August 2013 Epidemics and AIDS Update

1. Antibiotic resistance among hospital-acquired infections is much greater than prior CDC estimates
2. 3-D Molecular Syringes: Scientists Solve Structure of Infection Tool Used by Yersinia Bacterium
3. ‘HCC-4 risk score’ IDs hepatitis C patients likely to develop HCC
4. Sex, drugs and health inequalities: gay men and the public health system
5. FDA to Scrutinize HPV Test Linked to False Readings
6. Plant-Based Compound May Inhibit HIV
7. New findings could influence the development of therapies to treat dengue disease
8. As Climate, Disease Links Become Clearer, Study Highlights Need to Forecast Future Shifts
9. How 'Junk DNA' Can Control Cell Development
10. Trials challenging HIV drug doses could usher in huge cost cuts
11. How to achieve a well-balanced gut
12. Scientific breakthrough reveals how vitamin B12 is made
13. Hormone Receptors May Regulate Effect of Nutrition On Life Expectancy Not Only in Roundworms, but Perhaps Also in Humans
14. Human Epigenomic Map Extended
15. Is Sous Vide Cooking Safe?
16. FDA approves new drug to treat HIV infection
17. New Hepatitis B vaccine developed
18. Monkeys Achieve Drug-Free Control of SIV
19. Levels of HIV-Target Macrophages in Rectum May Facilitate Infection
20. As US FDA approves promising new HIV drug dolutegravir, MSF asks when people in developing countries will have access
21. Rapid HIV Test Approved by FDA
22. MRSA strain in humans originally came from cattle
23. Breaking up the superbugs' party
24. High-Angle Helix Helps Bacteria Swim
25. What If HIV Had Never Happened?
26. Why ACT UP Has Declared War on the New HIV Pandemic
27. Neutron studies of HIV inhibitors reveal new areas for improvement
28. Scripps Research Institute scientists reveal how deadly Ebola virus assembles
29. Tufts scientists develop new early warning system for cholera epidemics
30. Answering crucial questions about anthrax exposure
31. More Than 28 Cups of Coffee a Week May Endanger Health in Under 55s
32. Researchers Debunk Myth of 'Right-Brained' and 'Left-Brained' Personality Traits
33. New Strategy to Disarm the Dengue Virus Brings New Hope for a Universal Dengue Vaccine
34. Heat Waves Increase Incidence of Infectious Gastroenteritis and IBD Flares
35. High prevalence of CMV retinitis among HIV-positive patients in Asia and Africa
36. Low baseline CD4 cell count associated with greater bone loss after starting HIV therapy
37. Zimbabwe: Killed for Refusing to Take ARVs
38. Food fungi in developing countries linked to worse HIV infection
39. Bacterial toxins cause deadly heart disease
40. New explanation for key step in anthrax infection proposed by NIST and USAMRIID
41. Growing share of HIV/AIDS burden shifts to changing group of regions
42. A Home for the Microbiome: Biologists Identify How Beneficial Bacteria Reside and Thrive in Gastrointestinal Tract
43. Ingredient in Turmeric Spice When Combined With Anti-Nausea Drug Kills Cancer Cells
44. Coffee and Tea May Contribute to a Healthy Liver
45. Panel Eviscerates UK Forensic Science
46. Opinion: Statistical Misconceptions
47. Turmoil for AIDS Conference Organizers
48. When function isn’t always 'function' for non-coding RNAs
49. Double trouble: Mark Jobling on twin studies and the genetics of uniqueness
50. Cancer-Associated Viruses Overblown?
51. Q&A: NIH Brokers Hela Genome Deal
52. Cancer-Causing Herbal Remedies
53. Tumor-Targeting T Cells Engineered
Antibiotic resistance among hospital-acquired infections is much greater than prior CDC estimates

FDA 'reboot' of antibiotic development rules falls short

LOS ANGELES – (August 1, 2013) – The rise of antibiotic resistance among hospital-acquired infections is greater than the Centers for Disease Control and Prevention (CDC) found in its 2008 analysis, according to an ahead-of-print article in the journal, *Antimicrobial Agents and Chemotherapy*.

The article also finds that the Food and Drug Administration's (FDA) promise to "reboot" antibiotic development rules a year ago to combat the rise in resistance has fallen short.

The commentary, whose authors include Brad Spellberg, MD, a Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (LA BioMed) infectious disease specialist, analyzed privately gathered data and concluded antibiotic resistance among hospital-acquired infections is "at crisis levels."

The FDA’s "reboot" pledge to encourage the development of new antibiotics to battle this resistance "cannot come too soon" but "will not be enough," the authors conclude.

"With antibiotic-resistant microbes infecting more than 2 million Americans every year and killing more than 100,000 annually, we must act to find new weapons in the global battle against deadly Superbugs," said Dr. Spellberg, M.D., who authored "Rising Plague," a book on antibiotic resistance. "Our analysis found the rise in antibiotic resistance among three common forms of hospital-acquired infections is much greater than previously reported by the CDC based on older data, leading us to conclude that more than an FDA 'reboot' is needed. To encourage antibiotic development, the pharmaceutical industry must see that there is a path for a return on its investment in antibiotic development."

The authors found "very positive aspects" in the FDA's most recent guidance for antibacterial therapies for patients with unmet medical needs. But they said the FDA's approach to the development of antibacterials in traditional indications, such as pneumonia and urinary tract infections, "has been mixed."

Their findings on the rise on antibiotic resistance among hospital-acquired infections include:

- The resistance for *Acinetobacter (A. baumannii)* to carbapenems is more than 50%. The CDC found it to be 11%. Carbapenems are among the last available antibiotics. If they don't work, only one or two other drugs are left to battle these infections. Neither is very effective, and one is highly toxic.
- The resistance among E. coli to third generation cephalosporins (a class of antibiotics) was 8-11%. The CDC found it to be 5%.
The resistance to *klebsiella* (*K. pneumonia*) to third generation cephalosporins was 20-27%. The CDC found it to be 15%. Resistance to carbapenems among these isolates is now between 7 and 11%.

Carbapenems are already obsolete for a common Intensive Care Unit infection, *Acinetobacter baumannii*. "This holds true for both intensive care and non-intensive care patients and for urinary and non-urinary infections," the commentary says.

"None of the antibiotics under development today can address all of these antibiotic-resistant infections," said Dr. Spellberg. "A complete overhaul of the approaches to resistance, disease and prevention could change the continuing upward trajectory of antibiotic resistant infections. To do anything less invites a bleak post-antibiotic future, