.

**US youth, heterosexual men and African Americans losing out on HIV treatment benefits**

Gus Cairns, Roger Pebody
Published: 08 August 2012

A new study presented at the 19th International AIDS Conference shows that young people, African Americans, and heterosexual men have particularly low rates of retention in care and viral suppression and that there are also inequalities between cities.

A previous study published in November last year had caused concern by revealing that only about half the HIV-positive population of the US was in consistent care and that only 28% had an undetectable viral load.

The US has high rates of HIV testing, but this attrition of treatment, known as the “treatment cascade”, threatens the viability of using widespread antiretroviral therapy as one of the best ways to limit the spread of HIV, as discussed at the IAPAC Controlling the HIV epidemic with antiretrovirals summit in June.

**Treatment rates even worse than thought**

Irene Hall of the Centers for Disease Control said that the new estimates show that an even lower percentage of people are on treatment and virally suppressed – just a quarter (25%).

The calculations show that an estimated 1.15 million people are living with HIV in the US, of which about 205,000 (18%) remain undiagnosed, and nearly half of whom (45%) are African American, despite their forming only one in eight (12%) of the US population. Just over half (52%) are gay men/men who have sex with men.

Despite their higher prevalence, African Americans are less likely to be virally suppressed (21%), especially concerned with white people (30%). This is due to somewhat lower testing rates and lower rates of linkage to care. It they do see an HIV doctor after diagnosis, black Americans are just as likely to stay in care as white Americans.

Even lower rates of viral suppression were seen in heterosexual men (19% virally suppressed) and especially in younger people: only 15% of people aged 25-34 HIV were on treatment with an undetectable viral load compared with 36% of 55-64-year-olds, though this could be partly due to their being infected more recently and so fewer of them needing to be on ARVs; 24% of people aged 25-34 who were in care were not taking ARVs, compared with 13% of 55-64-year-olds.

**Big variations between cities**

Another study showed very different results across the continuum of care between four large cities with established HIV epidemics, highlighting the crucial role that state policies on health insurance, the leadership of public health departments and high quality local services can play.

Nanette Benbow found that on four different measures, Chicago and Philadelphia performed relatively poorly, whereas Los Angeles and San Francisco did somewhat better.

For example, in Chicago, just 30% of people previously diagnosed with HIV accessed care in 2009, whereas 57% of those in San Francisco did so. In Chicago, 21% of people with HIV had a suppressed viral load, while 44% of those in San Francisco were undetectable.

There were poorer outcomes for black people, women and the under-30s in some of the cities, but these differences were much less pronounced in San Francisco. In recent years, the city has aggressively promoted HIV testing and early treatment, and put considerable resources into to help patients stay in care and adhere to medication. Outreach teams follow up people who do not show up for appointments.
and work in co-operation with drug, mental health and housing services to address underlying problems; the outreach work is targeted to neighbourhoods with the greatest needs.

Limitations
A complex methodology was used to calculate the figures in the case of the CDC study, and Hall told the conference that they might underestimate the proportion of people in care by a few per cent.

Determining HIV prevalence and the proportion undiagnosed is not necessarily an easy thing to do, especially in a federal country like the US with different reporting requirements in different states. Prevalence and linkage to care figures were derived from the country’s National HIV Surveillance System, which gathers name-linked data on HIV cases from 46 states and AIDS data from the others. This system also documents which people have seen an HIV physician for assessment at least once post-diagnosis, which is the definition of linkage to care.

These figures have to be adjusted for delays in reporting new diagnoses and deaths (which mean recent years have to be ‘topped up’) and incomplete reporting of diagnosed cases; one of the most important facts that often goes missing is the route of HIV transmission.

The most uncertain figure is the one for the proportion of people who remain undiagnosed. The way the CDC calculate this is to estimate the average severity of disease at HIV diagnosis, for instance, by taking the proportion of people who have AIDS-defining illness at the time of HIV diagnosis. From this they make a rough back-calculation of the average number of years people have been living with HIV before diagnosis, and from that the number of people living with HIV who remain untested. This is then added to the diagnosed prevalence.

A rough estimate of HIV prevalence is then calculated by taking the cumulative number of reported HIV infections and subtracting from it the reported number of deaths.

‘Linkage to care’ is the proportion of people with at least one CD4 and viral load test result within three months of diagnosis.

‘Retention in care’ and the proportion of people on therapy and virally suppressed was taken from a sample of medical records, from 17 states and the District of Columbia, designed to be representative of the HIV population of the US. Retention in Care was defined as the proportion of adults with HIV who received at least one medical care visit between January and April 2009.

It was commented on at the conference that some people on stable ARV therapy might visit only every six months or so, and people with high CD4 counts who were off therapy even less often.

Hall admitted that this definition of retention in care might underestimate the proportion of people who were regularly attending medical appointments. Certainly, retention in care was the point at which the number of patients remaining in the ‘cascades’ fell of drastically; in many groups of people, only half of those initially linked to care stayed in care.

References

Comparative Effectiveness of Two Self-Collected Sample Kit Distribution Systems for Chlamydia Screening on a University Campus

Sexually Transmitted Infections Vol. 88; No. 5: P. 363-367, (08..2012) Wiley D. Jenkins; and others

Rates and incidence of Chlamydia trachomatis continue to increase, though studies of CT prevalence among university students, known to engage in high-risk activities, are limited by poor screening rates. Utilization of self-obtained sample (SoS) kits in private student residencies may reduce barriers to screening.

In the current study, the researchers sought to determine the relative effectiveness and comparative effectiveness of two SoS kit distribution mechanisms: one, in which kits were directly provided to students, and another, that encouraged students to order kits online.

During 2010-11, 391 residents of six university dormitories received training describing CT, the project and SoS kit use. A total of 163 students in three dorms were provided the kits, and 175 others were directed to a website (http://www.iwantthekit.org).

Of provided kits, 12 (8 females) were returned and 2 (16.7 percent; both females) were positive. Of just three website-requested kits, all were returned (all females) and none were positive. A post-project survey examining non-participation found 26.2 percent of students were unaware of the project (no
difference by gender or dormitory) and 58.5 percent of females cited prior CT screening as part of a medical exam.

“Though direct kit distribution was more effective in student screening engagement, overall participation was poor despite widespread advertising. The methodology of online testing and SoS kits has been well-validated elsewhere, but research is needed to successfully engage university students in screening and refine SoS target populations in light of changing health care policies,” the researchers concluded.

**Mylan Subsidiary Starts Operations in India**

Associated Press, (08.06.2012)

Pennsylvania-based Mylan Inc. said a subsidiary has launched commercial operations in India, beginning with HIV/AIDS drugs. After initially offering 18 antiretrovirals, Mylan Pharmaceuticals Private Ltd. plans to add therapeutic categories and enlarge its sales force. Mylan already is active in the nation, having acquired a majority stake in Matrix Laboratories of India in 2007 and bought the remainder of the company in 2009. India is home to the world’s third-largest population of HIV/AIDS patients, according to the National AIDS Control Organization.

**Scientists describe antibodies that protect against large variety of flu viruses**

LA JOLLA, CA – August 9, 2012 – A team led by scientists at The Scripps Research Institute and Crucell Vaccine Institute in the Netherlands describes three human antibodies that provide broad protection against Influenza B virus strains. The same team had previously reported finding broadly neutralizing antibodies against Influenza A strains. The isolation of the new broadly neutralizing antibodies, which was reported the journal *Science*’s advance online edition, *Science* Express, on August 9, paves the way for researchers to develop a universal antibody-based flu therapy for use in severe infections or to protect hospital staff during an outbreak. Importantly, these antibodies may provide key clues to the design of an active universal flu vaccine—designed to protect long-term against flu viruses, not just against the current season’s strains. "To develop a truly universal flu vaccine or therapy, one needs to be able to provide protection against influenza A and influenza B viruses, and with this report we now have broadly neutralizing antibodies against both," said Ian A. Wilson, the Hansen Professor of Structural Biology at Scripps Research, who was senior investigator for the new study with Crucell’s Jaap Goudsmit and Robert Friesen.

One of the newly discovered antibodies will be of special interest to flu researchers, because it appears to protect against essentially all influenza B and influenza A strains. "It’s the only one in the world that we know of that has been found to do this,” said Wilson.

**Looking for the Missing Pieces**

Influenza B viruses are considered less dangerous than Influenza A viruses, and have been less intensively studied because they have less capacity to mutate into deadly pandemic strains. However, influenza B viruses account for a significant part of the annual flu illness burden in humans.

To find broadly protective antibodies against Influenza B, the team at Crucell generated a large collection of flu antibodies from the immune cells of volunteers who had been given a seasonal flu vaccine.
The researchers then screened this collection for antibodies that could bind to a wide variety of influenza B strains.

Three of the antibodies they found in this manner—CR8033, CR8071, and CR9114—protected mice against normally lethal doses of the two major influenza B strains. CR9114 also protected mice against influenza A viruses, including the H1N1 subtype that killed about 17,000 people in a 2009 pandemic. The fact that these antibodies protected against a variety of flu strains suggested they mark functionally important sites, or "epitopes," on the virus that are relatively unchanging (conserved) from one flu strain to the next.

Wilson's team at Scripps Research characterized the newly discovered antibodies' binding sites on influenza viruses using electron microscopy and X-ray crystallography techniques. They found that CR8033 binds to a highly conserved epitope—a functionally important site—on the "head" of the hemagglutinin protein, a structure that studs the outer coat of flu viruses and allows the viruses to stick to vulnerable cells. CR8071 binds to the base of the hemagglutinin head. Most antibodies that bind to the hemagglutinin head and neutralize influenza do so by blocking the virus's attachment to host cells.

"The unique thing about these two antibodies is that they neutralize flu viruses chiefly by preventing virus particles from exiting infected cells," said Nick Laursen, a research associate in Wilson's laboratory who was a lead author of the study.

**A Weak Point on the Virus**

Antibody CR9114 turned out to bind to a site on the hemagglutinin stem. "It prevents the hemagglutinin protein from undergoing the shape-change needed for the virus to fuse to the outer membrane of a host cell," said Cyrille Dreyfus, a Wilson lab research associate who also was a lead author of the study. "This appears to be a real weak point of the virus, because this epitope is highly conserved among influenza A subtypes as well as influenza B."

Wilson notes that in a study published in 2009 his laboratory determined the structure of another Crucell antibody that broadly neutralizes influenza A viruses by binding to essentially the same site on the hemagglutinin stem—but in a subtly different way, so that it fails to get a grip on influenza B viruses, too. "With some tweaking of that antibody's binding domains, we might have been able to get a broader effect like CR9114's," Wilson said.

The viral epitope to which CR9114 binds will now be studied extensively by researchers as a target for vaccines and therapies, because it is the only one found so far that is broadly vulnerable to neutralization on both influenza A and B viruses.

Remarkably, CR9114 performed poorly against influenza B viruses in initial lab-dish tests known as microneutralization assays, which test the ability of an antibody to protect cells from viral infection. Yet CR9114 was clearly effective under more realistic conditions in mice, even at low doses. Because it attacks the stem rather than the head of flu virus hemagglutinins, CR9114 also failed to show effects in a widely used test known as the hemagglutinin-inhibition assay.

"As we move towards design of a universal flu vaccine, we need to find more inclusive assays to screen for antibodies such as CR9114, which may be highly effective but have novel mechanisms for neutralization that cannot be detected by the current methods used in influenza vaccine development," Goudsmit said.
Potential drug molecule shows enhanced anti-HIV activity
Small change locks molecule into shape, yields major effect

Researchers from Munich and Naples have shown that minimal modification of a synthetic peptide with anti-HIV activity results in a new compound with more than two orders of magnitude higher binding affinity to the chemokine receptor CXCR4 and greatly improved anti-HIV activity. This could be a step toward the design of new, more effective drugs against AIDS, inflammatory diseases, and some forms of cancer.

Different strains of HIV-1 use either the chemokine receptor CCR5 or CXCR4 for entry into immune cells. While drugs that block usage of CCR5 by the virus are already available for anti-HIV therapy, no drugs have been approved that prevent the virus from using the CXCR4 receptor. Because the new cyclic peptide may be used to block CXCR4, it is a promising new drug candidate to block HIV-1 infections.

An international, interdisciplinary team including researchers in pharmaceutical radiochemistry and chemistry at the Technische Universität München (TUM), a group of molecular modelers at the University of Naples, and virologists at the Helmholtz Zentrum München reported the results in *Angewandte Chemie International Edition*. This work was initiated by the radiochemists and organic chemists at TUM, who realized that their approach to modifying peptides as high-affinity CXCR4 ligands for imaging of cancers also has the potential to open a whole new area of drug research.

The researchers used a smart trick to augment both the binding affinity and the anti-HIV activity of an already known lead structure: They shifted one of the important side chains from the carbon to a neighboring nitrogen, thus fixing the skeleton of the molecule to present its binding groups in an improved orientation.

The cyclic structure of the peptide, with one unnatural D-amino acid (the mirror image of the natural amino acid tyrosine) and one so-called "peptoid" structure, makes the compound stable against enzymatic degradation and thus suitable for in vivo applications. Since CXCR4 receptors also play an important role in cancer metastasis, derivatives of this compound are also being tested as new agents for imaging and treatment of cancer. The team's "frozen peptoid" displays a 400 to 1500 times higher binding affinity to the CXCR4 ligand compared to other CXCR4-targeting compounds currently under clinical development, including one already involved in the treatment of non-Hodgkin lymphoma and multiple myeloma.

"We are very happy that the specific modifications designed by our team have led to a drug compound that may be useful for treatment of multiple life-threatening diseases," says Prof. Horst Kessler, a senior fellow of the TUM Institute for Advanced Study and "emeritus of excellence" in the TUM Department of Chemistry. "For anti-HIV therapy," adds Prof. Ruth Brack-Werner, a virologist from the Helmholtz Zentrum, "the new compound may provide a drug against particularly aggressive HIV-1 strains that come up in HIV-infected individuals after many years of infection." "We look forward with great enthusiasm to the next preclinical and clinical tests," says Prof. Hans-Jürgen Wester, TUM Chair of Pharmaceutical Radiochemistry. "These compounds offer exciting possibilities."

New Non-Toxic Disinfectant Could Tackle Hospital Infections

ScienceDaily (Aug. 6, 2012) — A new disinfectant, Akwaton, that works at extremely low concentrations could be used in healthcare settings to help control persistent hospital-acquired infections such as *Clostridium difficile*. The study is reported online in the *Journal of Medical Microbiology*.

Researchers from the Université de Saint-Boniface in Winnipeg, Canada tested the new compound, Akwaton, against bacterial spores that attach to surfaces and are difficult to destroy. Previous work by the group has shown Akwaton is also effective at low concentrations against strains of Meticillin-resistant *Staphylococcus aureus* and *Escherichia coli*. 
Spore-forming bacteria include *C. difficile*—a common bacterium found in healthcare settings whose spores can survive on surfaces for long periods of time. Spores are heat-tolerant and can survive a number of years in a dehydrated state before they are reactivated. Most chemical disinfectants control or prevent spore growth rather than irreversibly destroying them.

The present study showed that Akwaton was able to destroy *Bacillus subtilis* bacterial spores, suspended in water and attached to stainless steel or glass surfaces, at concentrations well below 1% after just 90 seconds' treatment. It was equally as effective at more dilute concentrations (below 0.1%) if left to act for longer periods.

Lead researcher Dr Mathias Oulé, explained the advantages over other chemical compounds currently used against bacterial spores. "Most disinfectants have to be applied at much higher concentrations—typically between 4-10%—to properly get rid of bacterial spores. Unfortunately such high levels of these compounds may also be harmful to humans and other animals. Akwaton is non-corrosive, non-irritating, odourless and is effective at very low concentrations," he said.

"Bacterial spores demonstrate a remarkable resistance to physical and chemical agents as well as ordinary antiseptics. On top of this micro-organisms are becoming increasingly resistant to disinfectants as well as antibiotics. Our latest study shows Akwaton is effective at destroying these spores as well as bacteria that are known problems in healthcare environments”

Akwaton is fast-acting and non-toxic for humans at low concentrations. Other studies have shown that the compound is also environmentally safe. "All these properties make it an ideal disinfectant for hospitals and laboratories. It may also have great value in the food industry to tackle spore-forming food pathogens such as *Bacillus cereus* and *Clostridium perfringens*,” explained Dr Oulé.

**Journal Reference:**

**'Green Biased' Yellow Fever Swept Through Irish Immigrants in 19th Century US**

ScienceDaily (Aug. 6, 2012) — New research by University of Warwick historian Dr Tim Lockley has found why yellow fever had a green bias in 19th century fever outbreaks in the southern states of the US. Almost half of the 650 people killed by yellow fever in Savannah Georgia in 1854 were Irish immigrants.

Dr Tim Lockley's study is based on four sources: the burial records of Laurel Grove cemetery; the records of the city's Catholic cemetery; the minutes of Savannah's Board of Health; and published lists of the dead in the Savannah Morning News. These sources yielded the names of 650 people who died of yellow fever between early August and the end of November 1854, of which 293 were Irish immigrants (and 10 others were of unknown nationality).

Savannah was not the only southern US city to witness this Irish susceptibility to yellow fever. In nineteenth-century New Orleans annual yellow fever outbreaks killed many Irish and German immigrants. This encouraged a view of yellow fever as less serious than other illnesses such as typhoid, and for some locals it was a welcome guarantee against being overrun by "foreigners."

Others were simply dismissive about the appearance of yellow fever as long as it was only affecting the Irish. Savannah doctor Phineas Kollock said at the time: 
'
..the extremely hot weather . . . has at length developed yellow fever among our Irish population. The disease is mostly confined to the Eastern part of the city. I do not feel apprehensive of its extending its ravages very much, although it is probable that we shall have cases occurring until frost."

However a week later his view had changed. The fever had become particularly "malignant" and he then wrote that "I have determined therefore to send my family to Habersham [County] immediately."

Yellow fever is a tropical disease, endemic in West Africa, the Caribbean and parts of Latin America. It is a virus that cannot be transmitted via normal human-to-human interaction but requires a vector, in this instance a mosquito. In the Americas this is the female *Aedes aegypti* mosquito. Once there are no more susceptible humans or no mosquitoes, then the disease cycle is broken and the epidemic ends. In Savannah the mosquitoes would have been killed by the first frosts that were reported on 13 November 1854, but even before then mortality had been declining for more than a month due to the reduced number of new victims, or 'non-immunes' that were available.

It seems likely, based on contemporary estimates, that more than 80 per cent of those infected with yellow fever during the 1854 epidemic recovered, and all of those people would have gained immunity from further infection as a result. If so many recovered why then did so many Irish immigrants die?
The mortality records from Savannah examined by Dr Lockley demonstrate that yellow fever affected certain segments of the population far more severely than others. It was, for instance, very evident at the time that black mortality was a mere fraction of white mortality. Slaves and free black people constituted just under half of Savannah’s population yet only fourteen black people died of yellow fever, prompting one doctor ‘to remark that the blacks formed the ”privileged class” among the inhabitants of the city’.

Black people were not immune from infection but, perhaps due to some genetic advantage, they seemed much less likely to die; Savannah Doctor Richard Arnold noted at the end of September 1854 that: 'There has been a great deal of sickness amongst the negroes within the last three or four weeks, fortunately not nearly so fatal as amongst the whites.'

Among caucasians it is immediately evident from the records that mortality from yellow fever among children was far lower than among adults. According to the 1850 census those under ten years old constituted 23 per cent of the white population, but in 1854 they accounted for fewer than 7 per cent of yellow fever deaths. As with many other diseases (for example, chickenpox, mumps and rubella), childhood infections of yellow fever were more likely to be ‘mild or asymptomatic’ than for adults.

Immigrants who had no prior exposure to yellow fever caught the disease as adults and as a result suffered high mortality. In nineteenth-century New Orleans annual yellow fever took a heavy toll among Irish and German immigrants but often by-passed those who had grown up in the city.

The newest immigrant arrivals to the city, particularly the Irish, were the most at risk and new ship loads of non-immune Irish immigrants provided fuel for the continuation of the epidemic. Parts of the city which had had very few new cases on 5, 6 and 7 October suddenly reported 12 new cases on 10 October and a further 20 cases on 13 October.

Yellow fever claimed a further 80 victims in Savannah in October and November, all but three of whom were recent immigrants; 23-year-old Irishman Bartholomew Stephens had only been in the city for two weeks when he died of yellow fever on 17 October, while his compatriot, 25-year-old Michael Bennet, lasted just ten days before he died on 23 October.

Another key factor was that the Aedes aegypti mosquito is more active in the day than many other mosquitoes, and is drawn to exposed sweaty flesh. Many Irish immigrants became labourers and men working outside during the day, and if engaged in manual labour in the heat of a Georgia summer were probably stripped to the waist. An early fatality precisely fits this description. James Gallagher was a 21-year-old carpenter who ‘had been working on the roof of a house which was just finishing’ and furthermore he had ‘walked nearly a mile two or three times daily to and from his work, which was in the north–eastern portion of the city, through the broiling sun’.

Dr Lockley said: ”Yellow fever certainly was a ‘strangers’ disease’ but not because strangers were not acclimatized to living in Savannah. Rather, it was a ‘strangers’ disease’ because strangers were also disproportionately male, in their twenties, working outside, and resided in neighbourhoods close to low swampy ground where mosquitoes thrived and in Savannah’s case a very large number of the ‘strangers’ in this position were newly arrived Irish.”

**Journal Reference:**

**Are antiretroviral switch or simplification studies of benefit for patients?**
Michael Carter
Published: 15 August 2012
The attitude of physicians, ethics committees and medical journals to antiretroviral switch and simplification studies needs to be radically reappraised, according to an article published in *PLoS Medicine.*

Before approval, studies of this type must show a clear potential advantage to patients and the risks and benefits need to be explicitly outlined to participants during recruitment, state the authors.

They add that commercial advantage for a pharmaceutical company is not a valid reason for approving a switch or simplification study.

The recent SWITCHMRK studies (substitution of raltegravir for lopinavir/ritonavir) and MONET trial (a simplification study exploring darunavir/ritonavir monotherapy) are highlighted by the authors as studies whose design and reporting failed to show any benefit to patients or healthcare systems. Indeed, for some patients participation in the study led to loss of virologic control.
Outcomes for patients taking HIV therapy in the UK and similar countries are hugely impressive. The majority of patients treated with antiretroviral drugs, regardless of their past treatment history and resistance profile, have an undetectable viral load, the primary goal of HIV therapy.

The safety and efficacy of antiretroviral treatment is demonstrated in phase III clinical studies. In these studies, a new drug is generally required to show virological superiority over either a placebo or the current standard of care.

Because of the substantial improvements seen in virological outcomes over the past 15 years, it is becoming increasingly difficult to recruit patients to clinical trials.

One solution has been to evaluate new drugs and treatment strategies in individuals whose existing therapy is effective and suppressing viral load. Many of these studies involve switching treatment to see if a new drug is non-inferior to an existing therapy, or if it leads to the simplification of treatment.

Switching studies have intended to show the non-inferiority of a new drug (no more than 10% to 12% worse than the existing therapy). If non-inferiority is proved, then the secondary end-points of these studies, such as the impact of the switch on quality of life and side-effects, can be of great interest.

Treatment simplification studies should also show that a new therapy if non-inferior to the pre-existing therapy. Simplification of treatment can include the replacement of two or three drugs with a co-formulation of these agents to reduce pill burden, or the cessation of one drug without the introduction of a new therapy.

There are undoubted benefits from switching or simplifying treatment. These can include reduced pill burden, greater tolerability and lower cost. However, there are also potential disadvantages. For instance, an effective and tolerable treatment may be abandoned.

Moreover, it has become clear that neither switching nor simplifying treatment reduces the risk of virological failure. Nor does a non-inferior finding in a study show that new agents or strategies are as potent as existing drugs. This can only be demonstrated in patients starting HIV therapy for the first time.

According to the Declaration of Helsinki, the benefits of a clinical trial should outweigh the potential risks.

“A switch or simplification study...with a primary end point of continued virological suppression and with no clinically useful impact on toxicity, costs, or quality of life cannot have any benefit to the participant,” write the authors. However, they found that 42% of HIV switch or simplification studies registered on Clinical-Trials.org “had virological non-inferiority as the primary end point.”

Rather, they believe that a particular disadvantage of a current treatment should be an explicit and well-defined entry criteria for the study. “Good examples of this approach are trials that evaluated the ability of drug switching to reverse objectively defined lipoatrophy and efavirenz-related central nervous symptoms.”

Moreover, the authors emphasise that the possible potential disadvantages of the switch should be “measured, analysed and reported.”

Patients must therefore be informed about the potential advantages and disadvantages and which is the primary focus of the study. If cost is the main focus, then the consent form must make it clear that the patient is not expected to derive any benefit from the study.

The authors also question whether some laboratory improvements reported as a benefit of a treatment switch are really of any clinical relevance. For instance, they suggest that reductions in cholesterol levels are likely only to be of meaningful benefit for patients with cardiovascular risk factors.

“No lipid switch study specifically enrolled patients with elevated cardiovascular risk,” note the authors.

Ethics committees should only approve studies if they are “convinced the potential gain is both clearly anticipated and clinically relevant to all participants and confident that patients are not likely to be at risk of virological failure,” write the investigators. “Trials that primarily benefit as pharmaceutical company should not be contemplated or approved.”

In terms of design, switch studies should be double-blind and have subjective end points. Any large switch study with a primary focus on toxicity should be preceded by a smaller pilot study. The virological efficacy of therapy should be assessed in trials involving treatment-naïve patients, not in switch studies.

Journal editors are asked by the authors to consider making it compulsory to submit patient information and consent forms with manuscripts reporting the findings of switch and simplification research. They would enable editors to “determine whether patients were fully informed about the risks and benefits of a trial, all risks and benefits were reported, and the principles of the Helsinki Declaration were upheld.”

Switching HIV treatment can be appropriate, conclude the authors, but it is essential to determine the full risks and benefits before and to communicate these to patients.
“The diminishing antiretroviral drug pipeline suggests greater care will need to be given in coming years to extending the benefits of existing drugs for what is likely to remain lifelong therapy.”

Reference

Researchers solve hepatitis C vaccine mystery
Published on August 13, 2012 at 11:58 PM
Researchers at the Burnet Institute have solved a hepatitis C vaccine mystery which, once developed could be the first ever preventative vaccine for the virus.

Currently undergoing formal preclinical studies, the vaccine is the result of breakthrough work done by Associate Professor Heidi Drummer with her team from the Institute’s Centre for Virology.

Hepatitis C affects around 200 million people around the world – a preventative vaccine has the potential to have a significant global health impact.

Associate Professor Drummer and her team have overcome a major hurdle in HCV vaccine research, developing a vaccine candidate that protects against a number of different HCV strains.

"Hepatitis C has a great ability to change its structure and evade the immune response. This makes vaccine development challenging," Associate Professor Drummer said.

"Our vaccine is unique as it contains only the most essential, conserved parts of the major viral surface protein, eliciting antibodies that prevent both closely and distantly related hepatitis C viruses from entering cells, thereby preventing infection."

Associate Professor Drummer unveiled the details about her HCV vaccine project at the prestigious Immunotherapeutics and Vaccine Summit (ImVacS) in Cambridge, Massachussets on August 13.

Shortage of circumcision tools amid high demand
Publish Date: Aug 13, 2012
By Francis Emorut
Health facilities across the country have run out of supplies for Safe Male Circumcision kits, an HIV expert has said.

Dr. Carol Nakkazi who is attached to Uganda AIDS Commission (UAC) says there is a huge demand for SMC across the country but the tool kits for conducting male circumcision procedure are inadequate.

“The Ministry of Health and Uganda AIDS Commission have done mass mobilization across the country and it has created high demand for male circumcision as men flock health facilities to be circumcised only to be disappointed after the tool kits have run out,” Dr. Nakkazi said.

The kit for carrying out surgical circumcision includes reusable and disposable supplies.

The items are scissors, forceps, knife handles, blades, needle holders, wrappers, aprons, surgical gloves, surgical caps and masks, cotton wool rolls, syringes, gauze rolls, spirit bottles and others.

Nakkazi observed that it is only the US Centres for Disease Control and Prevention (CDC) that procures male circumcision tool kits in the country.

Her appeal to government is to allow the National Medical Stores to procure male circumcision supplies to address the shortage in the country.

She said the shortage of tool kits for male circumcision has left many men who intend to be circumcised let down.

The districts where ministry of health and UAC have conducted safe male circumcision with a high demand are Rakai, Kasese, Mayuge, Kampala in Wakiso, Butambala, Gomba, Arua and the districts in Acholi and Lango subregion.

The executive director of RHU, Jackson Chekweko emphasized the need to incorporate sexual reproductive health into civil society organisations’ programming to prevent HIV/AIDS infection and unwanted pregnancies.

Denis Bakomesa, the technical coordinator on sexual reproductive health and HIV at RHU cited Kanungu district where hundreds of men turned up for circumcision.

He says they were overwhelmed by the huge number as well as those seeking family planning services.
The executive director of Mama’s Club, Dr. Lydia Mugherera urged civil society organizations and other stakeholders to involve men in the fight against the HIV/AIDS epidemic.

Safe Male Circumcision was introduced in the country by Makerere University Walter Reed Project (MUWRP) in partnership with Makerere University and the US Military HIV Research Program (MHRP) in the early 2000s.

The medical practice is intended to prevent HIV infection but it is not 100% safe, medical experts claim.

According to World Health Organisation and United Nations AIDS (UNAIDS) trials in Uganda, South Africa and Kenya have shown that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%.

Suit over wrong HIV diagnosis settled between ex-patient, Whitman-Walker
By Keith L. Alexander, Published: August 10
A seven-year court battle in the District over an HIV misdiagnosis ended this week when the Whitman-Walker Clinic quietly settled a $20 million lawsuit by a former patient who was mistakenly told he had the virus.

In 2005, Terry Hedgepeth, 52, sued Whitman-Walker because it had mistakenly told him five years earlier that he was HIV-positive. Since then, Hedgepeth, his attorney, Whitman-Walker, and judges in D.C. Superior Court and the D.C. Court of Appeals had been embroiled in legal wrangling.

On Tuesday, just a week before the case was to go to trial in D.C. Superior Court, an agreement was reached. Details of the settlement weren’t disclosed.

“We are happy to settle the case amicably,” said Don Blanchon, Whitman-Walker’s chief executive. He would not comment further on the case.

Hedgepeth’s attorney, Jonathan C. Dailey, said the “case was resolved amicably” and also declined to comment further on the agreement. But Dailey added that the agreement came a year after the D.C. Court of Appeals unanimously ruled in the case that medical patients who are given incorrect information from their doctors about a life-threatening illness can seek recourse through the courts for emotional distress.

That decision, Dailey said, paved the way for the agreement and could open the door for other cases in which doctors mistakenly misdiagnose a patient with a life-threatening illness.

“We changed 25 years of law. Now if a doctor misreads information, a patient can sue for negligent emotional distress,” Dailey said.

Dailey said his client, who is married and living in the Maryland suburbs, suffers from post-traumatic stress disorder because of the misdiagnosis.

“The effects of those five years have not worn off completely,” Dailey said. Repeated phone calls to Hedgepeth were not returned.

According to court records and interviews with Dailey, Hedgepeth went to Whitman-Walker after his then-girlfriend, with whom he had been sexually active, told him that she had AIDS and feared that she had infected him.

The test at the clinic, he would later discover, was negative. But a clinic employee mistakenly wrote in Hedgepeth’s files that he had taken two tests at the clinic and that one of them was positive. Then, a doctor at the clinic failed to carefully review Hedgepeth’s chart and instead began counseling him about the virus.

During the next four years, no further blood tests were done, and Hedgepeth continued to believe that he was HIV-positive. He became depressed, according to the court records, quit his job as a caterer, began using drugs and alcohol, and twice was committed to psychiatric wards because of suicidal thoughts.

Hedgepeth continued to be monitored at Whitman-Walker but was never medically treated for the virus. The clinic also arranged for Hedgepeth to live in a facility with HIV-positive people.

In June 2005, Hedgepeth decided to seek alternative treatment from the Abundant Life Clinic in Southeast Washington. The clinic conducted a routine blood test and discovered that he was not HIV-positive. A month later, Hedgepeth was referred to Johns Hopkins Bayview Medical Center to take a follow-up test, which confirmed that he had not contracted the virus.


Three years later, three judges on the D.C. Court of Appeals agreed with Morin’s decision, saying that Hedgepeth was not physically harmed by the misdiagnosis and noting that he had not been prescribed HIV medication that caused any side effects.
In 2009, Hedgepeth and his attorney petitioned for all 10 of the D.C. appellate judges to review the case. Last year, the judges reversed the lower court’s decision, finding that the case should move forward because serious emotional distress could result from a doctor’s negligence.

The ruling finally gave Hedgepeth a chance to be heard by a jury. On Tuesday, as both sides were preparing for trial, they resolved the case.

And although Dailey believes that the appellate judges’ decision gives people misdiagnosed with deadly diseases grounds for such lawsuits, some experts disagree.

Catherine Hanssens, executive director of the Center for HIV Law and Policy in New York, said that courts and juries realize doctors make mistakes.

“Most people who find out they are not HIV-positive view it as good news — they don’t run out and get a lawyer,” Hanssens said.

“Doctors are not infallible, and patients have to realize [the doctors] don’t, and should not, have the last say in their health.”

**Discussions of Viral Load in Negotiating Sexual Episodes with Primary and Casual Partners Among Men Who Have Sex with Men**

*AIDS Care Vol. 24; No. 8: P. 1052-1055*, (08..2012) Keith J. Horvath; and others

HIV-positive persons with lower viral loads are at reduced risk for transmitting the virus to their sex partners, recent studies indicate. As information about the association between viral load and HIV risk disseminates throughout high-risk communities, viral load discussions may be increasingly used as a risk-reduction strategy. In the current study, researchers sought to determine the frequency of viral load discussions and unprotected anal intercourse (UAI) in primary and casual sex partnerships among MSM.

In January 2011, 326 MSM (82 percent Caucasian, 62 percent college-educated, 7 percent HIV-positive, or thought they were) completed an online survey. The results showed that viral load discussions occurred in 93 percent of primary partnerships in which at least one partner was HIV-positive. UAI was reported with 46 percent of all primary partners and 25 percent of serodiscordant primary partners with whom viral load was discussed. Among casual sex partners, UAI was more common when viral load was not discussed compared to when it was (75 percent vs. 56 percent of encounters). Discussions about viral load were reported in 53 percent of the three recent sexual episodes with casual partners with whom respondents had sex—either once or multiple times—in the past three months.

“The finding that casual sexual episodes that did not include viral load discussions had a higher percentage of UAI than those that did include viral load discussions suggests either that men who do not discuss viral load may be higher risk-takers than men who do, or that the former are less adept at negotiating safer sex with casual sex partners than men who do discuss viral load,” the researchers concluded. “More research is needed to understand the role of viral load discussions in negotiating sexual activities among MSM.”

**India Launches New Laboratory For HIV Vaccine Research In Collaboration With IAVI**

India on Monday "opened a $12 million, government-backed laboratory whose mission is to create a new vaccine against HIV," *Science Insider* reports. "The HIV Vaccine Translational Research Laboratory, which aims to recruit about 30 scientists, is embedded within the Translational Health Science and Technology Institute, a $200 million facility under development on the outskirts of New Delhi" and "will work in collaboration with the New York based-International AIDS Vaccine Initiative (IAVI)," the news service writes, noting "operating costs will be shared equally" (Bagla, 8/14). "Former president A.P.J. Abdul Kalam launched the [laboratory] in New Delhi on Monday at a symposium on accelerating India’s search for an HIV vaccine," the Wall Street Journal's livemint.com writes. "Promising 'strong political will' at the highest level, health minister Ghulam Nabi Azad said, 'A preventive vaccine for HIV/AIDS is the best hope to end this epidemic,'" and "added that the step was an initiative to reinforce a national response in the global fight against disease," the news service notes (Krishnan, 8/13).

**IRIN Examines Expected Surge Of Doctors In Ethiopia**

"Ethiopia is preparing for a flood of medical doctors within 'three to four years,' an influx meant to save a public health system that has been losing doctors and specialists to internal and external migration," IRIN reports. "'We are now implementing strategies that intend to increase the current below-World Health Organization [WHO] standard number of medical doctors and retaining them in public hospitals,' Tedros
Adhanom, Ethiopia’s minister of health, told IRIN, "the news service writes. ""We have now reached an enrollment rate of more than 3,100," [Adhanom] said," adding, "The rate of enrollment in the country's medical schools has increased tenfold from 2005, when it was below 300," according to the news service.

"While WHO recommends countries have a minimum of one doctor per 10,000 people, Ethiopia has [less] than a fifth of that ratio, compared to a regional average of 2.2 physicians per 10,000 people," the news service notes. "Through the Medical Education Partnership Initiative (MEPI), the U.S. is supporting Ethiopia's efforts to improve the quality of medical training," according to the news service, which adds, "Challenges also remain in retaining doctors prone to migration. In 2006-2007, 37 percent of the country’s public-sector physicians worked in Addis Ababa, which was only home to less than four percent of the population" (8/14).

**Potential Hurdle to Universal Flu Vaccine Development May Be Overcome, Study Suggests**

ScienceDaily (Aug. 15, 2012) — In the quest for a universal influenza vaccine—one that elicits broadly neutralizing antibodies that can protect against most or all strains of flu virus—scientists have faced a sobering question: Does pre-existing immunity generated by prior exposure to influenza virus or vaccine hamper production of broadly neutralizing antibodies? If so, then a universal flu vaccine might work best (and perhaps only) in very young children who have had limited exposure to influenza viruses or vaccines.

Now, in studies using mice and ferrets, investigators from the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, have shown that broadly neutralizing influenza antibodies can indeed be elicited by a prime-boost vaccine regimen, even when the animals had pre-existing immunity to influenza.

The vaccine regimen consisted of a DNA vaccine prime followed by boosting with an inactivated seasonal vaccine. It did not matter if the pre-existing immunity was due to exposure to a flu virus or if it followed vaccination with standard seasonal influenza vaccine. Influenza-immune ferrets inoculated with the prime-boost regimen were protected against challenge with unmatched influenza virus strains. If the same effect is found in studies in people, it might be possible to develop vaccines that give long-lasting flu protection to people of all ages, according to the researchers.

Several clinical trials to examine the ability of first-generation universal flu vaccines to generate broadly neutralizing antibodies are either under way or planned at the VRC.

**Journal Reference:**


**Breastfeeding May Protect Infants from HIV Transmission**

ScienceDaily (Aug. 15, 2012) — An international team of researchers has found that certain bioactive components found in human milk are associated with a reduced risk of HIV transmission from an HIV infected mother to her breast-fed infant. Their study will be published in the August 15 online edition of *American Journal of Clinical Nutrition*.

"In developing countries, HIV-infected mothers are faced with the decision of whether or not to breastfeed their babies," said Lars Bode, PhD, assistant professor in the Department of Pediatrics at the University of California, San Diego School of Medicine. "Breastfeeding exposes the baby to the virus and increases the risk of the baby dying from HIV infection; but not breastfeeding increases the risk for the baby to die from other intestinal or respiratory infections."

Bode and colleagues set out to find why the vast majority of breast-fed infants do not acquire HIV-1, despite continuous exposure to the virus in their mother's milk over many months. Even in the absence of antiretroviral drugs, only 10 to 15 percent of infants will acquire HIV infection from their HIV-infected mothers.

They discovered that immunologically active components called human milk oligosaccharides (HMO)—a type of carbohydrate made up of several simple sugars linked together—may protect from HIV transmission. These complex oligosaccharides are the third-most abundant component of breast milk, yet are not digestible and therefore become highly concentrated in the mucosal surfaces of the infant's gastrointestinal tract.

"HMO act as prebiotics that promote the growth of desirable bacterial communities in the infant's intestine," said Bode. Additionally, HMO structurally resembles sugar chains called glycans that are normally found on epithelial cell surfaces, and can serve as "decoy" receptors to inhibit pathogens from
binding. Last, HMO exhibit anti-inflammatory activity and have been shown to modulate immune cell responses in cell and animal models.

The researchers analyzed HMO amount and composition in breast milk samples collected from more than 200 women as part of a larger study of HIV-infected women and their infants in Lusaka, Zambia, following them from birth to 24 months. (Most were recruited to the study and followed before antiretroviral therapy became available to them, thus offering a unique look at associations between HMO and HIV transmission.)

Higher concentrations of HMO in milk were associated with protection against postnatal HIV transmission, independent of other known risk factors. In the future, a better understanding of how individual HMO facilitate or obstruct HIV transmission may guide the development of interventions to complement antiretroviral strategies and more effectively prevent transmission, according to the researchers.

**Journal Reference:**
Lars Bode, Louise Kuhn, Hae-Young Kim, Lauren Hsiao, Caroline Nissan, Moses Sinkala, Chipepo Kankasa, Mwiya Mwiya, Donald M Thea, and Grace M Aldrovandi. *Human milk oligosaccharide concentration and risk of postnatal transmission of HIV through breastfeeding.* American Journal of Clinical Nutrition, 2012; DOI: [10.3945/ajcn.112.039503](http://dx.doi.org/10.3945/ajcn.112.039503)

**CDC to Baby Boomers: Get Tested for Hepatitis C**
Associated Press, (08.17.2012) Mike Stobbe
All baby boomers should receive a one-time test for hepatitis C virus, according to final CDC recommendations announced on Thursday. About 3 percent of baby boomers — those born from 1945 to 1965 — are infected with HCV. Those who have not been screened should get the blood test during their next visit to the doctor, said Dr. Thomas Frieden, CDC’s director.

Baby boomers are five times more likely to have HCV than other adults. Many of those with the blood-borne virus do not know they are infected, because symptoms can take decades to emerge. HCV, which can gradually scar the liver and lead to cirrhosis or liver cancer, is the leading cause of liver transplants.

Before widespread testing of blood donations began in 1992, HCV could be spread through blood transfusions. Today it is commonly transmitted through sharing needles to inject drugs. Some experts suggest that in some cases HCV could have spread through routes including shared razors and toothbrushes, manicures or sniffed cocaine.

Testing baby boomers can help avert major increases of liver disease and deaths — especially since two new drugs can cure many more people than older therapies. Of the estimated 3.2 million Americans with HCV, about two-thirds are baby boomers.

Deaths from HCV-related diseases have almost doubled from 1999 to 2007 and now amount to more than 15,000 US mortalities annually. “Unless we take action, we project deaths will increase substantially,” Frieden said.

The new approach is “a bold and important move,” said Dr. Andrew Muir, a Duke University physician and leader of an advocacy group, the National Viral Hepatitis Roundtable. “I have met too many patients who were diagnosed with hepatitis C at the time they developed liver cancer or when they needed a liver transplant.”

*[PNU editor's note: “Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945-1965” was published in CDC’s Morbidity and Mortality Weekly Report Recommendations and Reports (2012;61(RR04);1-18).]*

**Gilead Warned by Democrats over 'Quad' Pricing**
*Forbes*, (08.15.2012) Pharma & Healthcare blog
Fourteen Democratic members of Congress have written Gilead Sciences to ask that the company reasonably price its yet-to-be-approved AIDS drug "Quad". The once-a-day first-line AIDS treatment, which contains four medications, was recommended for approval by a Food and Drug Administration advisory panel. The congressional representatives fear that Gilead may charge as much as $34,000 per patient per year for Quad, which could further strain state AIDS funding programs.

Although Gilead froze prices through 2013 for drugs provided to AIDS Drug Assistance Programs (ADAPs), the company increased prices in the commercial market, raising costs for privately insured patients and those on Medicare.

According to the letter, “As a result, Ryan White Part B programs that help these patients afford their co-pays and deductibles now face overwhelming demand and instituted waiting lists. Given that Ryan White Part B funds both the co-pays and deductibles of privately insured patients as well as ADAP, price
increases for antiretroviral drugs in the commercial market diminish the ability of ADAPs to purchase drugs and sustain their case loads."

The representatives added, "We urge Gilead to consider sustainable pricing strategies for its products that would help allow ADAP to provide treatment to as many individuals as possible." As of August 9, 1,125 individuals were on ADAP waiting lists in seven states, according to the National Alliance of State & Territorial AIDS Directors.

AIDS Healthcare Foundation President Michael Weinstein praised the action to control Quad’s pricing and said, "In the long run, the cost to Gilead to actually produce the Quad will be a small fraction of its selling price, which means Gilead can show restraint on Quad pricing and still make an enormous profit."

**Climate Change Poses Risks To Food Supply, May Lead To Price Spike, Experts Warn**
"Downpours and heat waves caused by climate change could disrupt food supplies from the fields to the supermarkets, raising the risk of more price spikes such as this year’s leap triggered by drought in the United States," Reuters reports. "Food security experts working on a chapter in a U.N. overview of global warming due in 2014 said governments should take more account of how extremes of heat, droughts or floods could affect food supplies from seeds to consumers' plates," the news service writes (Doyle, 8/15). "The U.N. and global leaders have paid particular attention in recent weeks to U.S. biofuels policy as drought ravages corn supplies," The Hill's "E2 Wire" blog notes, adding, "They say the country needs to free up more of its corn for food to combat rising prices that heavily affect poor nations" (Colman, 8/16).

"[A] range of economists and food experts are also warning against overreaction that could create panic, causing governments to apply export controls that would restrict supplies of grains," according to IRIN. "This would affect markets and push prices still higher, they say," the news service adds. "The crisis is not here yet,' said Shenggen Fan, director of the International Food Policy Research Institute (IFPRI)," IRIN writes. "But if droughts in India, Russia and a couple of other major food producers become worse, we will see continued tightened food supply. Trade restrictions by these countries will make the situation worse," Fan added, the news service notes (8/16).

**Australia Upholds Cigarette Logo Ban, Dealing A 'Major Blow' To Global Tobacco**
"Australia’s highest court Wednesday rejected a challenge from big tobacco companies to tough new plain-packaging laws due to come into effect later this year, in a legal battle closely watched around the world," the Wall Street Journal reports, adding, "The ruling is a major blow for global tobacco giants that had been seeking to stop Australia implementing the new laws, fearing the move would set a precedent for other countries to follow" (Curran, 8/14). "Tobacco companies British American Tobacco, Britain’s Imperial Tobacco, Philip Morris and Japan Tobacco challenged the laws in Australia’s high court, claiming the rules were unconstitutional because they effectively extinguished the companies’ intellectual property rights," according to the Guardian (8/15). "The law, approved by Parliament last year, requires cigarettes to be sold in drab dark packaging starting in December, without logos but featuring graphic images of smoking-related diseases," the Washington Post writes, adding, "Brand names can still be used, but only in a standard font, size and position" (Hume, 8/15).

"The ruling is a victory for a government faced with A$31.5 billion ($33 billion) in annual health costs from smoking, a habit it estimates killed 900,000 Australians over six decades," Bloomberg Businessweek notes (Slind-Flor, 8/16). "The laws, the toughest in the world, are in line with World Health Organization recommendations and are being watched closely by Britain, Norway, New Zealand, Canada and India, which are considering similar measures," the Guardian writes, adding, "The tobacco companies are worried the law will set a global precedent that could slash billions of dollars from the value of their brands" (8/15). According to Reuters, "[t]he E.U. will publish a draft revision to its 2001 Tobacco Products Directive in the fall, and may introduce more stringent rules on packaging as well as extend legislation to newer tobacco products such as electronic cigarettes" (Davenport, 8/16). CNN examines tobacco health warnings around the world (Voigt, 8/16).

**Study Finds 'Alarming Patterns' Of Tobacco Use In Developing Countries**
"Two fifths of men in developing countries still smoke or use tobacco, and women are increasingly starting to smoke at younger ages, according to a large international study which found 'alarming patterns' of tobacco use," Reuters reports (Kelland, 8/17). The study, published Friday in the Lancet, "covered enough representative samples to estimate tobacco use among three billion people" and
"demonstrates an urgent need for policy change in low- and middle-income countries,' said lead researcher Gary Giovino," according to CNN (Levs, 8/17). "Although 1.1 billion people have been covered by the adoption of the most effective tobacco control policies since 2008, 83 percent of the world’s population are not covered by two or more of these policies,' said [Giovino]," Reuters adds (8/17).

"The data trawl covered a survey of tobacco habits among people aged over 15 in Bangladesh, Brazil, China, Egypt, India, Mexico, the Philippines, Thailand, Turkey, Ukraine, Uruguay and Vietnam, as well as Britain, Poland, Russia and the United States, from 2008 to 2010," Agence France-Presse writes, adding, "On current trends, as many as a billion people could die prematurely from tobacco use during this century, the study said, citing estimates by World Health Organization (WHO) experts" (8/16). In a statement from the Campaign for Tobacco-Free Kids, president Matthew Myers writes, "This study demonstrates how quickly the burden of tobacco use is moving to low- and middle-income countries and is a wake-up call for these countries to act now and address a crisis they can ill afford" (8/16).

Less commonly prescribed antibiotic may be better
Analysis compares vancomycin with cefazolin for treating certain bloodstream infections

Highlights

- Vancomycin was the most commonly prescribed antibiotic in dialysis patients for treating certain bloodstream infections, but cefazolin was 38% better than vancomycin at preventing hospitalizations and deaths from these infections.
- Cefazolin was also 48% better at preventing sepsis.
- Hundreds of thousands of Americans develop bloodstream infections every year.

Washington, DC (August 16, 2012) — The antibiotic most commonly prescribed to treat bloodstream infections in dialysis patients may not always be the best choice, according to a study appearing in an upcoming issue of the Journal of the American Society of Nephrology (JASN).

When *Staphylococcus aureus* bacteria gain access to a patient’s bloodstream, the infection then becomes life threatening. Antibiotics can often cure this infection, but without any antibiotic treatment, more than 80% of patients with bloodstream infections are likely to die. But what’s the most appropriate antibiotic to use?

Kevin Chan, MD (Fresenius Medical Care North America and Massachusetts General Hospital) and his colleagues compared the effectiveness of various antibiotics at preventing hospitalization and death from bloodstream infection. They reviewed more than 500,000 blood culture results from their chronic kidney disease database, looking for methicillin-sensitive strains of *S. aureus* bloodstream infection. They also identified when physicians used vancomycin or cefazolin to treat these infections. Vancomycin is often perceived as the better antibiotic because it has broad coverage against many strains of bacteria; however, other factors like the antibiotic’s killing power and tissue penetration are also important factors in selecting the best treatment.

Among the major findings:

- 56% of patients remained on vancomycin after blood culture results reported *S. aureus bacteria* were susceptible to cefazolin, while only 17% were treated with cefazolin.
- Cefazolin-treated patients experienced a 38% lower rate of hospitalization and death compared with vancomycin-treated patients.
- Cefazolin-treated patients also had a 48% lower rate of sepsis, which is the most serious form of bloodstream infection.

"I think the data suggest there is an opportunity to improve outcomes for patients through appropriate antibiotic selection," said Dr. Chan.


Poxviruses defeat antiviral defenses by duplicating a gene
Study helps explain how large DNA viruses undergo rapid evolution

SALT LAKE CITY — Scientists have discovered that poxviruses, which are responsible for smallpox and other diseases, can adapt to defeat different host antiviral defenses by quickly and temporarily producing multiple copies of a gene that helps the viruses to counter host immunity. This discovery provides new insight into the ability of large double-stranded DNA viruses to undergo rapid evolution despite their low
mutation rates, according to a study published by University of Utah researchers in the Aug. 17, 2012, issue of *Cell*.

Poxviruses are a group of DNA-containing viruses that are responsible for a wide range of diseases in both humans and animals, including smallpox. Unlike smaller RNA-containing viruses, such as those that cause influenza and HIV, which are able to evade host immune responses through rapid mutation, poxviruses have larger genomes and low mutation rates and little is known about their adaptive strategies against host defenses.

"Poxviruses encode a variety of genes that help them to counter host immune defenses and promote infection," says Nels Elde, Ph.D., assistant professor of human genetics at the University of Utah School of Medicine and first author on the study. "Despite ample evidence that the poxvirus genome can undergo adaptive changes to overcome evolving host defenses, we still don't know that much about the mechanisms involved in that adaptation."

To determine mechanisms of adaptation, Elde and his colleagues studied the vaccinia virus, a type of poxvirus best known for its role as the vaccine used to eradicate smallpox. Previous research has shown that vaccinia virus encodes two genes, known as K3L and E3L, which inhibit host defenses that normally block viral infection. In this study, Elde and his colleagues started with a strain of vaccinia virus that had been altered to delete the E3L gene and repeatedly propagated this E3L-deficient strain in human cells to see how well the virus would replicate. They found that this E3L-deficient strain was quickly able to increase infectious virus production by selectively increasing the number of copies of the K3L gene in its genome.

"This highly specific and rapid gene amplification was unexpected," says Elde. "Our studies show that increasing K3L copy number leads to increased expression of K3L and enhanced viral replication, providing an immediate evolutionary advantage for those viruses that can quickly expand their genome."

Elde and his colleagues also found that, in addition to K3L copy number amplification, some of the E3L-deficient vaccinia strains also acquired a mutation consisting of a single amino acid substitution in the K3L gene. Both the mutation-bearing and multicopy K3L viruses displayed improved viral fitness, or ability to replicate in the host environment, compared to wild-type vaccinia virus. The emergence of this beneficial amino acid substitution suggests that increasing K3L copy number facilitated the appearance of the variant by providing additional mutational targets, despite the virus' otherwise low mutation rate.

"We were able to demonstrate at least two strategies by which poxviruses are able to adapt diverse mechanisms of host immunity," says Elde. "Our observations reveal that, while poxviruses do undergo gene mutation, their first response to a new, hostile host environment can be rapid gene expansion. We also found evidence that the virus genome can contract after acquiring an adaptive mutation, thus alleviating the potential trade-off of having a larger genome, while leaving a beneficial mutation in place."

Although smallpox was officially eradicated by the World Health Organization in 1980, concerns about the use of smallpox as a bioterrorism agent have spurred renewed interest in the study of vaccinia and other poxviruses. In addition, poxvirus infections, such as monkeypox, can be transmitted from animals to humans and the adaptive strategies of poxviruses may be relevant for other infectious organisms.

**Common parasite may trigger suicide attempts**

Published: Aug. 16, 2012

EAST LANSING, Mich. — A parasite thought to be harmless and found in many people may actually be causing subtle changes in the brain, leading to suicide attempts.

New research appearing in the August issue of The Journal of Clinical Psychiatry adds to the growing work linking an infection caused by the Toxoplasma gondii parasite to suicide attempts. Michigan State University’s Lena Brundin was one of the lead researchers on the team.

About 10-20 percent of people in the United States have Toxoplasma gondii, or T. gondii, in their bodies, but in most it was thought to lie dormant, said Brundin, an associate professor of experimental psychiatry in MSU’s College of Human Medicine. In fact, it appears the parasite can cause inflammation over time, which produces harmful metabolites that can damage brain cells.

“Previous research has found signs of inflammation in the brains of suicide victims and people battling depression, and there also are previous reports linking Toxoplasma gondii to suicide attempts,” she said. “In our study we found that if you are positive for the parasite, you are seven times more likely to attempt suicide.”
The work by Brundin and colleagues is the first to measure scores on a suicide assessment scale from people infected with the parasite, some of whom had attempted suicide.

The results found those infected with T. gondii scored significantly higher on the scale, indicative of a more severe disease and greater risk for future suicide attempts. However, Brundin stresses the majority of those infected with the parasite will not attempt suicide: “Some individuals may for some reason be more susceptible to develop symptoms,” she said.

“Suicide is major health problem,” said Brundin, noting the 36,909 deaths in 2009 in America, or one every 14 minutes. “It is estimated 90 percent of people who attempt suicide have a diagnosed psychiatric disorder. If we could identify those people infected with this parasite, it could help us predict who is at a higher risk.”

T. gondii is a parasite found in cells that reproduces in its primary host, any member of the cat family. It is transmitted to humans primarily through ingesting water and food contaminated with the eggs of the parasite, or, since the parasite can be present in other mammals as well, through consuming undercooked raw meat or food.

Brundin has been looking at the link between depression and inflammation in the brain for a decade, beginning with work she did on Parkinson’s disease. Typically, a class of antidepressants called selective serotonin re-uptake inhibitors, or SSRIs, have been the preferred treatment for depression. SSRIs are believed to increase the level of a neurotransmitter called serotonin but are effective in only about half of depressed patients.

Brundin’s research indicates a reduction in the brain’s serotonin might be a symptom rather than the root cause of depression. Inflammation, possibly from an infection or a parasite, likely causes changes in the brain’s chemistry, leading to depression and, in some cases, thoughts of suicide, she said.

“I think it’s very positive that we are finding biological changes in suicidal patients,” she said. “It means we can develop new treatments to prevent suicides, and patients can feel hope that maybe we can help them.

“It’s a great opportunity to develop new treatments tailored at specific biological mechanisms.”

**Cholesterol Test With Only a Photo of Patient’s Hand**

ScienceDaily (Aug. 17, 2012) — Researchers in India have developed a total cholesterol test that uses a digital camera to take a snapshot of the back of the patient’s hand rather than a blood sample. The image obtained is cropped and compared with images in a database for known cholesterol levels.

Writing in the *International Journal of Medical Engineering and Informatics*, N.R. Shanker of the Sree Sastha Institute of Engineering and Technology and colleagues describe how they have developed a non-invasive way to test cholesterol levels in patients at increased risk of heart disease. Their approach is based on the creation of a large database of cholesterol levels recorded using standard blood tests and linked to a standardized photograph of the hand for each patient; cholesterol is concentrated in the creases of one’s fingers. They developed an image-processing computer program that compares the image from a new patient with the thousands of entries in the database and matches it to a specific cholesterol reading.

Measuring the amount and type of cholesterol circulating in the blood is an important risk factor in cardiovascular disease. Excess cholesterol not used by the body in making hormones and building cells is laid down on the inner wall of arteries as a waxy plaque, which can reduce the normal flow of blood potentially causing heart problems and increasing the risk of cerebral stroke. Total cholesterol is a useful early indicator, although more detailed testing that distinguishes between the HDL high-density lipoprotein) and LDL (low-density lipoprotein) and triglycerides are needed for a more accurate health assessment of patients found to have high total cholesterol. It is LDL, so-called “bad” cholesterol that contributes to the formation of arterial plaques, atherosclerosis. The presence of different total levels of cholesterol can be revealed through image analysis of the skin.

A non-invasive and inexpensive method for cholesterol screening would allow this risk factor be determined in much larger patient populations without the need for costly and inconvenient blood tests. The team will also soon publish details of the extension of this work to classifying cholesterol type using their approach.

**Journal Reference:**

Virus Throws a Wrench in the Immune System
ScienceDaily (Aug. 16, 2012) — The cytomegalovirus (CMV) is a member of the herpesvirus family. Although most people carry CMV for life, it hardly ever makes them sick. Researchers from the Helmholtz Centre for Infection Research and from the USA have now unveiled long term consequences of the on-going presence of CMV: Later in life, more and more cells of the immune system concentrate on CMV, and as a result, the response against other viruses is weakened. These research results help to explain why the elderly are often more prone to infectious diseases than young people.

The viral immunologist Professor Luka Cicin-Sain, head of the junior research group "Immune Aging and Chronic Infections" at the HZI in Braunschweig, Germany, and his colleagues have now published their discovery in the open access journal PLoS Pathogens. In the article, they describe that even months after infection with CMV, mice still show weaker responses against other viruses such as the flu virus.

Most adults are infected with CMV, yet this infection goes unnoticed. Usually that is of no consequence, because in the vast majority of cases, this herpesvirus does not make them sick. Only for people with a weak immune system, like organ recipients, AIDS patients, or unborn babies infected during pregnancy, the infection is dangerous. In everyone else, the virus becomes latent and persists in the body, but is kept at bay by the immune system. "In young people this lasting activation of the immune system might even be beneficial, because an active immune system may defeat other infections rapidly. But a bright candle burns down faster," says Cicin-Sain, to clarify that the immune defence will wear out over the years. In elderly, the immune system loses function and its changes that present a clear loss of immune protection are summarily termed the "Immune risk profile," shortly IRP. A relationship between IRP and the presence of CMV has been observed in several clinical studies. However, up to now it was unclear whether IRP is a consequence of the CMV infection or, vice versa, the IRP resulted in increased susceptibility to CMV infection.

The results of Cicin-Sain's group and his American colleagues from the Oregon Health and Science University in Portland and from the College of Medicine of the University of Arizona in Tucson show that the on-going CMV presence contributes to immune ageing. "Of course the immune system ages without CMV as well," Cicin-Sain explains. On the other hand, CMV is a permanent guest that demands a growing amount of attention from the T cells, an important group of immune defence cells. The longer the mice were infected with CMV, the more of these cells were engaged with the cytomegalovirus and were missing for the fight against other pathogens. Accordingly, the immune system of CMV-infected mice could not respond well to other infections, for instance to the flu- or the West-Nile-virus. "We believe that the large number of CMV-specific T cells in the lymph nodes is likely to impair the activation of the remaining cells," the researcher concludes. What accelerated the immune defence in the young organism now becomes a burden in an old organism and takes its toll. Luka Cicin-Sain thinks a little further and summarizes: "Our results clearly show how important it would be to develop a vaccine against the cytomegalovirus, despite its low direct impact on human health."

Journal Reference:
*Cytomegalovirus Infection Impairs Immune Responses and Accentuates T-cell Pool Changes Observed in Mice with Aging* PLoS Pathogens, 2012; 8 (8): e1002849 DOI: 10.1371/journal.ppat.1002849

Scientists Find an Important Molecular Trigger for Wound-Healing
ScienceDaily (Aug. 16, 2012) — Scientists at The Scripps Research Institute have made a breakthrough in understanding a class of cells that help wounds in skin and other epithelial tissues heal, uncovering a molecular mechanism that pushes the body into wound-repair mode.
The findings, which appear in an advance, online version of the Immunity on August 16, 2012, focus on cells known as γδ (gamma delta) T cells. The new study demonstrates a skin-cell receptor hooks up with a receptor on γδ T-cells to stimulate wound healing.

"This is a major activation pathway for γδ T-cells, and it may be a key to treating slow-wound-healing conditions, such as we see in diabetes," said Scripps Research Professor Wendy L. Havran, senior author of the study. "Chronic non-healing wounds among diabetics and the elderly are an increasing clinical problem."

**Rounding and Multiplying**

Havran's laboratory specializes in the study of γδ T cells, and the team has produced many of the findings in this research field, including the discovery of these cells' major role in epithelial wound repair. Epithelial tissues are barrier tissues to the outside world, such as skin and the inner surfaces of the gut and lungs.

Normally, γδ T cells reside in these tissues and extend finger-like projections, called dendrites, that contact neighboring epithelial cells. When injury or infection occurs, the epithelial cells signal their damaged condition to the γδ T cells. In response, the T cells retract their dendrites, become round, start proliferating, and secrete growth-factor proteins that stimulate the production of new epithelial cells in the vicinity—thus helping to repair the wound.

Researchers know of very few interactions between epithelial cells and γδ T cells that are involved in this process. Two, however, are known to be crucial. One of these is through the gd T cell receptor and the other was described in a 2010 Science paper, whose first author was Havran laboratory Senior Staff Scientist Deborah A. Witherden. But these two interactions don’t fully explain the transformation that γδ T cells undergo in the vicinity of wounds. "We've wanted to learn more about the molecules that mediate this dramatic change," Havran said.

**Signaling a Transformation**

To do that, Witherden identified an antibody that could block keratinocytes' ability to activate γδ T cells in culture. She found that the antibody bound to a keratinocyte surface receptor called plexin B2. She also found that when lab mice have small skin wounds, their injured keratinocytes express more plexin B2 soon after the wounding occurs—pointing to a role for plexin B2 in signaling skin-cell damage.

The next step was to find plexin B2's signaling partner on γδ T cells. "Plexin B2 is very similar to other plexin B family members, including plexin B1, which previously has been shown to bind the CD100 receptor on T cells," said Witherden. "So we thought that perhaps plexin B2 and CD100 can interact as well."

Further tests revealed that plexin B2 and CD100 do indeed bind tightly together; moreover, γδ T cells can't go fully into wound-repair mode when they lack CD100. Witherden found as well that skin wounds in mice take an extra day or two to heal when the mice don't have this receptor. "This is very similar to what we see in mice that lack γδ T cells altogether," she said.

Removing CD100 from other types of T cells had no effect on wound healing time, indicating that the absence of this receptor specifically on γδ T cells is the reason for the slower healing.

By stimulating CD100 with plexin B2 molecules or even with CD100-binding antibodies, the team showed that this receptor is the principal trigger for the dramatic appendage-retraction and rounding phenomenon seen in γδ T cells after nearby wounds. Without it, the T cells are largely unable to undergo this transformation. "This rounding process seems to be vital for these T cells to function normally in wound healing," said Witherden.

**Potential Clinical Significance**

In early follow-on work, the team has found evidence that this same plexin B2-CD100 interaction is also needed for the prompt activation of γδ T cells and wound healing in the lining of mouse intestines—which suggests that this receptor helps govern wound healing in epithelial tissues generally.

The finding clearly is important for the basic scientific understanding of T cells and their functions. But it is likely to have medical significance, too. Non-healing wounds affect more than 4 million people in the United States and are the leading cause of amputations. These chronic wounds have a major impact on patient’s lives and result in enormous health care costs. "If deficiencies in this γδ T cell activation pathway are even partly responsible, then we may be able to develop drugs to boost this pathway and treat conditions involving chronic non-healing wounds," said Havran.

The γδ T cell population appears to be involved not just in wound healing, but also in defending against other threats to epithelial tissues. "One of the future directions of our research will be to understand the roles of these molecules in gd T cell activation pathways in fighting infections and tumors," she added.
Hepatitis C Outbreak Could Boost Regulation Bill

*Associated Press*, (08.16.2012) Holly Ramer

The recent case of a medical technologist accused of infecting patients with hepatitis C at a New Hampshire hospital could build support for the creation of consistent national standards for such workers, advocates say.

Arrested in July, cardiovascular technologist David Kwiatkowski is accused of a drug-diversion scheme that contaminated syringes used on patients at Exeter Hospital. Before his arrest, Kwiatkowski worked at 18 hospitals in seven other states, moving from job to job despite being fired twice for allegations of drug use and theft. Lack of regulation, poor communication, and deception helped cover his trail.

“Unbelievable,” said US Rep. John Barrow (D-Ga.), lead sponsor of a bill that would require medical imaging and radiation workers to meet uniform national standards in order for employing hospitals to receive Medicare funding.

Education and certification standards vary in the 45 states that regulate at least one type of job involving medical imaging or radiation therapy. The American Society of Radiologic Technologists for years has lobbied for federal legislation like the bill under consideration. Sens. Mike Enzi (R-Wyo.) and Tom Harkin (D-Iowa) introduced their version in July, with Barrow one of 130 House co-sponsors. Congress has failed to pass any previous versions, despite no significant opposition, said Christine Lung, ASRT’s vice president of government relations.

“I think it’s going to take situations like Mr. Kwiatkowski ... to really make the public sit up and take notice,” Lung said.

“While medical licensing laws and regulations have traditionally been developed at the state level, Congress has an important oversight role in ensuring patient safety across the nation,” said John Billings, chief of staff for Rep. Charles Bass (R-N.H.). Sen. Kelly Ayotte (R-N.H.) said she would consider legislative remedies, but that hospitals bear the ultimate responsibility to prevent such incidents by conducting thorough background checks and strictly controlling access to narcotics.

Concern Rising over HIV Among Utah’s African Immigrants

*Salt Lake Tribune*, (08.13.2012) Julia Lyon

Utah’s Refugee Services Office (RSO) is one of several organizations encouraging African community groups to hold HIV/AIDS education events in a bid to address fear and confusion on the part of many immigrants.

According to community members, rumors abound about people transmitting HIV to others or refusing treatment. “The community is very worried now. It’s really spreading,” said Joseph Nahas, an immigrant from Sierra Leone who works at RSO overseeing grants for refugee groups.

But whether HIV actually is increasing among Utah’s African community is not clear. Newly analyzed data of state HIV diagnoses between 2007 and 2011 show roughly two-thirds of blacks with HIV were foreign-born, though this represented only 30 cases. Matt Mietchen, an epidemiologist with the Utah Department of Health (UDH), said, “If they’re getting here and are already infected, are we getting them the services they need? If they’re getting it here, why and what can we do?”

“If we did some more systematic testing, we would maybe find out it really isn’t a problem,” said Heather Bush, HIV education specialist for UDH. She hopes to see the data broken out further, as some others states have done, to clarify whether HIV actually is a growing problem in Utah’s African community. This knowledge would be key to accessing resources to target this population, she said.

Because HIV prevalence is so much lower in the United States than in Africa, a particular challenge is informing new arrivals that the virus exists here. “There’s the perception that there’s no HIV in the US anymore,” said Margaret Korto, a senior program analyst with the federal Office of Minority Health Resource Center, which is involved in the National African HIV/AIDS Initiative.
The Relationship Between Sexual Abuse and Risky Sexual Behavior Among Adolescent Boys: A Meta-Analysis

*Journal of Adolescent Health* Vol. 51; No. 1: P. 18-24, (07..2012) Yuko Homma, MS; and others

Sexual abuse during childhood and adolescence has been shown to lead to greater odds of sexual behaviors that can result in STIs and involvement with early pregnancy. While research, meta-analyses, and interventions have focused chiefly on young females who have experienced sexual abuse, some adolescent boys are sexually abused as well.

The authors conducted a meta-analysis of previous studies to assess the strength of the link between a history of sexual abuse and three risky sexual behaviors among North American adolescent males. The three outcomes were unprotected sexual intercourse, multiple sex partners, and pregnancy involvement. Weighted mean effect sizes were computed from 10 independent samples from nine studies published between 1990 and 2011.

Compared to boys who were not abused, sexually abused boys were significantly more likely to report all three risky behaviors (weighted mean odds ratios: 1.91 for unprotected intercourse, 2.91 for multiple sex partners, and 4.81 for pregnancy involvement).

“Our results indicate that childhood and adolescent sexual abuse can substantially influence sexual behaviors in adolescence among male survivors,” the authors concluded. “To improve sexual health for all adolescents, even young men, we should strengthen sexual abuse prevention initiatives, raise awareness about male sexual abuse survivors’ existence and sexual health issues, improve sexual health promotion for abused young men, and screen all people, regardless of gender, for a history of sexual abuse.”

Porn Industry Syphilis Cases in L.A. County Under Investigation

*Los Angeles Times*, (08.17.2012) L.A. Now blog

A possible cluster of syphilis cases among performers in the adult-film industry is under investigation by the Los Angeles County Public Health Department, officials announced Friday. Peter Kerndt, director of the county’s STD programs, said LACPHD has received reports of at least five possible cases in the past week. The county plans to follow up with those affected to ensure they have received proper treatment and to determine who else might have contracted the STD; workers also are trying to identify the source case. Kerndt expressed concern that the cluster “may be the tip of the iceberg” and added that it “is a serious health risk to workers in this industry.” Syphilis cases rose across the county in 2010-11, he noted.

In your future: More healthful foods to nourish the non-human you

PHILADELPHIA, Aug. 21, 2012 — The focus of nutrition for good health is quietly shifting to include consumption of food ingredients specifically designed to nourish the *non-human* cells that comprise 80 percent of the cells in the typical person, an authority on the topic said here today.

Speaking at the 244th National Meeting & Exposition of the American Chemical Society, the world’s largest scientific society, Robert Rastall, Ph.D., cited several factors driving these so-called "prebiotic" ingredients toward more foods. Food scientists, for instance, are developing new sources of the healthful substances for use in a variety of foods, and scientific evidence on the benefits of eating prebiotics is growing.

"Just as people need food to thrive, so do the billions of healthful bacteria that live in our guts, our gastrointestinal tract," Rastall explained. "There’s a large and expanding body of scientific evidence that bacteria in the gut play a role in health and disease. Prebiotics are foods that contain nutrients that support the growth and activity of these friendly bacteria."

Rastall contrasted prebiotics to the more familiar "probiotics," already being promoted on the labels of food like yogurt and some dietary supplements. He heads the Department of Food and Nutritional Sciences at the University of Reading in the U.K. and is co-author of widely used textbooks on prebiotics and probiotics.

Probiotic foods actually contain friendly bacteria like *Lactobacillus acidophilus* believed to release healthful substances as they grow in the GI tract. Prebiotics are indigestible food ingredients that provide no nutrition to people. Their purpose is to nourish the friendly bacteria among the estimated 100 trillion microbes living inside the human GI tract.

Foods promoted for a prebiotic effect already are on the market in the European Union, and Rastall predicted that probiotics will gain a greater foothold in Europe and the United States. One major advantage: Prebiotics do not require refrigeration like probiotic yogurt and other dairy products and could be incorporated into a wider range of foods.
Rastall noted that people get small amounts of one of the most common prebiotics, called inulin, from wheat, onions, garlic, chicory and certain other foods. He cited studies showing that when people eat more inulin and other prebiotics, the balance of microbes in the gut shifts to one linked to a range of health benefits.

To help people get more prebiotics in their diet, Rastall's team in the U.K., working with colleagues at the U.S. Department of Agriculture's Agricultural Research Service, is finding ways to make prebiotics from plant carbohydrates like pectins, mannans and xylans.

They are using plant biomass, like stems and husks, as sources for those carbohydrates, which then are converted to the shorter carbohydrates that make up prebiotics. The goal is preparation of prebiotic carbohydrates that have neutral tastes and can withstand heating so they could be easily added to processed foods. These new prebiotics also could be used as stand-alone dietary supplements, he added.

"Prebiotics may prove to be most useful in specific population groups and people with specific health problems rather than the general population," Rastall said. He cited, for instance, individuals with gastrointestinal diseases, Type-2 diabetes and low-grade inflammation linked to an increased risk of heart disease and other conditions, and people at risk for travelers' diarrhea.

**Anthrax Targets**

ScienceDaily (Aug. 20, 2012) — A trawl of the genome of the deadly bacterium *Bacillus anthracis* has revealed a clutch of targets for new drugs to combat an epidemic of anthrax or a biological weapons attack. The targets are all proteins that are found in the bacteria but not in humans and are involved in diverse bacterial processes such as metabolism, cell wall synthesis and bacterial persistence. The discovery of a range of targets might bode well for creating a drug cocktail that could preclude the emergence of drug resistance.

Ravi Gutlapalli of the Department of Biotechnology, at Acharya Nagarjuna University in Guntur, Andhra Pradesh, India, and colleagues there and at Osmania University College for Women in Hyderabad, suggest that the search for drugs to fight *Bacillus anthracis* is of increasing importance as we face an ongoing threat of its use as a biological weapon. The team has now carried out a search of the bacterial genome and identified 270 non-redundant, non-human homologous genes and 103 essential genes of the bacteria as possible drug targets.

The team explains that they have fished out sixteen membrane-bound proteins, seven proteases and three adhesion molecules that are all novel from their trawl any one of which might now be used in the rational design of new drugs with previously unused modes of action. This latter point is most important in reducing the chances of the bacteria quickly evolving resistance.

Early diagnosis and treatment with potent antibiotics is essential in any of the three clinical forms of anthrax: cutaneous, gastrointestinal and pulmonary. Unfortunately, the bacteria have evolved resistance to common antibiotics including ciprofloxacin, doxycycline and beta-lactam type drugs. The team now hopes that its identification of a range of novel targets for antibiotics will allow medicinal chemists to quickly screen for activity among diverse molecules as putative antibiotics.

With several possible targets in hand, researchers now need to create homology models of each against which potential drugs might be screened on the computer and thence synthesize in the laboratory and tested against the bacteria under secure conditions.

**Journal Reference:**


**Recipient of HIV-positive heart sues hospitals**


The National Cheng Kung University Hospital (NCKUH) heart transplant patient sued doctors from the hospital and from National Taiwan University Hospital (NTUH) for mistakenly transplanting the HIV-positive organ from a donor in Hsinchu.

The patient is one of five organ transplant patients who accidentally received an HIV-positive heart, liver, lung and kidneys prepared by NTUH.

Although, the patient's life was saved by the heart transplant, it has affected his feelings and marriage, and "it will not be easy for the person to get over this," said Lee Po-chan, a surgeon at NCKUH.
In addition, the patient has not decided whether he or she will continue with HIV drug therapy, Lee added.

Prosecutors have not yet brought the case to court and might be waiting for opinions from Department of Health (DOH) experts, Lee went on.

NTUH is considering compensating the patients by supplying and paying for AIDS drug therapy, which costs in excess of NT$22,000 (US$733.59) per month, said Chu Hsin-cheng, director of the hospital's public affairs department.

The four other patients have decided to continue taking medication, said Hung Chien-ching, a doctor at the NTUH's Department of Internal Medicine, who is also an AIDS expert.

Health officials announced earlier in the day that the patients can decide whether they want to continue or terminate anti-HIV drug treatment.

Although one patient’s HIV antibody dilution tests counts remains stable, while the counts have decreased in the four other patients, this is not enough evidence to prove conclusively that the patients have been infected with the virus, said Hung.

The Center for Disease Control (CDC) will perform virus counts in lymph cells, which is a more accurate test, Hung added.

Meanwhile, in a separate interview that day, CDC Deputy Director-General Chou Jih-haw said that a DOH task force decided after the mistake was discovered that the five patients should receive preventive HIV medication for at least 12 months, and undergo 18 months of observation before deciding whether to continue drug therapy.

It has been difficult to determine whether the patients are infected as they have been receiving both anti-HIV and anti-rejection drugs at the same time, said Chen Chang-hsun, the head of the center's third division.

There have been no similar cases in the past, and as long as the patients continue to use the anti-HIV drugs it will be difficult to determine whether or not they have been infected, explained Chen.

While one HIV-positive patient has lived for 27 years on anti-virus medication, the drugs used in the therapy can be hepatotoxic or put stress on the kidneys, to which organ transplant patients may need time to adopt, said Chen.

Should a patient decide to discontinue medication, it takes around six months to determine for sure whether he or she has been infected, Chen added.

**Better food seen as key in AIDS treatment**

*Erin Allday*

**Updated 11:40 a.m., Wednesday, August 22, 2012**

Inadequate access to nutritious food is associated with increased hospitalizations and emergency room visits among HIV-positive individuals, and ensuring that patients have enough to eat may need to be a priority for the doctors and nurses who treat them, UCSF researchers say.

In a paper released Wednesday, the scientists reported that 56 percent of HIV-positive patients who are homeless or living in substandard housing are also food insecure, which is defined as a regular inability to obtain enough healthy food. The researchers looked at 347 HIV patients, all of whom live in San Francisco.

The food-insecure patients were roughly twice as likely to have visited the ER or been hospitalized over a given three-month period, compared with patients who had enough to eat, the researchers found. Food insecurity was more likely than homelessness, drug abuse or depression—or just about any measurable problem associated with poverty—to lead to trips to the hospital.

Earlier studies, both in the United States and abroad, have found that food insecurity also is associated with missed doctors' appointments, less suppression of the HIV virus and greater risk of death.

**Strong correlation**

It's not shocking that inaccessibility to food would be tied to poorer health, said Dr. Sheri Weiser, a study author. But she was surprised at how strong the correlation was between not having enough to eat and needing to use health care resources like hospitals and emergency rooms.

"Food insecurity is a negative factor above and beyond other markers of poverty," said Weiser, an assistant professor of medicine in the UCSF HIV/AIDS Division at San Francisco General Hospital. "It is impacting basically every health outcome you could imagine."
The good news is that simply helping patients get food—an idea that seems less daunting than, for example, discovering the antiretroviral drugs used to treat HIV infections, study authors said—could have profound impacts on their health overall.

"If we can do the really hard things, why can't we figure out a way to make sure people get food?" said Dr. Margot Kushel, also a study author and an associate professor in the UCSF Division of Internal Medicine at San Francisco General Hospital. "I feel like, if we can give antiretroviral medications, why shouldn't we also be able to write a prescription for food?"

Kushel and other researchers pointed out that the study, along with earlier reports, doesn't conclusively prove that a lack of food causes poor health in HIV-positive patients.

The study authors found that food insecurity was a factor in poor health even when controlling for other possible risk factors like homelessness or drug abuse. But there still may be something about patients who aren't eating enough that makes them more prone to health problems—meaning, it's not the lack of food that's hurting them, but something related.

**On to the next step**

If a lack of adequate food is to blame for poor health, researchers will want to determine why that is. It could be as simple as missing key vitamins in their diet, or more complicated, like skipping medications that must be taken with a meal.

The authors, along with their peers in HIV research and treatment, said the evidence is strong enough that more research would be useful. The next step may be studying whether, when actually given more food to eat, food-insecure patients have better health outcomes.

"This study to me is really exciting because it raises an issue that many of us in San Francisco don't consider when we're taking care of our patients, which is their access to food," said Dr. Edward Machttinger, director of the Women's HIV Program at UCSF who wasn't involved in the study but has looked at the effects of trauma and post-traumatic stress in HIV patients.

"Whether it's preventing intimate partner violence or getting access to food, ignoring those factors limits our ability to have profound impacts on patients' lives," Machttinger said. "If we are trying to help our patients be healthy and powerful and independent, doing so requires more than simply giving them the medicine."

**Food stamps**

Of note, the authors said, was that only a fifth of participants in the UCSF study took advantage of federal food assistance programs over the course of a year, which means that there's probably room for improvement in either helping patients sign up for the programs or lowering the standards of who can receive aid. About 72 percent of participants received some form of food aid, including federal assistance or food from churches, clinics, food banks or other sources.

San Francisco resident Joey Massey, 43, was diagnosed with HIV four years ago and has since struggled financially, taking graphic design jobs when he's able. He often has a hard time getting enough to eat, even when he takes advantage of the resources available to him. He lost about 50 pounds after his diagnosis and struggles to avoid further weight loss.

"Every day is about consuming as many calories as I can, any way I can," Massey said. "Nausea is a big issue for me, so certain foods are problematic, and things like cereal or yogurt, simple things that would help, are prohibitively expensive.

"It's totally affected my health. I don't feel like I'm able to bounce back as much from stressful situations, from sicknesses," he said. "It's just stressful to wake up and not know how you're going to take care of yourself that day."

**Sexual Agreements in the Partnerships of Internet-Using Men Who Have Sex with Men**

*AIDS Care Vol. 24; No. 10: P. 1255-1263,* (10.,2012) Katherine Gass; and others

Among men who have sex with men (MSM), the majority of HIV transmission results from sex with a main partner, recent studies have shown. The authors noted that one factor likely to influence the risk of transmission is the type of agreements the couple has regarding sexual behavior both within the relationship and outside it.

In the current study, Facebook banner ads were used to recruit 732 MSM who use the Internet. The men completed an online questionnaire regarding demographic characteristics of the respondent, his main partner, their sexual behavior, whether they had a sexual agreement, “and the strength of investment in that agreement.”
The association between sexual agreements (categorized as open, closed or none) and the predictive variables was assessed using the Pearson chi-square test. The sexual agreement investment scale (a composite score of 0 to 52) was used to assess respondents’ investment in their sexual agreement.

Most respondents (91 percent) reported having some form of sexual agreement in place with their main partner. The presence and type of this agreement was strongly associated with many of the characteristics of the individual and the couple, including: the HIV status of the respondent; the length of time with the main partner; having unprotected anal intercourse with a man other than the main partner; and happiness in the relationship. The results indicated that increases in the strength of the respondents’ investment in the sexual agreement were associated with newness of the relationship; happiness in the relationship; having a closed relationship; and decreases in risky sexual behavior.

“This study offers further evidence of the important role that sexual agreements play in male couples,” the authors concluded. “The overwhelming prevalence of sexual agreements and their association with relationship happiness and risky sexual behaviors has important implications for future HIV prevention and control strategies, including the implementation of couples voluntary counseling and testing.”

Microbiologists Find New Approach to Fighting Viral Illnesses
ScienceDaily (Aug. 22, 2012) — By discovering how certain viruses use their host cells to replicate, UC Irvine microbiologists have identified a new approach to the development of universal treatments for viral illnesses such as meningitis, encephalitis, hepatitis and possibly the common cold.

The UCI researchers, working with Dutch colleagues, found that certain RNA viruses hijack a key DNA repair activity of human cells to produce the genetic material necessary for them to multiply.

For many years, scientists have known that viruses rely on functions provided by their host cells to increase their numbers, but the UCI study—led by microbiology & molecular genetics professor Bert Semler—is the first to identify how the RNA-containing picornaviruses utilize a DNA repair enzyme to do so.

Study results appear in the early online edition of the Proceedings of the National Academy of Sciences the week of Aug. 20.

RNA viruses have ribonucleic acid as their genetic material (rather than deoxyribonucleic acid, or DNA). Notable human diseases caused by RNA viruses include SARS, influenza, hepatitis C, West Nile fever, the common cold and poliomyelitis.

The UCI and Dutch researchers examined one group of RNA viruses, called picornaviruses, using biochemical purification methods and confocal microscopy to see how they co-opt the functions of a cellular DNA repair enzyme called TDP2 to advance their replication process.

"These findings are significant because all known picornaviruses harbor the target for this DNA repair enzyme, despite the fact that their genetic material is made up of RNA rather than DNA. Thus, identifying drugs or small molecules that interfere with the interaction between the virus and TDP2 could result in a broad-spectrum treatment for picornaviruses," said Semler, who also directs UCI's Center for Virus Research.

By targeting a host cell function required for viral replication and not the virus itself, he added, the primary challenge of antiviral drug resistance may be sidestepped.

As part of their survival mechanism, RNA viruses mutate often, and drugs intended for them usually become ineffective over time. HIV, for example, rapidly mutates, necessitating a combination therapy employing a number of antiviral agents.

A drug that blocks RNA viruses from hijacking DNA repair enzymes may avoid these resistance issues. Semler’s lab plans to screen mixtures of drug candidates to find ones that inhibit this process in cells infected by the human rhinovirus, the predominant cause of the common cold.

Journal Reference:

Low levels of innate immune activation and high levels of gut antibodies may protect people from HIV
Gus Cairns
Published: 24 August 2012
Several research papers published in the last month have reported strong correlations between specific immune responses and protection against HIV infection or its effects. These include a comparison of
women in the CAPRISA 004 microbicide trial who became infected and ones who did not, despite high exposure to HIV; an analysis of female sex workers in Kenya who similarly seem to be able to resist HIV infection; and a study of immune responses in a group of monkeys given pre-exposure prophylaxis (PrEP) who all became infected but subsequently developed much lower viral loads.

**The hunt for correlates of protection**

One of the most critical aspects of developing an effective vaccine against HIV is to define exactly what constitutes a protective immune response to the virus. Such immune responses could either be associated with protection against infection, so-called sterilising immunity, or protection against disease in people who are infected, so-called functional immunity.

Without reliable and consistent ‘correlates of protection’, developers of vaccines must rely on educated guesses and lucky finds in order to progress towards an effective vaccine.

In this hunt they are hampered by several factors. Animal immune responses do not always mimic human ones; resistance to infection or progression does not seem to be characterised by one type of immune response, but rather different ones in different people; there are a huge number of genetic variants that have to be searched through to find protective ones; and even if a strong correlate of protection is found, it is hard to ‘reverse-engineer’ a vaccine that will produce this response in the body.

**Infected and non-infected women in CAPRISA 004**

One way of looking for correlates of protection is to study so-called ‘highly exposed seronegatives’, people who do not acquire HIV despite frequent contact with it.

In a study that looked at women who took part in the CAPRISA 004 study of a vaginal tenofovir-gel microbicide, the researchers noted that while younger age and genital herpes (HSV-2) infection were both associated with infection with HIV in the study, factors such as the frequency of sex, number of partners and condom use were not, and a large amount of the variation in susceptibility to infection remained unexplained. They therefore compared immune responses to HIV in 44 selected women who became infected (33 on tenofovir gel and 11 on placebo) and 37 women who, despite higher levels of risk behaviour, did not (22 on tenofovir and 15 on placebo).

The infected women were on average younger (mean age 23.3 versus 27.6), but while the non-infected women had sex on average 11 times month, the infected women had it less than six times. These are baseline figures, but did not change during the trial.

The researchers found that women who were infected had higher levels of certain cytokines (immune-modulating chemicals) including TNF-α, IL-2, IL-7 and IL-12. They also found higher platelet counts in the blood of women in the visit immediately before infection compared with non-infected women, even though platelet counts were the same in both groups at baseline. All these factors point to a higher state of immune activation existing in infected women shortly before HIV infection.

When they looked deeper, the researchers found that the cytokine and platelet increases were manifestations of the activation of natural killer (NK) cells, a component of the so-called innate immune system.

Higher animals have three main branches to their immune system. They have the humoral system (antibodies) and the cellular system (T-cells), collectively called the acquired immune system, which are finely tuned to ‘remember’ specific infections and recognise and defeat them again if re-encountered. But we also share with all animals and plants the innate immune system, a less precise but faster response, which recognises general characteristics of infected cells and tissue damage. NK cells are central to this response; they send signals that increase production of broad-spectrum antibodies called immunoglobulins, which recruit acquired immune system cells to sites where the body’s defences are broken. They also stimulate blood platelet production, which prepares the body for wound healing and physically ‘tangles’ bacterial invaders in blood clots.

Women who were infected had higher levels of receptors (cell-surface proteins) called HLA-DR and CD69 on the surface of their NK cells than uninfected women, and lower levels of CD38. In T-cells, high levels of CD38 indicate activation, but in NK cells the reverse applies.

These differences were all significant in themselves, but when all three were lumped together, as composite indicators of innate immune activation or quiescence, they were much more so. In multivariate analysis, women with composite innate immune activation were eleven times more likely to acquire HIV and women with composite immune quiescence 17 times less likely.

In terms of other variables, women on placebo were seven times more likely to acquire HIV than women on tenofovir and HSV-2 positive women 22 times more likely. Women were also 28% less likely to acquire HIV for every year older.
The strength of correlation with particular immune indicators is not only good news in terms of being able to predict who may or may not be vulnerable to HIV infection, but, as the researchers point out, suggests new ways of making new HIV prevention technologies more effective. The researchers point out that the tenofovir-gel microbicide in CAPRISA 004 was only 54% effective even in women who claimed 100% adherence, but if it could be coupled with therapies that dampened down NK-cell activity, many more infections might be prevented.

**Antibody-driven responses in non-infected sex workers**

Meanwhile, a study presented at the recent 19th International AIDS Conference in Washington, of immune responses in highly exposed but uninfected Kenyan female sex workers, found evidence to corroborate a hypothesis already advanced in another paper published this month (see this report). In this paper, evidence from the trial of the first HIV vaccine to show some efficacy, RV144, show that it may have conferred some protection against disease progression in people who acquired HIV as well as some protection against infection. The RV144 researchers suggest that an antibody called immunoglobulin A (IgA), which is produced in large amounts by mucous membranes in the genitals and gut in response to foreign infections, may be responsible for some of this immunity/disease resistance.

Why would an antibody that has no direct effect against HIV produce immunity to it? The answer is that IgA and similar antibodies, like the NK cells that guide their production, congregate wherever there are cells that look as if they have been infected and attach themselves. These attached antibodies then act as ‘flags’ to alert the slower but more potent and precise CD8 cells and HIV-specific antibodies of the acquired immune system to come to the site and either destroy infected cells or neutralise free virus. This process is called antibody-driven cellular cytotoxicity (ADCC) and may be responsible for the somewhat unexpected success of the RV144 vaccine.

In the Kenyan sex workers’ study, researchers from Rush Medical Centre in Chicago studied the ADCC activity, against cells displaying the HIV gp120 envelope protein, of cells taken from cervico-vaginal fluid in ten highly exposed HIV-negative women and two who had acquired HIV. Cells from the non-infected women showed consistently high levels of IgA-driven ADCC activity. In contrast, the cells from the two infected women showed no or low levels of response involving IgA. They did show high levels of response of ADCC driven by another broad spectrum immunoglobulin, IgG, which only appeared several years after infection, though the researchers did not comment on whether this was associated with any kind of viral control.

**Immune responses in monkeys infected on PrEP**

Finally, a study of pre-exposure prophylaxis (PrEP) in monkeys, in which the PrEP regimen failed to prevent infection, nonetheless found that monkeys who were infected on PrEP developed viral loads two logs (one hundred times) lower than monkeys infected while not taking PrEP.

The monkeys infected while on PrEP had low levels of inflammatory cytokines (immune-modulating chemicals) around the time of infection, because their bodies were responding to a much lower peak level of virus in their blood. They also had 100 times the level of CD4 cells in their blood at this point (because there was less HIV destroying cells) and also – in a finding that brings us back to the findings in the CAPRISA study – about half as much interleukin-15 (IL-15), a cytokine that stimulates the activity of natural killer cells.

They also showed no signs of the decimation of gut-associated lymphocytes (white immune cells of all types) that is normally seen around the time of peak viral load in animals and humans who contract HIV, indicating that infection had happened without the long-term immune dysregulation that is normally a legacy of HIV infection.

A series of tests showed that the CD4 and CD8 T-cells in the monkeys given PrEP responded to a broader range of HIV proteins during the period of highest viral load, though this alertness to HIV was not maintained over time – a good thing if the idea is to avoid chronic immune over-activation. The monkeys given PrEP also had fewer chronically activated memory cells and relatively more of the quiescent central-memory cells than those not given PrEP.

Finally, the viral loads in the monkeys given PrEP were no longer suppressed and went up two logs if their CD8 cells were artificially depleted, showing that HIV-specific CD8 cells were playing an important part in viral control.

It is important to note that the blunted viral load seen in monkeys who are infected on PrEP is not a new phenomenon – researchers first saw this in studies published in 2008. So far, however, a similar study of ‘PrEP failures’ in humans had not been published. The kind of virus used in this study also does not exactly mimic HIV, as it is not pathogenic and the infection is eventually contained naturally, even in monkeys not on PrEP. Further studies using viruses more analogous to human ones are taking place.
However this study does clarify the sequence of immune events in animals that are receiving ARVs at the time of infection – as is inevitably likely to happen in some people taking PrEP. The researchers also tried to produce HIV drug resistance in the monkeys by continuing PrEP for several weeks past the date of infection, but no monkey developed drug resistance.

**Conclusions**

What should we make of these varied results? The studies show that the body’s immune response to HIV consists of a complex series of events, and that high levels of activation against HIV may be helpful at one point but harmful at another. It shows that activity in one part of the immune system may need to be coupled with quiescence in another part, if HIV is to be contained. And it shows that immune responses that later become harmful when they become systemic, such as the general level of inflammation provoked by the innate immune system, may in some ways be useful earlier on in infection when concentrated at the specific infection sites.

In general, they show that immune responses in the mucous membranes need to be much more carefully studied, as there is a lot we still do not know about how the body repels or, conversely, embraces HIV.

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**Glucose metabolism worsens in HIV treatment-experienced taking NRTI-sparing regimens**

Michael Carter
Published: 24 August 2012

Italian investigators have found evidence of worsening glucose tolerance in highly treatment-experienced HIV-positive patients treated with nucleoside-sparing regimens. The small study, which is published in the online edition of *AIDS*, monitored the glucose metabolism of 39 patients over three years.

“The drugs included in these regimens have not been specifically associated with worsening of glucose metabolism,” note the authors.

The patients were treated with two alternative combinations: raltegravir (*Isentress*), etravirine (*Intelence*) plus maraviroc (*Celsentri*); or raltegravir, etravirine with ritonavir-boosted darunavir (*Prezista*). A total of fifteen patients (39%) were treated with the maraviroc-containing regimen and 61% received the darunavir/ritonavir-based therapy. All were highly treatment experienced and were switched to these regimens because of virological failure.

The patients had normal fasting glucose levels (below 110 mg/dl) when they switched therapy. Fasting glucose and insulin levels were monitored every three months over three years of treatment. Impaired glucose tolerance was defined as a glucose level above 140 mg/dl, and diabetes as a basal glucose level of 126 mg/dl or a two-hour post-load level of 200 mg/dl.

The patients had an average age of 48 and 84% were men. They had extensive experience of treatment, the average duration being 16 years. All achieved an undetectable viral load after switching treatment, which was also associated with robust increase in CD4 cell counts.

After 156 weeks of treatment, fasting glucose levels had increased significantly (overall, p = 0.002; maraviroc-based treatment, p = 0.007; darunavir/ritonavir-containing therapy, p = 0.029). Insulin levels had also decreased in the darunavir/ritonavir group (p = 0.027).

Impaired glucose tolerance was observed in three patients (8%) and diabetes was diagnosed in five (13%), four of whom were taking maraviroc.

The investigators were surprised by this finding as maraviroc has been “postulated to have a protective effect on at least type-1 DM.”

Older age was the only significant risk factor for the development of impaired glucose tolerance or diabetes (p = 0.003).

However, the investigators also noted there was a significant relationship between increases in CD4 cell count and fasting insulin levels at week 156 (p = 0.018). There was also a relationship which bordered on significance between increase in waist circumference and the development of insulin resistance (p = 0.051).
They therefore conclude that the worsening glucose metabolism observed in their patients “may be a consequence of both antiretroviral drugs and restoration of health.”

Reference

Uninfected Infants May Carry Maternal HIV Antibodies Beyond 18 Months
By Will Boggs, MD
NEW YORK (Reuters Health) Aug 20—A significant percentage of infants born to HIV-infected mothers still have maternal HIV antibodies well beyond 18 months of age, which is the cutoff for the surveillance case definition for HIV infection currently used by the Centers for Disease Control and Prevention (CDC).

This means that HIV antibody tests should not be used to diagnose HIV infection before age two, according to Dr. Mavel Gutierrez from Florida’s University of Miami-Miller School of Medicine.

"Given the finding of delayed clearance of HIV antibodies in perinatally HIV exposed infants, the main concern is that HIV antibodies after 18 months of age may cause confusion among pediatricians causing children to be misclassified as HIV infected when they are not," Dr. Gutierrez told Reuters Health by email.

Dr. Gutierrez and colleagues describe the timing of seroreversion among 744 HIV-exposed uninfected infants born since 2000, as documented by enzyme-linked immunosorbent assay (ELISA).

In just over a third of the infants (273, 36.7%) included in the July 31 Clinical Infectious Diseases online report, antibody loss had occurred by their first ELISA test. The median age of seroreversion was 13.9 months.

A quarter of the infants seroreverted by 12 months, and 75% seroreverted by 16.4 months. More than 1 in 7 infants (14%) remained seropositive after 18 months, 4.3% after 21 months, and 1.2% after 24 months without other evidence of HIV infection.

The higher the IgG values and the higher the IgG rate of change, the earlier the clearance of antibodies took place. Other factors significantly associated with earlier seroreversion were birth by vaginal delivery, lower maternal viral load, and lower maternal CD4 count before delivery.

Maternal exposure to protease inhibitors was associated with later seroreversion.

"Further studies are needed to evaluate why these factors influence time to seroreversion," Dr. Gutierrez said.

"None of these children were infected with HIV," Dr. Gutierrez said. "However, in the case of persistence of antibodies after 18 months of age, the child should be evaluated for other modes of transmission of HIV and retested using virologic tests such as HIV DNA PCR or HIV RNA PCR assays."

"Non-perinatal HIV transmission, although rare, in the first two years of life include premastication of food for the infant by an HIV infected person, sexual abuse, or exposure to contaminated needles," Dr. Gutierrez added.


High levels of maraviroc in rectal tissue fail to protect macaques from SIV transmission following rectal exposure
1 August 2012.

Simon Collins, HIV i-Base
A poster from the group responsible for key animal PK studies looking at tenofovir and/or FTC for PrEP presented a poster with disappointing findings with maraviroc.

These results are important given the investigational use of maraviroc in prevention studies. Despite high levels of penetration in rectal tissue, maraviroc failed to show any impact on the risk of SIV infection.

Results were presented by Garcia-Lerma in an oral poster discussion session from a single dose PK study and a multiple dose SIV exposure study.

The maraviroc PK profile was determined using 12 macaques exposed to a single dose and was similar to human studies, with significantly higher rectal concentrations: peaking at two hours in plasma (median 451 ng/mL) and at 5–48 hours in rectal secretions (median 2,329 ng/mL) and with median AUC0-24 7.5-fold higher (12,720 vs 1,685 ng.hr/mL, respectively). At day 4 maraviroc concentrations in rectal tissue remained more than 20-fold higher than the IC50, and was sufficient to fully occupy CCR5 in PBMCs. The half-life of CCR5-bound MVC in PBMCs was 2.6 days.
The prevention study used a similar design to that used for tenofovir and FTC, dosing 6 macaques with oral maraviroc (44 mg/kg, comparable to the 300 mg human dose) 24 hours prior to rectal exposure and 2 hours post exposure, in a weekly cycle for five weeks, with an additional four macaques as controls.

Despite the strong PK profile there no evidence for prophylactic efficacy: 5/6 treated animals and 3/4 controls became infected over the five weeks. Infections occurred at week 1, 2, 4, 4 and 5 in the animals exposed to maraviroc which were similar to both these and historic controls.

While the study concluded, “that higher doses were needed to see protection” seems optimistic that an effect would necessarily be found, the concern about using a higher than therapeutic dose is likely to limit the interest in further human studies.

Reference:

Drug improves vaccine response in HIV patients
24 Aug 2012

The drug maraviroc could help some vaccines work more effectively in people with HIV infection, according to a study by Imperial College London researchers.

HIV causes a progressive weakening of the immune system, which results in patients responding poorly to vaccinations and becoming increasingly vulnerable to infectious diseases.

Maraviroc is already used in combination with other treatments for HIV as it prevents the virus from entering white blood cells, but now a clinical trial has found that it also enhances the body’s response to immunisation. The findings are published in the journal Molecular Medicine.

Forty-seven patients with HIV were given either maraviroc or a placebo in addition to their normal combination of antiretroviral drugs in a trial at Chelsea and Westminster Hospital, sponsored by St Stephen’s AIDS Trust. The patients were given vaccinations against meningitis, tetanus and cholera, and the researchers measured their biological responses.

After being given an injected meningitis vaccine, the levels of antibodies in the blood rose in the maraviroc group, but did not rise significantly in the placebo group. The maraviroc group also showed an increased response to an HIV protein, unlike the placebo group.

After a tetanus booster, the patients given maraviroc produced an increased amount of interferons – chemical signals that activate immune defences – and their tetanus-specific immune cells began to multiply at an earlier stage than those given a placebo.

Paradoxically, the maraviroc patients, unlike the placebo group, did not respond to the cholera vaccine, which contains killed cholera bacteria and is taken orally. The researchers believe a possible explanation is that the drug resulted in less of the vaccine crossing from the gut into the blood, but further investigation is needed to determine if this was the case.

Dr Samantha Westrop, the study’s first author, from the Department of Medicine at Imperial College London, said: “People with HIV are vulnerable to infectious diseases and they don’t respond as well to vaccinations, so there is interest in how to improve their immune response. The outcomes of our trial using maraviroc were very encouraging and we think as a result clinicians may, in future, be interested in prescribing maraviroc in conjunction with certain vaccines.”

Reference
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Sierra Leone Cholera Outbreak Continues To Spread

"Sierra Leone's health ministry said Thursday that deaths from a cholera outbreak had reached 220, affecting over 12,000 people in the west African nation, which is struggling to curb the disease," Agence France-Presse reports. "Some 12,140 people are affected nationwide in 10 of 12 districts,' the health ministry's director of disease prevention and control, Amara Jambai, told journalists, saying the figure included cases recorded up to Wednesday," the news service writes (8/23). "Early rains together with increasing overcrowding in cities such as the Sierra Leonian capital Freetown have pushed the number of reported cases ... well past the previous record of 10,000 in 1994," Reuters notes.

"Sierra Leone’s worst recorded outbreak of cholera risks sparking a wider health crisis unless its causes can be tackled more aggressively, the International Federation of Red Cross and Red Crescent Societies (IFRC) said on Thursday," the news service writes, adding, "The death toll in Sierra Leone is likely to rise further in coming weeks towards the late-September peak of the rainy season" (Akam, 8/23).
"The water-borne disease is also sweeping through neighboring Guinea and has been recorded in other countries in West Africa," AFP notes in a separate video report (8/23). "Some 82 deaths have been reported in neighboring Guinea, while other cases have been seen in Mali and Niger," according to the Associated Press/Seattle Times (8/23).

**Bushmeat Blamed For Ebola Outbreak In DRC**
"Health officials in the Democratic Republic of Congo's north-eastern Orientale Province are urging the population to desist from activities that could put them at risk of contracting the Ebola virus, including contact with infected individuals and the consumption of bushmeat," IRIN reports. "Ebola virus is an animal disease ... people in some parts of our country rely on bushmeat for their livelihood ... and don't care to avoid eating meat they've got from dead animals that they often find in the bush,' said Mondoge Vitale, head of disease control at WHO's Kinshasa office," according to the news service. "The health ministry has established national- and district-level taskforces and is working with partners, including the [non-governmental organization] Medecins sans Frontieres (MSF), the United States Centers for Disease Control and Prevention (CDC), the U.N. Children's Fund (UNICEF) and WHO," the news service notes, adding, "At least 10 people in the province had died from suspected Ebola by 20 August, according to the [WHO]," the news service writes. (8/23).

**Despite Controversy, WHO Not Likely To Change Its Stance On Misoprostol Use**
Highlighting a recent report by the Journal of the Royal Society of Medicine about the use of the drug misoprostol to prevent postpartum hemorrhage and the WHO's inclusion of the drug on its Essential Medicine List, Guardian health editor Sarah Boseley writes in this post in her "Global Health Blog," "Seldom has there been a drug that has excited as much controversy as misoprostol." She continues, "Misoprostol causes the uterus to contract, which is why it can stop postpartum hemorrhage, the cause of around a quarter of maternal deaths," but "there has been a huge fight over whether and how well it works, which in some quarters has been ideologically motivated, because misoprostol can also bring about an abortion."

Boseley presents a number of arguments from both sides of the debate. She notes ":[t]he International Federation of Gynaecology and Obstetrics recommends the use of misoprostol for prevention and treatment of postpartum hemorrhage and is part of a [Bill & Melinda Gates Foundation]-funded initiative to bring about wider distribution of the tablets," and concludes, "It will be surprising if the WHO changes its stance at the next meeting to discuss the essential medicines list, early next year" (8/23).

**International Community Must Address MSM Population In Order To End AIDS Epidemic**
"Over the 30 years of the AIDS epidemic, the disease has had a profound impact on every country in the world," and "in each country, that impact is experienced a different way," Vivek Anand, CEO of the Humsafar Trust, and Kenneth Mayer, medical research director of Fenway Health and co-director of the Fenway Institute, write in this post in Huffington Post's "Gay Voices" blog. "But one reality remains: In nearly every country, HIV rates are disproportionately high in gay and bisexual men, as well as men who have sex with men (MSM) who do not identify as either," they continue, adding, "The full scope of the epidemic simply cannot be addressed until we recognize that there is no country in the world where we can overlook the MSM population."

"Unfortunately, the scope of the epidemic has often been poorly understood, or left undiscussed, by those dedicated to HIV prevention," they write, noting, "Too often, their portrait of those at risk of HIV splits into a false dichotomy: Caucasian gay men, bisexual men, and MSM in wealthier countries, with the disease being a heterosexual epidemic in lower-income nations." They continue, "MSM are not only a at-risk population in wealthier countries but are present in every country in the world." They discuss the work of their respective organizations and conclude, "We have a long way to go in combating the stigma that drives many MSM and transgender people to engage in unsafe sexual practices, but we are reaching them. ... We cannot end this epidemic if we ignore any at-risk population" (8/23).

**'Naked Darth Vader' approach could tame antibiotic resistant superbugs**
Breakthrough offers completely new way to fight bacterial infections
Rather than trying to kill bacteria outright with drugs, Université de Montréal researchers have discovered a way to disarm bacteria that may allow the body's own defense mechanisms to destroy them.
"To understand this strategy one could imagine harmful bacteria being like Darth Vader, and the anti-virulence drug would take away his armor and lightsaber," explained Dr. Christian Baron, the study's lead author and Professor at the Department of Biochemistry. "A naked Darth Vader would be an easy target and similarly, pathogenic bacteria without their virulence factors would be rendered harmless and eliminated by our immune system." Virulence factors are what make certain bacteria harmful to our bodies and different from most bacteria that live on our body or inside the intestinal system, which are harmless or even useful for us. Baron's research group will publish an article outlining the details of their findings tomorrow in Chemistry & Biology.

Infectious diseases caused by pathogenic bacteria were a major scourge of mankind, but thanks to the introduction of antibiotics beginning in the middle of the 20th century, most bacterial infections were largely controlled. It was a widely held belief that biomedical research had largely won the battle against these diseases. However, as antibiotics kill by targeting the essential cell functions of most (not always all) bacteria, this leads to survival of the most adaptable. "Bacteria have the capacity to develop resistance to antibiotics and they transfer this capacity to their offspring and to other bacteria. As a consequence, resistance began to emerge among the bacteria soon after the introduction of antibiotics," Baron said. In their worst forms, "superbugs" have emerged, those resistant to all but a few or even to all antibiotics."

Baron's team has discovered small molecules that target proteins in a biological system (a type IV secretion system) that is required for many bacteria to be harmful. "As if we were pulling on a loose thread in Darth Vader's cape, we have found a way to unravel the molecular details of the binding of these molecules to a target protein known as VirB8, a key part of the virulence mechanism of human and animal pathogenic Brucella species of bacteria," Baron explained. This strategy has many advantages since resistance to such treatments would likely be slow or might not even occur. Virulent bacteria could be rendered as harmless as those that live in our gut.

The concept of anti-virulence drugs still has to be proven in the clinic, but in the new battles that will arise in our war on bacteria, such drugs could prove formidable new weapons.

Changing epidemiology of rare disease links sinus irrigation with contaminated tap water, 2 deaths
Cases highlight importance of using appropriately treated water for nasal irrigation
[EMBARGOED FOR AUG. 23, 2012] When water containing the Naegleria fowleri ameba, a single-celled organism, enters the nose, the organisms may migrate to the brain, causing primary amebic meningoencephalitis, a very rare—but usually fatal—disease. A new study published in Clinical Infectious Diseases describes the first reported cases in the United States implicating nasal irrigation using disinfected tap water in these infections. Now available online, the study highlights the changing epidemiology of this uncommon disease, as well as the importance of using appropriately treated water for nasal irrigation.

From 2002 to 2011, 32 N. fowleri infections were reported in the U.S., according to the Centers for Disease Control and Prevention (CDC). In this latest study, Jonathan Yoder, MPH, coordinator of waterborne diseases and outbreak surveillance at CDC, reports the work of the Louisiana Department of Health and Hospitals and CDC in investigating two cases in 2011 in Louisiana. Two unrelated patients, a 28-year-old man and a 51-year-old woman, each died within five days of being admitted to the hospital with meningitis-like symptoms. Both had used a neti pot for regular sinus irrigation. Because family members of both patients were certain the patients had no recent history of recreational freshwater contact, which is typically associated with the disease, sinus irrigation using disinfected (chloraminated) tap water was implicated.

"N. fowleri was found in water samples from both homes," Yoder said, but "not found in the treatment plants or distribution systems of the municipal water systems servicing the patients' homes." Although it was never clear how N. fowleri were introduced into the plumbing of the patients' houses, once there, the organisms were able to colonize the hot water systems.

In addition, Yoder's team also tested commercially available reconstituted salt packets for use with neti pots and found that these were unable to reduce the number of N. fowleri organisms within a four-hour timeframe—far outside the real world conditions of less than a minute that most people spend—showing that simply adding salt mixtures to tap water does not inactivate the organisms fast enough. As a result, Yoder advises that the simplest methods to avoid infection is to purchase water that is labeled as distilled or sterile, or use only water that was previously boiled for 1 minute (at elevations above 6,500
feet, boil for 3 minutes) that has been left to cool, or use water that has gone through a filter with a pore size of 1 micron or smaller.

Many infections from *N. fowleri* occur in warm freshwater locations following localized heat waves. Whether projected climate change could lead to an expansion of the ameba’s geographic range is unknown, the authors noted. They recommend that systematic environmental sampling be carried out to document changes in the ecology of *N. fowleri* so that measures to prevent its spread can be improved. It is also important to raise the level of awareness about the disease among physicians treating patients with meningitis-like symptoms, the authors wrote.

Deaths from *N. fowleri* infection, which remain very rare, "are tragic for the families of those infected," Yoder said. "The CDC is working to understand this organism so that we can improve prevention recommendations, identify *N. fowleri* infections, and improve clinical treatment."

**Fast Facts**

1. Primary amebic meningoencephalitis is a very rare but usually fatal disease caused when water containing *Naegleria fowleri* amebae enters the nose, allowing the single-celled organisms to migrate to the brain.
2. In 2011, two fatal cases of the disease reported from Louisiana occurred in persons following nasal irrigation. This is the first time that contaminated tap water coming from a disinfected municipal water system has been linked to *N. fowleri* infections in the United States.
3. For prevention, health officials advise using only previously boiled, filtered, distilled, or sterilized water when making solutions for irrigating, flushing, or rinsing the sinuses.

**Gene 'switch' may explain DiGeorge syndrome severity**

The discovery of a ‘switch’ that modifies a gene known to be essential for normal heart development could explain variations in the severity of birth defects in children with DiGeorge syndrome.

Researchers from the Walter and Eliza Hall Institute made the discovery while investigating foetal development in an animal model of DiGeorge syndrome. DiGeorge syndrome affects approximately one in 4000 babies.

Dr Anne Voss and Dr Tim Thomas led the study, with colleagues from the institute’s Development and Cancer division, published today in the journal *Developmental Cell*.

Dr Voss said babies with DiGeorge syndrome have a characteristic DNA mutation on chromosome 22 (22q11 – chromosome 22, long arm, band 11), but exhibit a range of mild to severe birth defects, including heart and aorta defects. "The variation in symptoms is so prominent that even identical twins, with the exact same DNA sequence, can have remarkably different conditions," she said. "We hypothesised that environmental factors were probably responsible for the variation, via changes to the way in which genetic material is packaged in the chromatin," Dr Voss said.

Chromatin is the genetic material that comprises DNA and associated proteins packaged together in the cell nucleus. Chemical marks that sit on the chromatin modify it to instruct when and where to switch genes on or off, making a profound difference to normal development and cellular processes.

The research team found a protein called MOZ, the ‘switch’ which is involved in chromatin modification, was a key to explaining the range of defects seen in an animal model of DiGeorge syndrome. "MOZ is what we call an chromatin modifier, which means it is responsible for making marks on the chromatin that tell genes to switch on or off," Dr Voss said.

"In this study, we showed that MOZ regulates the major gene, called Tbx1, in the 22q11 deletion. Tbx1 is responsible for heart and aortic arch development. In mouse models that have no Moz gene, Tbx1 does not work properly, and the embryos have similar heart and aorta defects to those seen in children with DiGeorge syndrome. We showed that MOZ is crucial for normal activity of Tbx1, and the level of MOZ activity may contribute to determining how severe the defects are in children with DiGeorge syndrome," Dr Voss said.

Dr Voss said the study also showed that the severity of birth defects in DiGeorge syndrome could be compounded by the mother’s diet, particularly if the MOZ switch is not working properly. The research team showed that reduced MOZ activity could conspire with excess retinoic acid (a type of vitamin A) to markedly increase the frequency and severity of DiGeorge syndrome.

"In our mouse model, we saw that retinoic acid exacerbated the defects seen in mice with mutations in the Moz gene. In fact, in mice that had one normal copy of MOZ and one mutated copy, the offspring look completely normal, but if the mother’s diet was high in vitamin A, the offspring developed a
DiGeorge-like syndrome. This suggests that MOZ, when coupled with a diet high in vitamin A (retinoic acid), may play a role in the development of DiGeorge syndrome in some cases.

"This interaction between the chromatin modifier MOZ, the Tbx1 gene, and retinoic acid in the diet gives a rare insight of how the environment and genetic mutations can interact at the chromatin level to cause birth defects."

More Clues About Why Chimps and Humans Are Genetically Different
Posted August 23, 2012 Atlanta, GA
Ninety-six percent of a chimpanzee’s genome is the same as a human’s. It’s the other 4 percent, and the vast differences, that pique the interest of Georgia Tech’s Soojin Yi. For instance, why do humans have a high risk of cancer, even though chimps rarely develop the disease?

In research published in September’s American Journal of Human Genetics, Yi looked at brain samples of each species. She found that differences in certain DNA modifications, called methylation, may contribute to phenotypic changes. The results also hint that DNA methylation plays an important role for some disease-related phenotypes in humans, including cancer and autism.

“Our study indicates that certain human diseases may have evolutionary epigenetic origins,” says Yi, a faculty member in the School of Biology. “Such findings, in the long term, may help to develop better therapeutic targets or means for some human diseases."

DNA methylation modifies gene expression but doesn’t change a cell’s genetic information. To understand how it differs between the two species, Yi and her research team generated genome-wide methylation maps of the prefrontal cortex of multiple humans and chimps. They found hundreds of genes that exhibit significantly lower levels of methylation in the human brain than in the chimpanzee brain. Most of them were promoters involved with protein binding and cellular metabolic processes.

“This list of genes includes disproportionately high numbers of those related to diseases,” said Yi. “They are linked to autism, neural-tube defects and alcohol and other chemical dependencies. This suggests that methylation differences between the species might have significant functional consequences. They also might be linked to the evolution of our vulnerability to certain diseases, including cancer.”

Virus detector harnesses ring of light in ‘whispering gallery mode’
By affixing nanoscale gold spheres onto a microscopic bead of glass, researchers have created a super-sensor that can detect even single samples of the smallest known viruses. The sensor uses a peculiar behavior of light known as "whispering gallery mode," named after the famous circular gallery in St. Paul’s Cathedral in London, where a whisper near the wall can be heard around the gallery.

In a similar way, waves of light are sent whirling around the inside of a small glass bead, resonating at a specific frequency. Just as a small object on a vibrating violin string can change its frequency – ever so slightly – so too can a virus landing on the sensor change the resonant frequency of the light.

With the initial glass sphere, researchers were able to detect changes in frequency from viruses about the size of influenza, a relatively large virus. The system, however, was not sensitive enough to detect anything smaller, such as the Polio virus.

The researchers were able to increase the sensitivity of the device nearly seventyfold by adding gold nanospheres to the surface of the glass, which created what the researchers referred to as "plasmonic hot spots" – areas where the light waves coupled with waves of electrons. This hybrid sensor not only detected the presence of the MS2 virus – the current light-weight in the world of RNA viruses – it also was able to determine the weight of the virus by measuring the precise frequency change of the light. With a few minor adjustments, the sensor should also be able to detect single proteins, such as cancer markers that appear in the blood long before outward signs of cancer can be detected.

The results were published in the American Institute of Physics (AIP) journal Applied Physics Letters. Article: "Taking whispering gallery-mode single virus detection and sizing to the limit" is published in Applied Physics Letters.
Link: http://apl.aip.org/resource/1/applab/v101/i4/p043704_s1

University of Minnesota engineering researchers discover new non-invasive method for diagnosing epilepsy
Findings could help millions of people who are unable to control seizures
Contacts: Matt Hodson, University News Service, mjhodson@umn.edu, (612) 625-0552, Rhonda Zurn, College of Science and Engineering, rzurn@umn.edu, (612) 626-7959
A team of University of Minnesota biomedical engineers and researchers from Mayo Clinic published a groundbreaking study today that outlines how a new type of non-invasive brain scan taken immediately after a seizure gives additional insight into possible causes and treatments for epilepsy patients. The new findings could specifically benefit millions of people who are unable to control their epilepsy with medication. The research was published online today in Brain, a leading international journal of neurology.

The study’s findings include:

- Important data about brain function can be gathered through non-invasive methods, not only during a seizure, but immediately after a seizure.
- The frontal lobe of the brain is most involved in severe seizures.
- Seizures in the temporal lobe are most common among adults. The new technique used in the study will help determine the side of the brain where the seizures originate.

“This is the first-ever study where new non-invasive methods were used to study patients after a seizure instead of during a seizure,” said Bin He, a biomedical engineering professor in the University of Minnesota’s College of Science and Engineering and senior author of the study. “It’s really a paradigm shift for research in epilepsy.”

Epilepsy affects nearly 3 million Americans and 50 million people worldwide. While medications and other treatments help many people of all ages who live with epilepsy, about 1 million people in the U.S. and 17 million people worldwide continue to have seizures that can severely limit their lives.

The biggest challenge for medical researchers is to locate the part of the brain responsible for the seizures to determine possible treatments. In the past, most research has focused on studying patients while they were having a seizure, or what is technically known as the “ictal” phase of a seizure. Some of these studies involved invasive methods such as surgery to collect data.

In the new study, researchers from the University of Minnesota and Mayo Clinic used a novel approach by studying the brains of 28 patients immediately after seizures, or what is technically known as the “postictal” phase of a seizure. They used a specialized type of non-invasive EEG with 76 electrodes attached to the scalp for gathering data in contrast to most previous research that used 32 electrodes. The researchers used specialized imaging technology to gather data about the patient. The findings may lead to innovative means of locating the brain regions responsible for seizures in individual patients using non-invasive strategies.

“The imaging technology that we developed here at the University of Minnesota allowed us to tackle this research and gather several thousand data points that helped us determine our findings,” He said. “The technical innovation was a big part of what helped us make this discovery.”

He, who was recently appointed the director of the University of Minnesota’s Institute for Engineering in Medicine, said this study was also a good example of a true partnership between engineering and medicine to further medical research.

“The innovations in engineering combined with collaborations with clinicians at Mayo Clinic made this research a reality,” He said.

To read the full research paper in Brain, visit http://z.umn.edu/brain.

Human Lungs Brush out Intruders

ScienceDaily (Aug. 23, 2012) — A runny nose and a wet cough caused by a cold or an allergy may not feel very good. But human airways rely on sticky mucus to expel foreign matter, including toxic and infectious agents, from the body.

Now, a study by Brian Button and colleagues from the University of North Carolina at Chapel Hill, NC, helps to explain how human airways clear such mucus out of the lungs. The findings may give
researchers a better understanding of what goes wrong in many human lung diseases, such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma.

The researchers' report appears in the 24 August issue of the journal Science.

"The air we breathe isn't exactly clean, and we take in many dangerous elements with every breath," explains Michael Rubinstein, a co-author of the Science report. "We need a mechanism to remove all the junk we breathe in, and the way it's done is with a very sticky gel called mucus that catches these particles and removes them with the help of tiny cilia."

"The cilia are constantly beating, even while we sleep," he says. "In a coordinated fashion, they push mucus containing foreign objects out of the lungs, and we either swallow it or spit it out. These cilia even beat for a few hours after we die. If they stopped, we'd be flooded with mucus that provides a fertile breeding ground for bacteria."

Until now, most researchers have subscribed to a "gel-on-liquid" model of mucus clearance, in which a watery "periciliary" layer acts as a lubricant and separates mucus from epithelial cells that line human airways. But this old explanation fails to explain how mucus remains in its own distinct layer.

"We can't have a watery layer separating sticky mucus from our cells because there is an osmotic pressure in the mucus that causes it to expand in water," Rubinstein says. "So what is really keeping the mucus from sticking to our cells?"

The researchers used a combination of imaging techniques to observe a dense meshwork in the periciliary layer of human bronchial epithelial cell cultures. The brush-like layer consists of protective molecules that keep sticky mucus from reaching the cilia and epithelial cells, thus ensuring the normal flow of mucus.

Based on their findings, Button and the other researchers propose a "gel-on-brush" form of mucus clearance in which mucus moves atop a brush-like periciliary layer instead of a watery one. They suggest that this mechanism captures the physics of human mucus clearance more accurately.

"This layer—this brush—seems to be very important for the healthy functioning of human airways," according to Rubinstein. "It protects cells from sticky mucus, and it creates a second barrier of defense in case viruses or bacteria penetrate through the mucus. They would not penetrate through the brush layer because the brush is denser."

"We found that there is a specific condition, below which the brush is healthy and cells are happy," Rubinstein explains. "But above this ideal condition, in diseases like CF or COPD, the brush becomes compressed and actually prevents the normal cilia beating and healthy flow of mucus."

The researchers explain that, whenever the mucus layer gets too dense, it can crash through the periciliary brush, collapse the cilia and stick to the cell surface.

"The collapse of this brush is what can lead to immobile mucus and result in infection, inflammation and eventually the destruction of lung tissue and the loss of lung function," says Rubinstein. "But our new model should guide researchers to develop novel therapies to treat lung diseases and provide them with biomarkers to track the effectiveness of those therapies."

Journal Reference:

New Strain of Hand, Foot and Mouth Virus Worries Parents, Pediatricians
ScienceDaily (Aug. 24, 2012) — Your child goes to bed in perfect health. The next morning she wakes up with high fever, malaise and bright red blisters erupting all over her body. Johns Hopkins Children's Center dermatologists say the disturbing scenario has become quite common in the last few months, sending scared parents to their pediatrician's office or straight to the emergency room.

Bernard Cohen, M.D., director of pediatric dermatology at Johns Hopkins Children’s Center, and colleague Kate Puttgen, M.D., have seen or consulted on close to 50 such cases in the last few months and have received countless phone calls from scared parents and concerned physicians. Cohen believes this number may be just the tip of the iceberg with primary care pediatricians seeing the bulk of new cases.

Cohen and Puttgen want to reassure parents that most cases of the disease are benign and that nearly all patients recover in seven to 10 days without treatment and without serious complications.

"What we are seeing is relatively common viral illness called hand-foot-and-mouth disease but with a new twist," Cohen says.
The culprit is an unusual strain of the common coxsackie virus that usually causes the disease. The new strain, coxsackie A6, previously found only in Africa and Asia, is now cropping up all over the United States.

The coxsackie virus strikes infants and children under age 5 in the summer and autumn months. Symptoms include fever and malaise and, a day or two later, a non-itchy skin rash with flat or raised red spots on the hands and feet and/or mouth sores. The new strain, however, behaves somewhat differently from its homegrown cousin, Cohen says. It carries a slightly higher risk for more serious illness and more widespread rash that can involve the arms, legs, face and diaper area. The new strain also seems to affect older as well as younger children.

"We've talked with many of our pediatric dermatology colleagues around the country and the number of cases and the severity of the rash is clearly new and different from the typical hand, foot and mouth disease we are used to seeing," adds Puttgen. "The good news is that it looks bad but hasn't actually caused severe symptoms for our patients."

The new virus can also cause a rash that mimics lesions of herpes simplex virus, which requires treatment with antivirals.

"It can look like disseminated herpes simplex, and parents may panic if they don't know what it is," Cohen says. "But unlike herpes simplex, this rash evolves very fast. It's bad for a few days and then gets better very quickly without any treatment at all."

To reduce the spread of the virus, Cohen and Puttgen advise frequent hand washing and good general hygiene. Pediatricians need not refer patients to a specialist if they recognize the rash for what it is and if the child is otherwise healthy, they say. "If the child has low-grade fever, but is otherwise well, waiting and watching is appropriate," Cohen says. "If the child is having problems with feeding or drinking or acting ill, it's time to call the doctor." Specifically, Cohen says, children with immune deficiencies, cancer or other serious illness should be followed closely by their pediatrician to avoid or promptly treat any complications.

Atazanavir/ritonavir more likely to cause kidney stones than other ritonavir-boosted protease inhibitors

Michael Carter
Published: 29 August 2012

Treatment with ritonavir-boosted atazanavir is associated with a much higher risk of kidney stones compared to other ritonavir-boosted protease inhibitors, Japanese investigators report in the online edition of the Journal of Acquired Immune Deficiency Syndromes. There was also a high recurrence rate of kidney stones in people who continued to take atazanavir/ritonavir.

“With the incidence of renal stones in patients on ATV/r [atazanavir/ritonavir] was approximately 10 times higher than those on other PIs [protease inhibitors],” comment the investigators. “Replacement of ATV/r with other drugs should be considered in patients diagnosed with renal stones to prevent further deterioration in renal function.”

Ritonavir-boosted atazanavir (Reyataz) is among the drugs recommended for first-line antiretroviral therapy. Taken once daily, it has a potent anti-HIV effect and a mild side-effect profile.

Nevertheless, there is some evidence that therapy with the drug may increase the risk of kidney stones. Despite this, relatively little is known about the incidence of this side-effect in people treated with atazanavir/ritonavir compared to other ritonavir-boosted protease inhibitors.

Investigators in Tokyo therefore designed a retrospective study involving 1240 people who were treated with antiretroviral therapy based on a ritonavir-boosted protease inhibitor between 2004 and 2010.

Just over a third (38%) of the people in the study received atazanavir/ritonavir.

Kidney stones were diagnosed in a total of 35 people, 31 of whom were taking atazanavir/ritonavir. This meant that 7% of people in the study who were treated with atazanavir/ritonavir developed kidney stones, compared to 0.5% in people taking other ritonavir-boosted protease inhibitors.

The incidence of kidney stones was 24 per 1000 person years in the atazanavir/ritonavir group. This compared to just 2 per 1000 person years in the people taking another boosted protease inhibitor.

The authors’ first statistical analysis showed that atazanavir/ritonavir was associated with a tenfold increase in the risk of kidney stones (HR = 10.44; 95% CI, 3.68-29.59; p < 0.001).

This association was largely unchanged after taking into account factors such as age, gender, weight and other risk factors for kidney stones (HR = 10.08; 95% CI, 3.48-29.17; 0 < 0.001).
Treatment with atazanavir has been associated with a non-dangerous increase in bilirubin. However, there was no association between this and the risk of kidney stones.

A total of 18 people continued to take atazanavir/ritonavir after the diagnosis of kidney stones. There was a recurrence of renal stones in six of them. This occurred a median of five months after the first diagnosis.

Kidney function (measured by eGFR) declined more significantly in people with kidney stones than in people who did not develop this complication (p < 0.001).

Indeed, the investigators note “the development of renal stone is a risk factor for CKD [chronic kidney disease].” They caution “the high incidence of renal stone with ATV/r use may in part contribute to ATV/r being a risk for CKD. Thus, ATV/r should be carefully introduced in patients with concomitant predisposing risk factors for CKD.” The authors speculate that the high incidence of kidney stones in the atazanavir/ritonavir-treated people could be because the drug is partly excreted in urine.

They conclude, “ATV/r use was an independent risk factor for renal stones in a robust statistical model.”

Reference

Quad approved in US: exorbitant cost likely to block use in Europe

Stri-bild: strive to build profit
Simon Collins, HIV i-Base
On 27 August 2012, both the US Food and Drug Administration (FDA) and Gilead Sciences issued news releases confirming the approval for Quad, a new 4-in-1 combination pill. [1, 2]

But the expected welcome for an important new option for treatment has been firmly squashed by the indication that Gilead plan to market Quad at a price that will exclude access for most HIV positive patients in Europe.

So August 27 is more likely to be remembered for a day when HIV care become more decisively divided in Western countries between those who can pay and those who cannot. Quad is to be launched in the US at a 36% hiked increase over current market leader Atripla, which is incidentally also marketed by Gilead. The trade name for Quad is Stri-bild: perhaps truncated from Strive to Build Profit.

While drug pricing can be complex, a similar price differential launched in Europe, and certainly in the UK, would see Quad placed squarely on the top shelf, where it could perhaps be seen, but would be well out of the reach for all but the wealthiest citizens or health care providers. It is a move that will make it unlikely to find its way into the bloodstream of patients, where it might have been able to demonstrate its marginal level of non-inferiority compared to current options: a non significant 4% difference in the percentage of patients with undetectable viral load after 48 weeks of treatment. While Quad offers potential advantages in care, these were not demonstrated in the clinical trials that led to approval based on finding it is “not likely to be worse” than current treatment. Without demonstrable advantages, public health care providers, including the NHS, are likely to find it difficult to make a case for its routine use.

The annual wholesale list price for Quad is expected to be close to $28,500, which compares to $21,000 for Atripla. Although Atripla is one of the most widely prescribed combinations, use of this 3-in-1 tablet is likely to change as the patent comes to an end for one of its component drugs. When this occurs in 2013, the economic pressure on public health systems is likely to lead to switching to prescribing the individual drugs as separate pills. Unless Gilead reduces their price for Atripla to match the new market, the shift to effective generic alternatives will save the NHS millions of pounds annually. Health care systems in the US are predicting similar changes: with a potential to save close to $900 million if a similar policy to switch to generic versions of efavirenz and 3TC was adopted. [3]

New drugs are commonly marketed at a higher price than existing treatments. This is usually justified by a company to cover their research investment and to recognise qualitative benefits from a demonstrably more effective medicine. As many early HIV medicines come to the end of their patent life, the sustainability of this model is in question, especially for health care systems that are already creaking under the burgeoning role of universal care. A more realistic model – and a long standing activist demand – is for new drugs to be comparable to existing options, and a company should benefit from increased
profits based on widespread use of better medicines, not from excessive profits derived from a much smaller number of patients paying exorbitant prices. Health care should not be based on exclusive branding like cars or mobile phone technology.

The strategic decision to price Quad beyond the reach of most people threatens to undermine Gilead’s reputation with doctors, researchers, patients and ultimately shareholders. The easiest way to recoup investment costs for development of a new drug is to price it at a level where it will be widely used. The underlying greed from the current proposed price will make it impossible for activists to argue for patient choice when scarce funding is merely being diverted to pharmaceutical profits. Ultimately, from 27 August onwards, most people in Europe are likely to continue on existing treatments only, and new approvals will become only aspirational care, lanquishing underutilised until their patent expires, just after the announcement of a cure.

The missed opportunity by Gilead to market their newest approval at an affordable price for Western markets casts a dark shadow over their remaining development pipeline which includes several other single and reduced pill formulations, including to the new integrase inhibitor (elvitegravir) and a booster drug called cobicistat (both included in Quad). This short-sighted decision, unless reversed, jeopardises patient care far more seriously than any other drug price launch in the last ten years. [4]

It may also miss its window of opportunity for the optimum time to increase use. Another single-pill integrase combination based on the integrase compound dolutegravir is already advanced in studies, though if joint developers Shionogi/ViiV follow a similar pricing strategy it will also become difficult to use. Ultimately patients lose out. Current treatments are effective but also far from perfect. Atripla, despite elevation in clinical guidelines is difficult to tolerate for 20 percent of patients, with rare side effects including an increased rate of suicide. This is not a reason to premium price Quad though, but it is an indication of the size of an unmet medical demand. New treatments are needed but subtle differences seen in studies will not persuade the NHS to pay for them.

Last month Gilead posted second quarter financial results that include antiviral product sales of over $2 billion in this three month period and that this was a 14 percent increase compared to 2011. This included a 10% increase for Atripla taking sales during the period to over $900 million, a 10% increase for Truvada (the combination of tenofovir and FTC, also included in both Atripla and Quad) to over $785 million and a 16% increase for tenofovir with sales over $215 million. [5]

The increased use of all medicines were driven by greater increases in the US compared to Europe, where sales for tenofovir actually fell by 2% – an indication that a switch to competitively priced but less expensive alternatives is already taking place.

The FDA’s own press release for approval of Quad was somewhat ominously prescient in announcing “FDA approves new combination pill for HIV treatment for some patients”, where “some” could be interpreted as a euphemism for “exclusively wealthy”.

Requests for comment from Gilead are currently unanswered.

Quad is a formulation of four compounds, all developed by Gilead: elvitegravir, cobicistat, tenofovir and FTC. It is a once-daily treatment, and can be taken with or without caviar.

Atripla is a formulation of three compounds: efavirenz, tenofovir and FTC. It is marketed by Gilead and Bristol-Myers Squibb.

References
4. See the i-Base/TAG pipeline report published in July 2012 for a recent review of HIV compounds in development and a discussion drug pricing. http://i-base.info/htb/16882

A Pill that Treats and Tells
Reuters, (08.27.2012) Esha Dey

Sensors small enough to be placed in patients’ medications are being tested as a means to provide digital feedback about patient adherence to drug-taking regimens. This new technology will be pilot tested in China for treating TB.
About the size of a salt grain, the sensor is activated when it gets wet from stomach juices, completing a circuit that generates a tiny voltage. The sensor has no battery or antenna. Digital data from the sensor, recorded by a skin patch worn on the torso, can be sent to a phone or computer. The data can then be viewed on a computer network by patients, caregivers, and physicians. The technology, devised by Redwood City, Calif.-based Proteus Digital Health Inc., was approved last month by the Food and Drug Administration.

“Overall, people only take their medications half of the time ... adherence is a really big issue across all treatments,” said Eric Topol, chief academic officer of Scripps Health, a nonprofit medical service provider.

Proteus has partnered with the Bill & Melinda Gates Foundation and China’s Center for Disease Control to test the technology for TB treatment. With the help of a $560,000 Gates Foundation grant, Proteus will test the sensors in Chinese TB patients. Treatment for TB can have unpleasant side effects, leading some patients to drop out of treatment and place others at risk.

Health experts question whether patients will accept the monitoring system. “People may not want to wear the patch and have the medications because they might feel like big brother is watching,” Topol conceded.

“The point of this technology is not to say you are being a bad patient. The point is to have accurate data,” said George Savage, Proteus’ chief medical officer and co-founder.

Is There an Association Between Maternal Pap Test Use and Adolescent Human Papillomavirus Vaccination?

*Journal of Adolescent Health* doi:10.1016/j.jadohealth.2012.05.015, (08.03.2012) Shannon M Monnat, PhD; Sherrie Flynt Wallington, PhD

In the current study, the authors sought to “identify the association between mother’s recent receipt of a Pap test and daughter’s update and completion of the three-shot human papillomavirus (HPV) vaccination series.”

Cross-sectional data for the study came from the 2008 to 2010 Behavioral Risk Factor Surveillance System in nine US states and Puerto Rico. Logistic regression models examined the association between mother’s Pap test in the past three years and daughter’s uptake and completion of the HPV series among girls ages nine to 17 (n=4,776).

Roughly one-quarter of the girls started the three-shot HPV vaccine series, and 13.6 percent completed it. Uptake and completion were more likely among girls whose mothers had had a Pap test within the previous three years—for HPV uptake, odds ratio: 1.342, 95 percent confidence interval: 1.073-1.692; for HPV completion, OR: 1.904; 95 percent CI: 1.372-2.721. However, the relationship between mother’s recent Pap test and vaccine uptake was explained by the mother’s use of a personal doctor and receiving a routine physical examination in the past year.

“HPV vaccination uptake and completion were more likely among adolescent girls whose mother obtained a recent Pap test. Interventions designed to educate mothers on the importance of HPV vaccination and to facilitate relationships between physicians and mothers may prove successful at increasing HPV vaccination among adolescent girls,” the study authors concluded.

**Guinea Worm Disease On Verge Of Eradication, WHO Reports***

"The World Health Organization reports Guinea worm disease, which has plagued people for thousands of years, is on the verge of eradication," *VOA News* reports. "The U.N. agency says fewer than 400 cases of the infectious parasitic disease exist in four African countries, and that it will soon become only the second, after smallpox, to be wiped off the face of the earth," the news service writes (Schlein, 8/28). "The number of Guinea worm disease cases has dropped from 3,190 in 2009 to just under 396 cases during the first six months of 2012, according to the WHO," the U.N. News Centre notes, adding, "Gautam Biswas of WHO's Department of Control of Neglected Tropical Diseases told a news conference in Geneva ... that aggressive public health and hygiene awareness among the communities where the disease is still endemic is vital to eradicating it" (8/28).

**Cuban Government Says Cholera Outbreak That Sickened 417, Killed 3, Has Ended**

"Cuba’s government declared Tuesday that health workers had eradicated a cholera outbreak that infected 417 people and killed three, according to a statement from the country’s Health Ministry," *CNN* reports (Oppmann, 8/28). The government said this year’s heavy rains and high temperatures raised the risk of
waterborne diarrheal diseases, the Associated Press/Boston.com notes (8/28). The cholera outbreak began in Granma province’s Manzanillo, about 560 miles east of Havana, and the government said other cases “associated” with the outbreak occurred in other areas of the province, the neighboring provinces of Santiago de Cuba and Guantanamo, and in the capital of Havana, according to EFE/Fox News Latino. "Despite the fact that it said the outbreak was 'concluded,' the Cuban government is also saying it will maintain its vigilance to avoid 'the recurrence of new cases,'" the news service writes (8/28).

NYU-Poly Researchers Set Record for Detecting Smallest Virus, Opening New Possibilities for Early Disease Detection

Posted August 28th, 2012

Researchers at Polytechnic Institute of New York University (NYU-Poly) have created an ultra-sensitive biosensor capable of identifying the smallest single virus particles in solution, an advance that may revolutionize early disease detection in a point-of-care setting and shrink test result wait times from weeks to minutes.

Stephen Arnold, university professor of applied physics and member of the Othmer-Jacobs Department of Chemical and Biomolecular Engineering, and researchers of NYU-Poly's MicroParticle PhotoPhysics Laboratory for BioPhotonics (MP3L) reported their findings in the most recent issue of Applied Physics Letters, published by the American Institute of Physics.

Their technique is a major advance in a series of experiments to devise a diagnostic method sensitive enough to detect and size a single virus particle in a doctor’s office or field clinic, without the need for special assay preparations or conditions. Normally, such assessment requires the virus to be measured in the vacuum environment of an electron microscope, which adds time, complexity and considerable cost.

Instead, the researchers were able to detect the smallest RNA virus particle MS2, with a mass of only 6 attograms, by amplifying the sensitivity of a biosensor. Within it, light from a tunable laser is guided down a fiber optic cable, where its intensity is measured by a detector on the far end. A small glass sphere is brought into contact with the fiber, diverting the light’s path and causing it to orbit within the sphere. This change is recorded as a resonant dip in the transmission through the fiber. When a viral particle makes contact with the sphere, it changes the sphere’s properties, resulting in a detectable shift in resonance frequency.

The smaller the particle, the harder it is to record these changes. Viruses such as influenza are fairly large and have been successfully detected with similar sensors in the past. But many viruses such as Polio are far smaller, as are antibody proteins, and these require increased sensitivity.

Arnold and his co-researchers achieved this by attaching gold nano-receptors to the resonant microsphere. These receptors are plasmonic, and thus enhance the electric field nearby, making even small disturbances easier to detect. Each gold “hot spot” is treated with specific molecules to which proteins or viruses are attracted and bind.

Arnold explained that the inspiration for this breakthrough technique came to him during a concert by violinist Itzhak Perlman: “I was watching Perlman play, and suddenly I wondered what would happen if a particle of dust landed on one of the strings. The frequency would change slightly, but the shift would be imperceptible. Then I wondered what if something sticky was on the string that would only respond to certain kinds of dust?”

In experiments, the researchers successfully detected the smallest RNA virus in solution, and they are now training their sights on detecting single proteins, which would represent a major step toward early disease detection.

“When the body encounters a foreign agent, it responds by producing massive quantities of antibody proteins, which outnumber the virus. If we can identify and detect these single proteins, we can diagnose the presence of a virus far earlier, speeding treatment,” Arnold said. “This also opens up a new realm of possibilities in proteomics,” he said, referring to the study of proteins. “All cancers generate markers, and if we have a test that can detect a single marker at the protein level, it doesn’t get more sensitive than that.”

This patent-pending technology, co authored with postdoctoral fellow Siyka Shopova and graduate student Raaj Rajmangal, is ultimately designed for a point-of-care device capable of detecting viruses or disease markers in blood, saliva or urine. Testing for commercial applications is already under way.

The sensor itself, called a Whispering Gallery-Mode Biosensor, is unique to Arnold’s work. Its name derives from the famous Whispering Gallery in the dome of St. Paul’s Cathedral in London. Much the way
its unique acoustics allow a whisper to be heard anywhere within the circular gallery, light traveling
within the glass sphere of the biosensor orbits many times, ensuring nothing on the surface is missed.

**New antibacterial coating for sutures could reduce infections after surgery**

Responding to an urgent need for better antibacterial coatings on surgical sutures, scientists are reporting the discovery of a new coating that is almost 1,000 times more effective than the most widely used commercial coating. Their report appears in ACS’ journal *Langmuir*.

Professor Gregory Tew, who is from UMass-Amherst, and colleagues explain that infection at the site of surgical incisions is one of the most common post-surgical complications that keep patients hospitalized longer and boost hospital bills. The most common antibiotic coating contains triclosan, but its use in many consumer products over the years has led to the emergence of strains of bacteria that shrug off its effects. Triclosan also can be absorbed into the body, raising concerns about possible adverse health effects. Another downside to triclosan: It slows the growth of bacteria, but does not actually kill those already present. That’s why the scientists turned to PAMBM, a new substance designed from naturally occurring antimicrobial peptides that can kill a wide range of bacteria. And because of the way it works, PAMBM has a very low chance of causing bacterial resistance and the emergence of so-called superbugs.

The report described laboratory tests in which PAMBM greatly reduced the amount of bacteria compared to triclosan. In a head-to-head test with triclosan-coated sutures, those coated with PAMBM were much more effective against bacteria. "As bacterial resistance to current agents continues to increase and with resistance to triclosan now documented, the discovery of new antimicrobial agents that remain active in biomedical device coatings is essential,” say the researchers.

**Method to Simplify Production of Proteins Used in Many Types of Drugs Developed**

ScienceDaily (Aug. 28, 2012) — Engineering researchers at the University of Arkansas have developed a method to simplify the pharmaceutical production of proteins used in drugs that treat a variety of diseases and health conditions, including diabetes, cancer, arthritis and macular degeneration.

With assistance from the National Science Foundation Innovation Corps program, Ellen Brune, the primary researcher and inventor of the technology, has started a company to shorten development time so that new drugs can get to patients faster. Current protein pharmaceutical development is a complicated, time-consuming and expensive process because manufacturers must separate and extract contaminant proteins.

Brune, a doctoral student in chemical engineering, created a series of custom strains of the bacteria Escherichia coli that express minimized sets of contaminants or "nuisance" proteins. Brune then sought assistance to commercialize the technology. In an entrepreneurship class taught by Carol Reeves, associate vice provost for entrepreneurship and management professor in the Sam M. Walton College of Business, Brune created Boston Mountain Biotech LLC, a research and biotechnology firm that will save significant time by preparing the proteins for the manufacturing process.

"Millions of people across the globe are suffering from treatable diseases because manufacturers cannot afford to make the drugs they need,” Brune said. "These companies have to spend too much time and money getting rid of stuff that doesn’t work to get to the stuff that does. Our work addresses this problem. Our cell lines reduce the garbage, so to speak, before the manufacturing process begins.”

Current protein pharmaceutical manufacturing involves separating or cleaning up "background" contamination to reach the target protein—a long and expensive process. Background contamination is undesirable and unnecessary proteins that are prohibited by the U.S. Food and Drug Administration in the final drug product. The FDA requires that the final product be 99 percent pure.

Drug companies spend roughly $8 billion a year trying to clean up these contaminants during production. Brune compares the process to making orange juice by blending the peel and seeds along with the meat of an orange. Once the juice is made, producers would then have to filter out the chunks of seeds and peel.

In the laboratory, Brune worked under the direction of chemical engineering professor Bob Beitle, one of several researchers who have been investigating this problem for more than a decade. Brune designed custom strains of "Lotus" E. coli. Lotus refers to a suite of cell lines optimized to work with specific separation techniques and characteristics. She accomplished this through bio-separation and genetic manipulation, specifically by removing the sections of DNA that code for the contaminant regions. Her work simplifies the purification process on the front end of protein pharmaceutical production, so
that the cell line is specifically developed for manufacturing. Current cell lines used for protein production look nothing like what has to be achieved for large-scale manufacturing, Brune said.

**Weighing Molecules One at a Time: Physicists Create First-Ever Mechanical Device That Measures Mass of Single Molecule**

ScienceDaily (Aug. 26, 2012) — A team led by scientists at the California Institute of Technology (Caltech) have made the first-ever mechanical device that can measure the mass of individual molecules one at a time.

This new technology, the researchers say, will eventually help doctors diagnose diseases, enable biologists to study viruses and probe the molecular machinery of cells, and even allow scientists to better measure nanoparticles and air pollution.

The team includes researchers from the Kavli Nanoscience Institute at Caltech and Commissariat à l’Energie Atomique et aux Energies Alternatives, Laboratoire d’électronique des technologies de l’information (CEA-LETI) in Grenoble, France. A description of this technology, which includes nanodevices prototyped in CEA-LETI’s facilities, appears in the online version of the journal Nature Nanotechnology on August 26.

The device—which is only a couple millionths of a meter in size—consists of a tiny, vibrating bridge-like structure. When a particle or molecule lands on the bridge, its mass changes the oscillating frequency in a way that reveals how much the particle weighs.

"As each particle comes in, we can measure its mass," says Michael Roukes, the Robert M. Abbey Professor of Physics, Applied Physics, and Bioengineering at Caltech. "Nobody’s ever done this before."

The new instrument is based on a technique Roukes and his colleagues developed over the last 12 years. In work published in 2009, they showed that a bridge-like device—called a nanoelectromechanical system (NEMS) resonator—could indeed measure the masses of individual particles, which were sprayed onto the apparatus. The difficulty, however, was that the measured shifts in frequencies depended not only on the particle’s actual mass, but also on where the particle landed. Without knowing the particle’s landing site, the researchers had to analyze measurements of about 500 identical particles in order to pinpoint its mass.

But with the new and improved technique, the scientists need only one particle to make a measurement. "The critical advance that we’ve made in this current work is that it now allows us to weigh molecules—one by one—as they come in," Roukes says.

To do so, the researchers analyzed how a particle shifts the bridge’s vibrating frequency. All oscillatory motion is composed of so-called vibrational modes. If the bridge just shook in the first mode, it would sway side to side, with the center of the structure moving the most. The second vibrational mode is at a higher frequency, in which half of the bridge moves sideways in one direction as the other half goes in the opposite direction, forming an oscillating S-shaped wave that spans the length of the bridge. There is a third mode, a fourth mode, and so on. Whenever the bridge oscillates, its motion can be described as a mixture of these vibrational modes.

The team found that by looking at how the first two modes change frequencies when a particle lands, they could determine the particle’s mass and position, explains Mehmet Selim Hanay, a postdoctoral researcher in Roukes’s lab and first author of the paper. "With each measurement we can determine the mass of the particle, which wasn’t possible in mechanical structures before."
Traditionally, molecules are weighed using a method called mass spectroscopy, in which tens of millions of molecules are ionized—so that they attain an electrical charge—and then interact with an electromagnetic field. By analyzing this interaction, scientists can deduce the mass of the molecules. The problem with this method is that it does not work well for more massive particles—like proteins or viruses—which have a harder time gaining an electrical charge. As a result, their interactions with electromagnetic fields are too weak for the instrument to make sufficiently accurate measurements.

The new device, on the other hand, does work well for large particles. In fact, the researchers say, it can be integrated with existing commercial instruments to expand their capabilities, allowing them to measure a wider range of masses.

The researchers demonstrated how their new tool works by weighing a molecule called immunoglobulin M (IgM), an antibody produced by immune cells in the blood. By weighing each molecule—which can take on different structures with different masses in the body—the researchers were able to count and identify the various types of IgM. Not only was this the first time a biological molecule was weighed using a nanomechanical device, but the demonstration also served as a direct step toward biomedical applications. Future instruments could be used to monitor a patient's immune system or even diagnose immunological diseases. For example, a certain ratio of IgM molecules is a signature of a type of cancer called Waldenström macroglobulinemia.

In the more distant future, the new instrument could give biologists a view into the molecular machinery of a cell. Proteins drive nearly all of a cell's functions, and their specific tasks depend on what sort of molecular structures attach to them—thereby adding more heft to the protein—during a process called posttranslational modification. By weighing each protein in a cell at various times, biologists would now be able to get a detailed snapshot of what each protein is doing at that particular moment in time.

Another advantage of the new device is that it is made using standard, semiconductor fabrication techniques, making it easy to mass-produce. That's crucial, since instruments that are efficient enough for doctors or biologists to use will need arrays of hundreds to tens of thousands of these bridges working in parallel. "With the incorporation of the devices that are made by techniques for large-scale integration, we're well on our way to creating such instruments," Roukes says. This new technology, the researchers say, will enable the development of a new generation of mass-spectrometry instruments.

"This result demonstrates how the Alliance for Nanosystems VLSI, initiated in 2006, creates a favorable environment to carry out innovative experiments with state-of-the-art, mass-produced devices," says Laurent Malier, the director of CEA-LETI. The Alliance for Nanosystems VLSI is the name of the partnership between Caltech's Kavli Nanoscience Institute and CEA-LETI. "These devices," he says,"will enable commercial applications, thanks to cost advantage and process repeatability."

**Journal Reference:**

**Opinion: What Is the Human Genome?**
The human genome that researchers sequenced at the turn of the century doesn’t really exist as we know it.
**By Ken Weiss | August 17, 2012**
The Human Genome project sequenced “the human genome” and is widely credited with setting in motion the most exciting era of fundamental new scientific discovery since Galileo. That's remarkable, because in important ways “the human genome” that we have labeled as such doesn’t actually exist.

Plato essentially asserted that things like chairs and dogs, which we observe in this physical world, and even concepts like virtues, are but imperfect representations or instances of some ideal that exists, but not in the material world. Such a Platonic ideal is “the human genome,” a sequence of about 3 billion nucleotides arrayed across a linear scale of position from the start of chromosome 1 to the end of the sex chromosomes. Whether it was obtained from one person or several has so far been shrouded in secrecy for bioethical reasons, but it makes no real difference. What we call the human genome sequence is really just a reference: it cannot account for all the variability that exists in the species, just like no single dog on earth, real or imagined, can fully incorporate all the variability in the characteristics of dogs.

Nor is the human genome we have a “normal” genome”. What would it mean to be “normal” for the nucleotide at position 1,234,547 on chromosome 11? All we know is that the donor(s) had no identified disease when bled for the cause, but sooner or later some disease will arise. Essentially all available whole genome sequences show potentially disease-producing variants, even including nonfunctional genes, in donors who were unaffected at the time.
Furthermore, the current reference genome sequence is haploid, which means that even if it were compiled from just one donor, the single reference sequence does not report the variation at millions of nucleotide positions between the donor’s two copies (except for X and Y) that we know exist. I understand that the DNA template is being resequenced, to be reported as a diploid sequence, which is progress. Hopefully this will be done in a way that produces phased sequence, in which each chromosome is reported separately, rather than just identifying the two alleles at each variable site along the genome without specifying on which chromosome it lies. Only the former format will represent sequences as they actually exist in the sequenced person, identifying which alleles go together on a chromosome, and are thus linked evolutionarily.

Even so the reference human genome will keep changing! Corrections and refinements of problematic regions that are technically difficult to sequence are made, though nobody claims it will ever identify 100 percent of the 3.1 billion nucleotides without mistakes. But forgetting such minor errors, if such a diploid sequence were obtained from a single person, rather than a composite of several, one might think we finally have an actual set of sequences rather than a non-existent Platonic ideal. That would then be like the authorized type specimens of real plants and animals in museums.

Of course, biologists realize that it’s only a reference sequence, and they think of each of us carrying “copies” of the human genome referent, with some variants of that sequence. But even that idea is wrong. Calling them copies would be Platonic, as if our individual sequences came directly, if imperfectly, from this ideal as their shared template. More accurately, we should use a term like “instance” rather than copy. But a fundamental point is that the resemblance among instances is not due to descent from a single ideal, but for the evolutionary reason that they are homologous, that is, are from a chain of descent from the gene’s common ancestor. Homology is not the manifestation of an ideal, because the original ancestral instance really did exist.

Biologists take advantage of this fundamental fact of life when inferring ancestral sequences from the observed variation in today’s populations. One might suggest that instead of a rather arbitrary reference sequence from some donor, “the human genome” sequence should be this inferred ancestral sequence. But that doesn’t work either. The ancestral sequence for human genes usually goes back far beyond the origin of humans, and the ancestral sequences for each gene will have existed in vastly different times, places, individuals, and species. The intervening noncoding sequences between such genes, which is generally less constrained by natural selection, vary so much that we often can’t really guess their ancestral state. Further, genes have been rearranged among the chromosomes over time, so that gene A and B that are chromosomal neighbors in human genomes today may have been on entirely different chromosomes in the past, or vice versa. Finally, the ancestral gene may have been so different from today’s that using that as our reference would not serve the biomedical research community from a functional point of view.

The same is true to a lesser extent even among modern human genomes: in addition to single nucleotide variation, millions of bits of DNA large and small have been deleted, inserted, inverted, or rearranged in every human genome instance. This variation, and the variation that will continue to accrue in the human population, distances us from any single reference sequence even further.

Reference sets?
If a single reference sequence, even the ancestral sequence that really did exist, is problematic, could there be a better way? An appealing possibility is to use a set of DNA sequences, perhaps all known instances, to characterize human genomes. Instead of a single string, suppose we represented each part in the format of what is known as a gene or sequence “logo.” Here is an example:
This shows the relative frequency of each nucleotide at every point along the sequence. One would have to add a way to visualize insertions and deletions and so on, but computer technologies should be up to that task. If “The Human Genomes” sequence was portrayed in this way, we might replace our arbitrary type-specimen with more natural, biologically accurate, population thinking. Efforts are under way to create a biological reference along these lines.

Of course, a reference like this would have to be constantly updated, and still could not keep up with the changing frequencies at each position as people die and babies are born all the time. But there’s a more important and even deeper problem—with Platonic implications. Every time an individual cell divides, new mutations arise; no two cells even within any individual have the identical sequence. Because of this somatic mutation, the single sequence obtained from each individual is an imperfect representation even of that person’s genome. We can never know the variants in each of his/her billions of cells.

**Coming to terms with Plato**

We routinely use an arbitrary reference and/or ancestral sequences in our daily research. We develop phylogenies, and identify variation responsible for traits, including disease. We comparatively consult arbitrary references for humans and mice to design experiments that work only because of our evolutionary relationship. As limited human beings, we cannot grasp everything in our heads, and representations and reference guidelines are immensely useful.

In fact, in many ways, the human reference genome is an ideal, but not in the way Plato had envisioned ideal. In a deep and interesting way, he had things backward. His idea was that we are only able to see imperfect images, of ideals that really have some separate existence. But actually, the ideals are neural constructs built inside our very material heads, and it is they that are imperfect representations of the actual world, not the other way round as Plato had it.

Thus, while any human reference genome may be far from perfect, it’s what we have to work with today, and it helps shed light on all aspects of human biology. Representations are fundamental to science. The danger is if we don’t understand them and they become misrepresentations.

**Ken Weiss** is a geneticist and evolutionary biologist at Penn State University. A fuller discussion of these points is available at *The Mermaid’s Tale*, a blog to which Weiss is a contributor.

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**Dan Arul** • 11 days ago

i would support a national project where everyone had their genome cataloged, for medical reasons, criminal reasons, but also, i think that we could learn so much if we had a sample size that large.

**John P Remillard** • 10 days ago • parent

IBM & National Geographic teamed up to capture as many human genes as possible. It is called the: Genographic Project at: https://genographic.nationalge...

**Sherry Lewis** • 8 days ago • parent

Unfortunately, this is not the case for Aboriginal or Native Americans. The US government is using blood quantum to determine how much ‘Indian blood’ a person has and this determines how much Native American rights can be accessed.

Just imagine if this method was used to determine how much ‘American blood’ every American person has that has to be linked to the people who came over with Christopher Columbus and this then determined the American rights you can access.

As a First Nations person, I have nothing to hide, but it has never been in my best interest to allow the government to take control.

**James Kohl** • 10 days ago

We currently have not only a human reference genome but also a model of how to compare it to the genomes of other species. Within the confines of that model, we know that the epigenetic effects of nutrient chemicals and pheromones cause changes in intracellular signaling and stochastic gene expression. The changes in gene expression allow sensory input from the environment to cause speciation. We also know that olfaction and odor receptors provide a clear evolutionary trail that can be followed from unicellular organisms to insects to humans.

Clearly, the genetic predisposition of the first living cell allowed the required receptor-mediated events for food acquisition and stochastic gene expression, which are linked directly to the de novo production of additional chemical (i.e., odor) receptors. Those receptors are unequivocally required for adaptive evolution via ecological, social, neurogenic, and socio-cognitive niche construction.

If the molecular biology that is common to all species did not ensure that the epigenetic effects of nutrient chemicals and pheromones altered gene expression in every species we would have limited genetic variation instead of the variation that is obviously required to link us—via adaptive evolution—to the origins of the human reference genome. That is the representation we now have to work with. What we observe is genetic diversity that can be sniffed out, even if it cannot be seen.

As Decartes probably meant: I think I need to eat; therefore I am. And I am tired of misrepresentations and constructs that do not incorporate the molecular biology that is common to all species. The human reference genome did not suddenly materialize so that it could be sequenced. Did it?

**EllenHunt** • 10 days ago

Ken, it’s way worse than that. The genome that was sequenced is a partial one and we know it. We didn’t sequence any chromosome in the region near the centromere because it was too hard. That’s about 5%-10% of the genome. Is that area inactive? Probably not. We depend on BLAST to be right, but know that there are parts of the genome
where it is most certainly wrong. And since the first sequencings, all further sequences use the baselines as templates to "speed up assembly".

In other words, the genome we have is wrong and we know it. And we are using the first, known to be incorrect version to "correct" and as a scaffolding for everything after it.

But the "story" of completion is just too good, too compelling, to tell the truth. Wouldn’t be so good for grant writers would it? And there was that infamous competition too.

ihatesnow
check out this research group out of the University of Washington http://boinc.bakerlab.org/rose...
Dale Yuzuki • 10 days ago
Speaking with a member of the 1000 Genomes Project analysis team a week ago about this topic, there is active work on refining the human reference sequence, along with an active discussion of whether there should be separate ethnicity reference sequences, which makes sense.

For those interested, here’s a GenomeWeb piece from 2009 about the 5 million bases missing from the reference. http://www.genomeweb.com/seque... And I comment further on this topic here. http://www.yuzuki.org/error-al...

**DNA, Contortionist**
The DNA forms known as G-quadruplexes are finally discovered in human cells.

By Kerry Grens | August 1, 2012

**DECONSTRUCTING QUADRUPLEXITY:** Parts of the genome containing strings of guanines, such as within the proto-oncogene SRC 1, can form four-stranded structures called G-quadruplexes 2. The small-molecule drug pyridostatin binds G-quadruplexes in vitro, and researchers used the drug to test whether G-quadruplexes also occur in vivo 3. Exposing human cells to pyridostatin elicits a DNA damage response, resulting in the formation of phosphorylated histones called γH2AX 4. By cross-linking γH2AX to DNA, researchers could extract these regions of the genome using antibodies. DNA sequencing showed that pyridostatin’s in vivo targets did indeed have a high probability of G-quadruplex formation.

**Editor’s Choice In Structural Biology**

In 1962, researchers at the National Institutes of Health identified peculiar twists of DNA shaped into four-stranded structures, rather than the double helix that had come to define DNA. For much of the 50 years since the discovery of these structures, now known as G-quadruplexes, “it was felt that those findings were a laboratory curiosity, an artifact if you will,” says Stephen Neidle of University College London. Still, researchers were intrigued by these test-tube structures because they were made exclusively from guanines and were stable at physiological conditions. Yet evidence for their existence in human cells remained elusive. “It’s almost become more religion than science,” says Steve Jackson of the University of Cambridge. “Some believed in them, some didn’t.”

To end the debate, Jackson’s lab teamed up with the lab of Shankar Balasubramanian, also at Cambridge. They used a small molecule called pyridostatin, which binds to G-quadruplexes in vitro, to try to ferret out these structures in human cells, and found that, like other small molecules that bind quadruplexes in vitro, pyridostatin induces a DNA damage response. The team took advantage of this response by exposing cells to pyridostatin and cross-linking the DNA to a damage-response protein, a histone called γH2AX. After zeroing in on the genomic foci of this damage response, the group used high-throughput sequencing to determine which genes pyridostatin had targeted and determined that they were indeed regions with a high tendency toward G-quadruplex formation. “It shows that G-quadruplexes really [do exist] in human cells in culture,” Jackson says.
The findings are a triumph for those who had believed that G-quadruplexes exist in vivo. Pyridostatin doesn’t induce G-quadruplexes to form, Jackson points out, but binds to those that already exist.

What G-quadruplexes are doing in the genome still remains unanswered. “I think probably in some cases G-quadruplexes are problems that need to be resolved by the cell,” says Jackson. For instance, others have reported that in yeast it appears that the helicase Pif1 unwinds G-quadruplex structures to maintain genomic stability. Jackson’s group also found overlap between pyridostatin damage and Pif1 targets.

“I think in other cases, the idea that they can have positive functions is very appealing,” says Jackson. Given that telomeres can form G-quadruplexes, it’s possible that the structures are involved in facilitating telomeres’ unique structure or preventing them from being recognized as broken bits of DNA, Jackson speculates. Or perhaps G-quadruplexes are involved in regulating transcription, since they also form in promoter regions, making them possible targets for small-molecule therapies to arrest cancer’s cell cycle. Although G-quadruplex research has been conducted for half a century, Jackson says, “it’s still early days.”

The paper

Blood Spots Are Epigenetic Time Capsules
Researchers show that blood spotted onto Guthrie cards, usually at birth, can be a high quality source of methylated DNA for long-term epigenetic studies.

By Sabrina Richards | August 22, 2012

Blood samples spotted onto Guthrie cards at birth could prove a valuable source of genomic DNA for epigenetic studies. They could potentially allow scientists to peer into the history of a patient’s epigenome and reveal which epigenetic patterns helped cause disease, and which resulted from disease, researchers at the University of London report in tomorrow’s (August 23) online issue of Genome Research.

“If validated, this could indeed add a much needed time scale to correlation studies of methylation and disease,” L. H. Lumey, a medical epidemiologist at Columbia University, who did not participate in the research, wrote in an email.

Research into the genetic basis of complex diseases has demonstrated that a fair portion of heritability can’t be accounted for by genetic sequence alone, explained first author Vardhman Rakyan, a senior lecturer at the University of London. “Genetics contributes only about 15 to 20 percent of heritability of diabetes. Clearly environment plays a role,” Rakyan noted. Epigenetic modifications to DNA are one way in which environment can influence gene expression.

But it’s more difficult to find epigenetic patterns that contribute to disease than it is to identify genetic sequences, Rakyan said. Genetic sequence is stable in most tissues, so “if we find a germline [gene] variant, we know it contributed to disease,” Rakyan said—but epigenetic modifications are not stable. Many epigenetic modifications result from environmental signals, so an epigenetic pattern linked to a disease may have contributed to causing the disease, or may have resulted from the disease. To add another layer of complexity, genetic differences between individuals can also contribute to epigenetic differences. This makes discovering which environmental signals—like diet or smoking—cause specific epigenetic changes complicated.

It helps to have epigenetic information over time. If researchers have information about an individual’s epigenome at birth, it becomes clearer which patterns contributed to disease early on, and which appeared later in life, said Rakyan. “We wanted to see if we could find epigenetic changes before disease occurs—but how do you go back in time?”

Rakyan and his collaborators looked to Guthrie cards. Around since the 1960s, Guthrie cards are slips of filter paper containing 4 blood spots from one individual, usually taken at birth. They were devised to
provide an easily stored and transportable medium for blood storage, so that researchers could screen infants for diseases like phenylketonuria, which can result in mental retardation and seizures.

Although DNA is stable, Rakyan and his colleagues needed to check whether Guthrie card DNA was of sufficient quality to detect epigenetic changes, which are more delicate biochemically. They tested two well-established protocols for identifying a type of epigenetic modification known as DNA methylation with Guthrie cards, and found that the cards were well suited to both methods, allowing Rakyan to identify and compare methylation sites between three individuals.

“Our other objective was to look at whether epigenetic variation exists at birth,” Rakyan said. “Is this stable? If we look a few years later, will we still see this?”

Epigenetic changes can be influenced by genetics or the environment. In order to measure contribution of the environment only, Rakyan and his colleagues removed epigenetic markers within 10 kb of any genetic variant from their analysis. This left them with about 10 to 15 different methylation events between the three individuals. When they looked at epigenetic marks from patients’ blood taken at age three, most of the differences remained. Although 15 differences seems small, Rakyan pointed out that his sample size was limited. There are about 25 million epigenetic modifications to the genome, said Rakyan, and he and his colleagues only screened about 1 in 50.

Further validation of the Guthrie cards will require a larger sample size, said epigeneticist Manel Esteller of the University of Barcelona, who was not involved in the research. An additional issue, said Lumey from Columbia University, is that the search is still on for epigenetic patterns that correlate well with disease state, prognosis, or treatment response.

Researchers also need to “look into logistics of how to use Guthrie cards,” noted Bas Heijmans, a molecular epidemiologist at Leiden University Medical Center in The Netherlands who did not participate in the study. Depending on a country’s regulations, Heijmans points out, Guthrie cards may be stored for anywhere from a few months, as in Germany, to a lifetime, as Scandinavian countries do. Permission to use and store the cards can be difficult to obtain, as the recent destruction of 5 million Guthrie cards in Texas showed. “It would be terrible for more cards to be destroyed,” said Rakyan.

If Guthrie cards provide information about an individual’s epigenome at birth, they can be used in two ways, said Lumey. Researchers examining a patient population can look back at their infant epigenomes; conversely, they can start with Guthrie cards and follow the effect of patterns known to be correlated with a specific disease. “You can go backwards from disease conditions, or forward from Guthrie cards, and incorporate time dimension in a creative way,” Lumey explained.


Learning During Sleep
Information picked up while we slumber can stay with us in waking hours, even if we aren’t aware of it.
By Ed Yong | August 26, 2012

Israeli scientists have found the strongest evidence yet that people can learn new information while they are sleeping, rather than simply strengthening memories already made.

Anat Arzi from the Weizmann Institute of Science in Rehovot, Israel played tones to sleeping volunteers before wafting smells of deodorant, shampoo, rotten fish, or dead animals past their noses. The smells triggered a sniffing reflex and the pleasant ones drew stronger sniffs. Then, when Arzi played the tones alone, the volunteers still sniffed, and more strongly to tones that had been paired with nice odors.

This conditioned response lasted through the night and into the next morning when the volunteers woke up. Although they still sniffed when they heard the tones, none of them were aware of what they had learned.

“This work is transformative in that it shows that humans can acquire information not only without awareness but also in a non-conscious state,” says Kimberly Fenn, a psychologist from Michigan State University, who was not involved in the study.

“There’s a kind of dogma that says the brain encodes new information when it’s awake, and consolidates memory while asleep,” explained Jan Born, a sleep researcher from the University of Lübeck. “This paper shows that the contrast between these two modes of activity isn’t that sharp.”

Decades of research has already shown that the brain actively processes information while we sleep, and we can strengthen existing information with the right triggers, such as odors present at the time of initial learning. But its ability to learn while snoozing has been less clear.
Several groups have tested for advanced forms of learning during sleep, like picking up the links between pairs of words. All such experiments have failed. The only positive results came from studies showing that a very basic form of learning known as classical conditioning can occur in sleeping rats and infants, which begin to associate two stimuli—say, a tone and a puff of air—if they are presented together.

By contrast, Arzi’s experiments used a different technique called “trace conditioning,” where the tone and the smells are separated by more than a second. “This is considered a more advanced type of learning, and unlike classical conditioning, it depends on the hippocampus,” she said. “This is the type of learning associated with more complicated cognitive tasks, and therefore finding it in sleep is potentially important and novel.”

Arzi also took steps to ensure that her subjects were not inadvertently waking up. Throughout her study, a sleep technician monitored the volunteers’ brain activity and halted the experiment whenever they showed signs of rousing. All such trials were left out of the final analysis.

Arzi’s volunteers only learned a very simple response, and it is not clear if we can pick up more complex information while sleeping. “This does not imply that you can place your homework under the pillow and know it in the morning,” she said. “There will be clear limits on what we can learn in sleep, but I speculate that they will be beyond what we have demonstrated.”

Fenn agreed. “It is difficult to imagine that any form of declarative information, even simple vocabulary learning, could be accomplished in a sleep state,” she said. “That being said, this study may have strong implications for conditioning of undesirable behaviours.”

Addictions, for example, are sometimes treated by teaching people to associate the drugs they crave with something repulsive. Although such approaches are controversial, our hours of slumber could provide a prime opportunity to enshrine such associations, and the lack of awareness when we wake up would only be a bonus, Arzi noted. “If you have some bad habit that you want to get rid of, awareness may only hinder your efforts,” she said. “If you could learn to get rid of the habit during sleep, you may do it without awareness as to why.”


Second Victim of Hantavirus
Another person has died from the rodent-borne disease after visiting Yosemite National Park.

By Jef Akst | August 28, 2012
Hantavirus, a rare but potentially fatal disease caused by exposure to urine, droppings, or saliva of infected rodents, has now claimed the lives of two visitors to a popular location within Yosemite National Park in California, The Huffington Post reported, and a total of four are suspected to have contracted the infection.

Only 587 cases of hantavirus infection have been documented in the United States since the virus’s discovery in 1993. There is no treatment for the infection, and about one-third of cases prove fatal.

Park officials say that exposure likely came from Curry Village, an area of rustic cabins where visitors can stay, and are warning people to be alert for any symptoms of hantavirus, including fever, aches, dizziness and chills, which can develop as long as 5 weeks after exposure. The park is also making an effort to contact all visitors who stayed in one of Curry Village’s 91 Signature Tent Cabins, which are more insulated than the other accommodations and where all four cases of suspected hantavirus patients stayed.

“They’re doing everything they can to eliminate areas where mice can get into the cabins,” Yosemite spokesman Scott Gediman told the San Francisco Chronicle. “This was never because the cabins were dirty, it was never because we didn’t take care of them. This is just because approximately 20 percent of all deer mice are infected with hantavirus. And they’re here in Yosemite Valley.”

Proteome Portraits
Innovations in mass spectrometry are making quick, comprehensive, and easy proteome mapping more attainable than ever.

By Sabrina Richards | August 1, 2012
Proteomics, the analysis of proteins present in a cell under different conditions, has always lagged behind genomics, as a rush of technological innovations made comprehensive genome mapping dizzyingly quick and achievable even for laboratories without access to core facilities. But unlike the main goal of
genomics—laying out a primarily static sequence of base pairs—proteomics, with its diversity of shape, size, and sequence, presents more problems to tackle.

“Some scientists have proposed that the complexity of the proteome is unbounded,” explains Bradford Gibson of the Buck Institute for Research on Aging in Novato, California, citing splice variation, phosphorylation, time-dependent changes in protein expression, turnover, and interactions as examples of what makes proteomics complicated. But for all its infinite variability, proteomics is on the cusp of a sea change in technology that will help scientists get a better grip on what’s going on in the cells they study.

Mass spectrometry, long an integral technique in protein research, has finally achieved the sensitivity, resolution, and speed necessary to make proteome mapping a feasible undertaking. “We need to be able to comprehensively cover all the proteins in a cell,” says Andreas Huhmer, director of proteomics marketing at Thermo Scientific, a manufacturer of mass spectrometers. Proteomics labs are racing to see who can map fastest and most fully, he says, calling it the next wave in mass spectrometry technology.

All protein mass spectrometry works by the same basic principle: proteins or peptides are ionized in some fashion, then fragmented, and the mass-to-charge ratio is measured, yielding characteristic spectra. A comprehensive proteome map requires that the mass spectrometer be sensitive, detecting both rare and abundant peptides; that it have high resolution to help discriminate a complex cocktail of protein species; and ideally, that the instrument be fast, so analyzing a single proteome doesn’t take all year. Time-of-flight (TOF) instruments, which have existed in basic form since the late 1940s, shoot ionized peptides through an electromagnetic field in a vacuum tube and rely on the fact that ions of different masses traverse the tube at different speeds. This method resolves peptides well, but has a tendency to miss rare peptides. Quadrupole-ion-trap analyzers separate ions based on their stability as they pass through an oscillating current moving between four conducting rods; these instruments are sensitive, but not ideal for differentiating peptides of similar mass. It’s only recently that engineers have been able to combine the advantages of different mass-spec instruments into the same machine. A new type of mass-spec analyzer manufactured by Thermo Scientific, called the Orbitrap, which oscillates ions and uses complex mathematics to get high accuracy, resolution, and range, only appeared on the scene in 2005, but the machine’s speed and range have increased dramatically since then. And a new strategy for collecting data enables the newest of the venerable TOF instruments to survey an entire proteome, helping to speed and deepen proteomic analysis.

A Spike in Spectra
Matthias Mann’s group at the Max Planck Institute for Biochemistry in Martinsried, Germany, used recent innovations to the Orbitrap to produce some of the most complete yeast and human proteome maps to date.
In 2008, when Mann and his colleagues attempted the most complete mass spectrometry-based yeast proteome identification and quantification ever, they relied on the novel features of Thermo Scientific’s LTQ-Orbitrap, which had only been on the market for about 3 years but had significant advantages over its predecessors in detecting and distinguishing peptides.

In contrast to most other mass analyzers, ions enter an Orbitrap’s electromagnetic field at an angle, which traps them and forces the ions to oscillate around a central electromagnet. The oscillating ions generate currents as they pass detector electrodes, and a complex mathematical conversion called a Fourier transform translates the currents into mass spectra. The early Orbitrap machines were able to combine high resolution, wide dynamic range, and mass accuracy. Mann’s group relied on their fine resolution because their experiments depended on a subtle shift in spectra. They used a procedure Mann developed 10 years ago, called SILAC (stable isotope labeling by amino acids in cell culture), to label yeast metabolic proteins. By mixing labeled and unlabeled samples together, they could see the subtle shift produced by heavier isotope-labeled amino acids in certain peptides, which allowed the researchers to use ratios of heavy and light to both identify and quantify proteins in the same experiment. They were even able to compare protein levels in diploid versus haploid yeast, which gave insight into pathways that differed in these two life stages.

In 2010, the group decided to tackle the human proteome, which contains about two to three times as many proteins as the yeast proteome. They employed Thermo Scientific’s LTQ Orbitrap Velos, which applied a series of voltages to focus the ion beam entering the instrument, improving the efficiency of ion transfer into the instrument by 10-fold. Using HeLa cells, a human cell line, they identified more than 10,000 proteins, which they matched to just over 9,000 genes.

Thermo Scientific’s newest Orbitrap, the Q-Exactive, adds a quadrupole mass filter, which was not available on the LTQ Orbitrap in 2008. The quadrupole helps rapidly separate peptide ions of different masses for fragmentation, allowing the ions to be broken apart almost as quickly as they’re selected in the filter, which increases speed. The Q-Exactive also increases speed by fragmenting and analyzing in parallel rather than sequentially, allowing the instrument to analyze one set of ions while the next is being fragmented. A comparable resolution can be reached in half the time of the Velos. Coupling the Q-Exactive to the latest high-pressure liquid chromatography allowed Mann’s group to produce a complete yeast proteome in a single experiment, eliminating the need to separate the peptides prior to mass-spectrometry analysis. The researchers were able to compare yeast grown under different conditions, and quantify changes in heat shock proteins and stress-related pathways.

In 2008, using the LTQ-Orbitrap, says Mann, it took 3 months to generate the yeast proteome map, which included almost 4,000 proteins. Now, the Q-Exactive’s advances enable the same procedure to be done in about 4 hours.

Another of the Orbitrap’s assets is its small size, adds Mann. “It’s not tiny, but it still fits on a bench top,” he says, and also notes its relative ease of use, which puts complex proteomics experiments within reach of mass spectrometry neophytes. A mass spectrometry expert himself (Mann helped develop the electrospray ionization technology that, equally with matrix-assisted laser desorption/ionization [MALDI], is one of the standard ionization strategies in mass spectrometry), Mann collaborates with many biologists who aren’t specialists. He doesn’t see any big changes on the Orbitrap’s horizon: “The hardware’s very good. There are no big conceptual problems,” he explains, forecasting that “in the next 2 years it will become more robust and cheap.”

**Cutting a New SWATH**

Another strategy takes the latest in mass spectrometry instrumentation, uses it differently, and captures the data differently. SWATH technology, so called after the “swaths” of mass ranges used to scan peptide ions, has been developed by Ruedi Aebersold at the Institute of Molecular Systems Biology in Zurich, Switzerland, with mass spectrometer manufacturer AB SCIEX. The concept was first published online in January 2012, in *Molecular & Cellular Proteomics*.
The idea, says Gibson of the Buck Institute for Research on Aging, is to collect information on as many peptides as possible during one mass spectrometry run, creating a library of mass spectra that can later be mined for proteins, without the need to perform the experiment anew. SWATH technology “came from the understanding that there’s a lot of undersampling in data-dependent experiments,” such as shotgun proteomics, says Gibson, who has been implementing the new methodology in his lab. Mass spectrometers don’t, and can’t, record data on all ions produced; instead, high peptide concentrations trigger data acquisition, but this means that more data is collected on proteins that are abundant. Proteins that are rare in the sample, or don’t fractionate or ionize well, will often be missed. But this bias also opens the possibility for scientists to use relative sampling to ascertain protein abundance, both identifying and quantifying peptides in the same experiment. The strategy relies on the idea that the frequency at which a peptide is detected correlates well to its relative abundance in the samples.

“It’s not a new idea,” says Gibson, who notes that John Yates at Scripps Research Institute proposed a similar strategy in 2004, but at the time, the mass spectrometry technology on the market couldn’t support the strategy well enough.

Gibson’s lab, which uses mass spectrometry to investigate the utility of phosphoproteins as cancer biomarkers, among other projects, recently upgraded to AB SCIEX’s TripleTOF 5600, the machine Aebersold’s group used to develop SWATH. Already, says Gibson, his lab members are noticing a positive impact on their experiments. Ten years ago, scanning the peptides in a sample would have taken 2 seconds; current technology can do 30 scans in 1 second.

SWATH technology comes into play during a second pass through the mass analyzer, after peptide ions have fractionated a second time via collision. The spectrometer is set to analyze the ions in clearly defined spectral ranges called swaths, says Ron Bonner a principle scientist at AB SCIEX. The quadrupoles’ quick switching between swaths allows the instrument to cycle through 32 swaths and gather information on all detectable ions. Using this protocol to examine how comprehensively SWATH methodology could map a proteome, Aebersold’s group identified almost 4,000 yeast proteins, essentially corresponding to the complete yeast proteome, confirming the method’s utility. One of the best features of this new setup is speed, says Bonner. Only a few years ago, a shotgun approach aimed at mapping a proteome could take a month, because it required prefractionating the proteins and running each fraction as many as 8 times to avoid missing peptides. SWATH requires no prefractionation before the samples are applied to liquid chromatography columns, and Aebersold has mapped about 2,000 yeast proteins in a 2-hour run, says Bonner.

Combining quantification and identification in one experiment has changed how Gibson’s lab approaches experiments such as biomarker discovery projects. Before, he says, it could be a laborious, months-long process to first begin identifying possible proteins of interest, and then perform the necessary experiments to quantify their abundance. Now lab members are planning experiments that identify and quantify in one run. Researchers in Gibson’s lab are pleased with the 5600’s sturdiness as well, he says. Previous instruments sometimes needed frequent servicing or required a month’s worth of troubleshooting to identify why detection sensitivity had dropped off, but the new instrument’s detectors have remained stable for months, which also helps when scientists want to compare experiments done half a year apart.
“It’s changed the game of how we do experiments in the lab,” Gibson says. “Now when we sit down to design, we build SWATH acquisition into almost everything. It works.”

**WSU researchers discover mechanism leading from trichomoniasis to prostate cancer**

**Finding could lead to better diagnosis and treatment**

PULLMAN, Wash.—Researchers have identified a way in which men can develop prostate cancer after contracting trichomoniasis, a curable but often overlooked sexually transmitted disease.

Previous studies have teased out a casual, epidemiological correlation between the two diseases, but this latest study suggests a more tangible biological mechanism.

John Alderete, a professor at Washington State University's School of Molecular Biosciences, says the trichomoniasis parasite activates a suite of proteins, the last of which makes sure the proteins stay active.

"It’s like switching a light switch on," he says. "Then, if you don’t control the brightness of that light, you can go blind. That’s the problem."

Alderete and colleagues at WSU and Washington University in St. Louis report their findings in the recent *PLoS Pathogens*.

Caused by a protozoan parasite, trichomoniasis is often referred to as the most common curable sexually transmitted infection. However, most infected people have no symptoms, so it often goes untreated.

"Most women, it’s the Number One sexually transmitted infection," says Alderete. "We’re going to have at least 10 million women infected this year and an equal number of men because they all get infected if they come into contact with an infected partner."

Infected women have a greater risk of pregnancy complications and HIV. Infected men have a 40 percent greater chance of developing prostate cancer, according to a 2006 study led by Siobhan Sutcliffe, a Washington University epidemiologist and co-author of the recent *PLoS Pathogens* paper.

Sutcliffe cautions that the epidemiological link she found is not conclusive and compares the science to the early connections drawn between smoking and lung cancer.

"It’s still in a really exploratory phase," she says.

A study after her 2006 research found no connection between trichomoniasis and prostate cancer, while a third out of Harvard found an even greater likelihood of cancer in infected men.

Much of the study was done in a single building, WSU’s Biotechnology and Life Sciences Building, and involved two of the more accomplished researchers on the Pullman campus.

"This is just coincidence. I’ve only been here five years," says Alderete. "And when I arrived here five years ago, I had no clue that we would be going in this kind of direction. But the more I read and the more we talked in the hallways, the more it became clear that, wait a minute, we may have something here between us."

WSU cancer researcher Nancy Magnuson is an expert on the protein PIM1, a promoter of cancer cell growth, and identified the protein in the cascade of proteins leading from trichomoniasis to prostate cancer. WSU molecular biologist Ray Reeves brought to bear his expertise in HMGA1. The protein turns genes on and off and ended up being the actor making sure other proteins in the trichomoniasis-to-cancer sequence stay on.

Alderete hopes knowledge of the mechanism will lead to better diagnosis and treatment.

"What this is also doing is telling the world, 'People, this is a latent infection,’” he says. "'You guys out there, if you’ve been exposed to it, you’ve got it in there, and we need now a diagnostic for you.’"


**Study gives new insight on inflammation**

Scientists’ discovery of an important step in the body’s process for healing wounds may lead to a new way of treating inflammation.

A study published today in *Current Biology* details how an international team of researchers led by Monash University's Australian Regenerative Medicine Institute (ARMI) discovered the mechanism, which shuts down the signal triggering the body's initial inflammatory response to injury.

When the body suffers a wound or abrasion, white blood cells, or leukocytes, travel to the site of the injury to protect the tissue from infection and start repairing the damage. However, this period of
inflammation need only be temporary. If the body allows the inflammatory stage to continue for too long, the next phase of healing is compromised.

Previous research identified the initial signal that calls the leukocytes to the site of the injury, but how this early signal was switched off, letting the leukocytes know that they were no longer urgently needed, was unknown. The latest findings show that an enzyme called myeloperoxidase is the key to this process.

The team studied zebra fish with modified leukocytes and tissues that fluoresced different colours, enabling leukocyte movement and the concentration of chemical signals to be monitored simultaneously. By observing the tiny, transparent fish under a microscope, the researchers were able to observe individual white blood cells and how they are regulated in the inflammatory phase of the healing process.

Lead researcher Professor Graham Lieschke of ARMI said the findings suggested new possibilities for treating inflammation.

"White blood cell activity is important for determining the balance between repair, scarring and healing. Understanding what regulates leukocyte activity during inflammation should ultimately allow us to manipulate this system and maximise healing and repair," Professor Lieschke said.

"Our research has identified a new pathway to target with anti-inflammatory drugs. There is a significant need for new treatment options as current drugs are not effective in all circumstances."

Professor Lieschke said the findings were especially relevant to understanding and treating the hereditary disease myeloperoxidase deficiency, which affects leukocyte function in approximately one in every 2000 people.

Cancer 'turns off' important immune cells, complicating experimental vaccine therapies

New research published in the Journal of Leukocyte Biology suggests monocyte-derived dendritic cells may not be as effective in inducing desired immune responses as previously expected

Bethesda, MD—A research report published in the September 2012 issue of the Journal of Leukocyte Biology offers a possible explanation of why some cancer vaccines are not as effective as hoped, while at the same time identifies a new therapeutic strategy for treating autoimmune problems. In the report, scientists suggest that cancer, even in the very early stages, produces a negative immune response from dendritic cells, which prevent lymphocytes from working against the disease. Although problematic for cancer treatment, these flawed dendritic cells could be valuable therapeutic tools for preventing the immune system from attacking what it should not, as is the case with autoimmune disorders and organ transplants.

"Immunotherapy of cancer has been an elusive research target that, though promising, never seems to 'get there,'" said José Alexandre M. Barbuto, Ph.D., from the Laboratory of Tumor Immunology, Department of Immunology, Institute of Biomedical Sciences at the University of São Paulo, in São Paulo, Brazil. "This study helps us to better understand the mechanisms by which tumors avoid immune recognition and rejection and may, therefore, teach us how to actually engage effectively the immune system in the fight against tumors, thus achieving much better clinical responses and, consequently, quality of life, in our therapeutic approaches."

To make this discovery, researchers obtained a small sample of blood from breast cancer patients, and from healthy volunteers. The blood cells were then separated and induced to become dendritic cells. Researchers then used these laboratory-generated dendritic cells to induce responses from other immune system cells, namely lymphocytes. While dendritic cells from the healthy donors induced vigorous lymphocytic responses, dendritic cells from cancer patients induced mainly the activation of a specific type of lymphocyte, a regulatory lymphocyte that works as a "brake" for other types of lymphocytes.

"Understanding why the immune system does not recognize and eliminate cancer is critical to developing effective immunotherapies to fight the disease," said John Wherry, Ph.D., Deputy Editor of the Journal of Leukocyte Biology. "Immunologists have been trying to unravel the answer to this question for decades and have realized that the problem is both on the immune system side, and because cancer cells appear to actively 'fly under the radar' avoiding immune system detection. This article offers insights into the underlying mechanisms regulating a key immune cell type, the dendritic cell, involved in initiating anti-tumor responses."
**Flu Is Transmitted Before Symptoms Appear, Study in Ferrets Suggests**

ScienceDaily (Aug. 29, 2012) — Research at Imperial College London examining influenza transmission in ferrets suggests that the virus can be passed on before the appearance of symptoms. If the finding applies to humans, it means that people pass on flu to others before they know they’re infected, making it very difficult to contain epidemics.

The research was supported by the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre.

Knowing if people are infectious before they have symptoms is important to help authorities plan for an epidemic, but has been difficult to establish this from data collected during outbreaks. Previous research using mathematical models estimated that most flu transmission occurs after the onset of symptoms, but some happens earlier.

The new study, published in the open access journal *PLoS ONE*, is the first to investigate this question experimentally in an animal model. Ferrets are commonly used in flu research because they are susceptible to the same virus strains and show similar symptoms to humans.

Ferrets with flu were put in contact with uninfected ferrets for short periods at different stages after infection. Transmission occurred before the first symptom, fever, appeared, both when the ferrets were in the same cage and when they were in adjacent cages.

Professor Wendy Barclay, the study’s lead author from the Department of Medicine at Imperial College London, said: "This result has important implications for pandemic planning strategies. It means that the spread of flu is very difficult to control, even with self-diagnosis and measures such as temperature screens at airports. It also means that doctors and nurses who don’t get the flu jab are putting their patients at risk because they might pass on an infection when they don’t know they’re infected."

The flu strain used in the study was from the 2009 swine flu pandemic, which killed almost 300,000 people worldwide.

The researchers found that ferrets were able to pass on flu to others just 24 hours after becoming infected themselves. The animals did not suffer from fever until 45 hours after infection and began sneezing after 48 hours. The results are consistent with earlier studies which found that sneezing is not necessary to transmit flu—droplets of virus are expelled into the air during normal breathing.

In the late stages of infection, after five or six days, flu was transmitted much less frequently, suggesting that people can return to work or school soon after symptoms subside with little risk of passing flu on to others.

The first author, Dr Kim Roberts, who is now based at Trinity College Dublin, said: "Ferrets are the best model available for studying flu transmission, but we have to be cautious about interpreting the results in humans. We only used a small number of animals in the study, so we can’t say what proportion of transmission happens before symptoms occur. It probably varies depending on the flu strain."

**Journal Reference:**

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**Malaria Nearly Eliminated in Sri Lanka Despite Decades of Conflict**

ScienceDaily (Aug. 29, 2012) — Despite nearly three decades of conflict, Sri Lanka has succeeded in reducing malaria cases by 99.9 percent since 1999 and is on track to eliminate the disease entirely by 2014.

According to a paper published August 29 in the online, open-access journal *PLoS ONE*, researchers from Sri Lanka’s Anti-Malaria Campaign and the UCSF Global Health Group examined national malaria data and...
interviewed staff of the country's malaria program to determine the factors behind Sri Lanka's success in controlling malaria, despite a 26-year civil war that ended in 2009.

Typically, countries with conflict experience a weakening of their malaria control programs and an increased risk of outbreaks and epidemics, the researchers said.

Chief among its keys to success was the program's ability to be flexible and adapt to changing conditions, the study found. For instance, to protect hard-to-reach, displaced populations, public health workers deployed mobile clinics equipped with malaria diagnostics and antimalarial drugs, whenever it was safe to do so. Likewise, when it was impossible to routinely spray insecticides in homes in conflict zones, the malaria program distributed long-lasting insecticide-treated nets, engaging non-governmental partner organizations familiar with the areas to help with distribution.

The program was able to sustain key prevention and surveillance activities in conflict areas through support from partner organizations and support from the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Otherwise, researchers found that the keys to Sri Lanka's success were the same as those deployed in non-conflict areas: rigorously and consistently providing interventions to prevent malaria among high-risk populations; proper and prompt diagnosis and treatment of all confirmed malaria cases; and maintenance of an effective surveillance system to quickly detect and respond to spikes in cases. Still, challenges remain.

"Sustaining the gains of elimination efforts and preventing resurgence is even more challenging today, especially in tropical settings such as Sri Lanka," said Rabindra Abeyasinghe, MD, the paper's first author, who led the research at the Sri Lankan Anti-Malaria Campaign. "In this era, sustaining the interest of partners and local decision makers, and ensuring continued funding, are becoming increasingly difficult. To avoid the tragic mistakes of the past, we must resolve to continue to devote the necessary resources and energy to the fight against malaria in Sri Lanka."

Sri Lanka has an extensive history of battling malaria, and nearly eliminated it once before. In 1963, during the era of global eradication efforts, the country achieved a low of only 17 cases, down from 92,000 cases in 1953. With funding declines and reduced spraying and surveillance, the country saw a massive resurgence to 1.5 million cases in 1967-1968.

Since 1970, Sri Lanka has worked to bring malaria back under control, with compelling success, the authors said. In 2011, the country recorded just 124 locally acquired cases—about six cases per million people. This reduction is particularly noteworthy, the researchers noted, given that much of the progress was made during the civil war.

"It is very exciting to document Sri Lanka's current progress toward malaria elimination, to add another chapter to our country's ongoing fight against the disease," said Gawrie Galappaththy, MD, a study coauthor at the Anti-Malaria Campaign at Sri Lanka's Ministry of Health. However, she said, achieving zero malaria will require continued investments and hard work.

"There is no silver bullet for malaria elimination," Galappaththy said. "Instead, it's a daily commitment to finding the cases, treating the patients and preventing transmission."

Today, even with the country's great progress, Sri Lanka continues to face hurdles in its goal of driving malaria transmission to zero. Total malaria cases have dramatically dropped, but the proportion of Plasmodium vivax malaria infections—the more difficult to diagnose and treat form of malaria most common in Sri Lanka—is on the rise.

Another challenge is the shift in the population group at highest risk for malaria. In most of the world, children and pregnant women are most at risk; however following the success of Sri Lanka's control program in protecting and treating these populations, the researchers found that the group most at risk today in Sri Lanka is adult men, particularly those exposed to malaria-carrying mosquitoes through their work, such as gem mining, military service and farming. Sri Lanka is developing new strategies to target these groups.

"Sri Lanka is showing the world how to eliminate malaria," said Sir Richard Feachem, KBE, FREng, DSc(Med), PhD, director of the Global Health Group and senior author of the paper. "The country has made extraordinary progress, reducing malaria by 99.9 percent in the past decade. And all this achieved during a particularly nasty civil war. With continued commitment from the country's Government and supporters, we are confident that Sri Lanka will finish the fight and become a malaria-free country."

Journal Reference:
Long-Held Theory On Human Gestation Refuted: Mother’s Metabolism, Not Birth Canal Size, Limits Gestation

ScienceDaily (Aug. 27, 2012) — New research by a University of Rhode Island professor suggests that the length of human pregnancy is limited primarily by a mother’s metabolism, not the size of the birth canal. The research, published in the Proceedings of the National Academy of Sciences the week of August 27, challenges the long-held notion of an evolutionary trade-off between childbirth and a pelvis adapted for walking upright.

Two traits that set humans apart from other primates—big brains and the ability to walk upright—could be at odds when it comes to childbirth. Big brains and the big heads that encase them are hard to push through the human birth canal, but a wider pelvis might compromise bipedal walking. Scientists have long posited that nature's solution to this problem, which is known as the "obstetric dilemma," was to shorten the duration of gestation so that babies are born before their heads get too big. As a result, human babies are relatively helpless and seemingly underdeveloped in terms of motor and cognitive ability compared to other primates.

"All these fascinating phenomena in human evolution—bipedalism, difficult childbirth, wide female hips, big brains, relatively helpless babies—have traditionally been tied together with the obstetric dilemma," said Holly Dunsworth, an anthropologist at the University of Rhode Island and lead author of the research. "It's been taught in anthropology courses for decades, but when I looked for hard evidence that it's actually true, I struck out."

The first problem with the theory is that there is no evidence that hips wide enough to deliver a more developed baby would be a detriment to walking, Dunsworth said. Anna Warrener, a post-doctoral researcher at Harvard University and one of the paper’s co-authors, has studied how hip breadth affects locomotion with women on treadmills. She found that there is no correlation between wider hips and a diminished locomotor economy.

"That throws doubt on the assumption that the size of the birth canal is limited by bipedalism," Dunsworth said. "Wide hips don’t mean you can’t walk efficiently."

Then Dunsworth looked for evidence that human pregnancy is shortened compared to other primates and mammals. She found well-established research to the contrary. "Controlling for mother's body size, human gestation is a bit longer than expected compared to other primates, not shorter," she said. "And babies are a bit larger than expected, not smaller. Although babies behave like it, they're not born early."

For mammals in general, including humans, gestation length and offspring size are predicted by mother's body size. Because body size is a good proxy for an animal's metabolic rate and function, Dunsworth started to wonder if metabolism might offer a better explanation for the timing of human birth than the pelvis.

To investigate that possibility, she enlisted the help of Peter Ellison of Harvard University and Herman Pontzer of Hunter College in New York, two experts in human physiology and energetics. Building on Ellison's prior work on human pregnancy and childbirth, the researchers developed a new hypothesis for the timing of human birth called the EGG (energetics, gestation, and growth).

"Under the EGG, babies are born when they’re born because mother cannot put any more energy into gestation and fetal growth," Dunsworth explains. "Mom's energy is the primary evolutionary constraint, not the hips."

Using metabolic data on pregnant women, the researchers show that women give birth just as they are about to cross into a metabolic danger zone.

"There is a limit to the number of calories our bodies can burn each day," says Pontzer. "During pregnancy, women approach that energetic ceiling and give birth right before they reach it. That suggests there is an energetic limit to human gestation length and fetal growth."

Those metabolic constraints help explain why human babies are so helpless compared to our primate kin, like chimpanzees. A chimp baby begins crawling at one month, whereas human babies don’t crawl until around seven months. But for a human to give birth to a newborn at the same developmental level as chimp, it would take a 16-month gestation. That would place mothers well past their energetic limits. In fact, even one extra month of gestation would cross into the metabolic danger zone, the researchers found.

"It would be physiologically impossible, regardless of pelvic bone anatomy, to birth a more developed baby," Dunsworth said. "Our helplessness at birth is just a sign of how much more brain growth we have to achieve once we start living outside our mother."
The energetics, gestation and growth hypothesis would downplay an implication of the obstetric dilemma that Dunsworth finds odd.

"We've been doing anthropology with this warped view of the male pelvis as the ideal form, while the female pelvis is seen as less than ideal because of childbirth," she said. "The female births the babies. So if there's an ideal, it's female and it's no more compromised than anything else out there. Selection maintains its adequacy for locomotion and for childbirth. "If it didn't, we'd have gone extinct," Dunsworth said.

**Alarming Levels of Drug-Resistant TB Found Worldwide**

*Reuters*, (08.30.2012)  Kate Kelland

A large international study published Thursday shows rates of both multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB) in Africa, Asia, Europe, and Latin America are much higher than previously thought.

MDR TB is resistant to at least two first-line treatments—isoniazid and rifampicin—and XDR TB is resistant to these two as well as fluoroquinolone and a second-line injectable antibiotic. The rise of drug-resistant TB is partly due to patients failing to complete the lengthy six-month regimen of powerful antibiotics used to treat regular TB.

Treatment for drug-resistant TB can cost 200 times more than regular TB and take up to two years to complete, said Tom Evans, chief scientific officer at Aeras, a nonprofit working to develop new TB vaccines. Medical options for XDR TB patients, he said, are "limited, expensive, and toxic."

CDC’s Tracy Dalton, who led the study, said the spread of drug-resistant TB is “particularly worrisome” in areas with limited health care resources and poor access to effective drugs. So far, she said, XDR TB has been reported in 77 countries worldwide. "As more individuals are diagnosed with, and treated for, drug-resistant TB, more resistance to second-line drugs is expected to emerge," she noted.

The study found resistance to at least one second-line TB drug in nearly 44 percent of patients overall, ranging from 33 percent in Thailand to 62 percent in Latvia.

In about one-fifth of cases, resistance was seen to at least one second-line injectable drug, ranging from 2 percent in the Philippines to 47 percent in Latvia. XDR TB was detected in 6.7 percent of patients overall. XDR TB rates in South Korea (15.2 percent) and Russia (11.3 percent) were more than double the World Health Organization’s global estimate of 5.4 percent.


**Nurses, Midwives Can Safely Perform Abortions, Review Of Evidence Suggests**

"Abortions are just as safe when performed by trained nurse practitioners, midwives and physician assistants as when doctors do them, a new review of the evidence suggests," Reuters reports. "Researchers analyzed five studies that compared first-trimester abortion complications and side effects based on who performed the procedures in close to 9,000 women—and typically found no differences," the news service writes. The review is published in BJOG: An International Journal of Obstetrics and Gynaecology, according to the news service.

"Having trained nurses and midwives perform abortions could also allow some women to get care before they would be able to see a doctor—and earlier access typically means fewer complications and better outcomes. [Amy Levi, a professor of midwifery at the University of New Mexico in Albuquerque who was not involved in the study,] said," the news service writes, adding, "That's especially the case in developing countries, where doctors who perform abortions may be few and far between." However, "Nathalie Kapp from the World Health Organization in Geneva, Switzerland, and her colleagues said the findings don't apply to nurses and midwives who perform abortions without access to emergency care nearby, or to abortions done after the first trimester," Reuters notes (Pittman, 8/30).

**Challenges To Eradicating Polio In Nigeria**

John Campbell, Ralph Bunche senior fellow for Africa policy studies at the Council on Foreign Relations, writes in his "Africa in Transition" blog that "[t]he Global Polio Eradication Initiative (GPEI) reports eight new polio cases in Nigeria, bringing the total in that country to 70 for 2012," with most of the cases occurring in the predominantly Muslim north. "Despite efforts by the Nigerian government and the international community, polio is far from being eradicated in Nigeria," he states and discusses challenges to fighting the disease in the country (8/30).
Danish scientists solve old blood mystery

New intriguing knowledge on blood haemoglobin has just been published in Nature

Scientists at the research centre MEMBRANES at Aarhus University, Denmark, have completed an old puzzle, which since the 60s from many sides has been regarded as impossible to complete. The challenge was to solve the structure of the protecting protein complex that forms when haemoglobin is released from red cells and becomes toxic. This toxic release of haemoglobin occurs in many diseases affecting red cell stability, e.g. malaria.

Technically, the most important finding in this report in Nature is a high-resolution three-dimensional mapping of the so-called 'haptoglobin-haemoglobin complex'.

"After many failing experiments, our breakthrough came when we gave up using human material and went to the local slaughterhouse to purchase pig blood. Not a particular high-technological approach, but this transition from studying human blood to blood from a species with close homology had magic effects. After running into dead ends for two years and trying out the most complex gene-technological ways to produce the right material, it suddenly worked", says Søren Kragh Moestrup, the head of the research group at Department of Biomedicine.

The discovery provides new essential information on haemoglobin that makes up most of the red cell interior. Haemoglobin is an essential blood component for transport of oxygen, but it becomes toxic with potent damaging effects on tissues, in particular the kidneys, when it is released from the red cells. An excessive release can occur in many diseases, such as malaria and other infections.

However, the body has a sophisticated defence system. The first line defence is carried out by the blood protein haptoglobin, which captures haemoglobin and gates it to a receptor that engulfs the haemoglobin-haptoglobin complex. This function of the receptor named CD163 was originally discovered by the same group.

"We have now shown how this unique protein complex forms by generation of a detailed 3-dimensional map of each atom. This shows for the first time how the complex is formed and explains the tight protein association", says PhD Christian Brix Folsted Andersen. He has together with Master's student Morten Torvund-Jensen been an essential driving force in the project.

The results have also led to an unexpected discovery of a novel type of protein structure and a new patent submission on exploitation of the discovery for use in generation of a new type of synthetic proteins to be used in therapy and diagnostics.

The Nature paper "Structure of the haptoglobin-haemoglobin complex" is available.

Bacterium Transforms Into Weapon Against Sleeping Sickness

ScienceDaily (Aug. 30, 2012) — Scientists of the Antwerp Institute of Tropical Medicine (ITG) opened a new front against the cause of sleeping sickness. This parasite is transmitted between humans by tsetse flies. The researchers learned a bacterium living in those flies how to produce antibodies against the parasite. Application in the field is still a long way of, but the technique shows quite some promise.

Sleeping sickness is caused by trypanosomes, parasites being transmitted by the bite of a tsetse fly. The World Health Organization estimates the yearly death toll at between 10,000 and 20,000 people. On top of that, the parasite also infects cattle, causing considerable economic loss. Many small African farmers depend on their cattle.

Without treatment, an infection is irrevocably fatal. Unfortunately, many poor people present at the hospital only in a late stadium. At that time the Trypanosoma parasites have lodged themselves in the brain, behind the notorious blood-brain barrier that keeps most drugs out. Arsenic compounds can pass the barrier and kill the parasite, but they also kill five per cent of the patients. New drugs are not in the pipeline.

Besides the parasite, one may also attack its vector, the tsetse fly. But insecticides may be detrimental to the environment, certainly in the long run. Therefore scientists look for alternative strategies. For instance genetically modified insects that are incapable of being infected by the parasite, or do not transmit it. But germline transformation of tsetse flies is unfeasible. To do so, one must be able to handle the eggs, but tsetse flies do not lay eggs, they directly bring forth a larva.

Therefore, the Antwerp researchers took another road. Tsetse flies harbour, as is the case with many insects, resident bacteria. One of them, Sodalis glossinidius (literally: companion of the tsetse fly) exclusively lives in tsetse flies. And it can be cultivated in the lab. De Vooght was the first to genetically modify the bacterium so it produces, and excretes, a very efficient type of antibody, called a nanobody.
She identified two different secretory pathways that transported the nanobodies out of the bacterium. She also demonstrated that the bacterium was not hampered by its modification, so it can stand its ground amidst non-modified, ‘wild type’ congeners inside the fly.

Next, with antibiotics she cleared tsetse flies of their wild type bacteria and replaced those by the modified bacteria. These successfully colonized the flies and started producing nanobodies. The nanobodies also were present in the midgut, where the sleeping sickness parasite also is to be found.

De Vooght demonstrated the feasibility of the technique, but it still needs some development before it can be used to control sleeping sickness in the field. For instance, the antibodies now produced by the bacteria, are directed against a form of the parasite occurring in humans, not in flies. This is simply because this antibody was available, while the one against the fly form still has to be developed. De Vooght: "We wanted to demonstrate first that the technique works in principle. Now we have achieved that, we can tackle the technical details."

To the scientists it is just as important that symbiotic bacteria producing all kinds of substances are a means to getting insight into the interactions between disease-causing organisms and their insect vectors. The Antwerp researchers already demonstrated that the sleeping sickness parasite interferes with the saliva production of tsetse flies, forcing them to bite more humans than they otherwise would do. Insight in that kind of interactions might be instrumental to opening new ways of attacking diseases.

**Bacterial Cause Found for Skin Condition Rosacea**

ScienceDaily (Aug. 28, 2012) — Scientists are closer to establishing a definitive bacterial cause for the skin condition rosacea. This will allow more targeted, effective treatments to be developed for sufferers, according to a review published in the *Journal of Medical Microbiology*.

Rosacea is a common dermatological condition that causes reddening and inflammation of the skin mostly around the cheeks, nose and chin. In severe cases skin lesions may form and lead to disfigurement. Rosacea affects around 3% of the population—usually fair-skinned females aged 30-50 and particularly those with weak immune systems. The condition is treated with a variety of antibiotics, even though there has never been a well-established bacterial cause.

A new review carried out by the National University of Ireland concludes that **rosacea may be triggered by bacteria that live within tiny mites that reside in the skin.**

The mite species *Demodex folliculorum* is worm-like in shape and usually lives harmlessly inside the pilosebaceous unit which surrounds hair follicles of the face. They are normal inhabitants of the face and increase in number with age and skin damage—for example, following exposure to sunlight. The numbers of Demodex mites living in the skin of rosacea patients is higher than in normal individuals, which has previously suggested a possible role for the mites in initiating the condition.

More recently, the bacterium *Bacillus oleronius* was isolated from inside a Demodex mite and was found to produce molecules provoking an immune reaction in rosacea patients. Other studies have shown patients with varying types of rosacea react to the molecules produced by this bacterium—exposing it as a likely trigger for the condition. What’s more, this bacterium is sensitive to the antibiotics used to treat rosacea.

Dr Kevin Kavanagh who conducted the review explained, "The bacteria live in the digestive tracts of Demodex mites found on the face, in a mutually beneficial relationship. When the mites die, the bacteria are released and leak into surrounding skin tissues—triggering tissue degradation and inflammation."

"Once the numbers of mites increase, so does the number of bacteria, making rosacea more likely to occur. Targeting these bacteria may be a useful way of treating and preventing this condition," said Dr Kavanagh. "Alternatively we could look at controlling the population of Demodex mites in the face. Some pharmaceutical companies are already developing therapies to do this, which represents a novel way of preventing and reversing rosacea, which can be painful and embarrassing for many people."

**Journal Reference:**
Stanisław Jarmuda, Niamh O'Reilly, Ryszard Żaba, Oliwia Jakubowicz, Andrzej Szkaradkiewicz and Kevin Kavanagh. **The potential role of Demodex folliculorum mites and bacteria in the induction of rosacea.** *Journal of Medical Microbiology*, 2012 DOI: [10.1099/jmm.0.048090-0](https://doi.org/10.1099/jmm.0.048090-0)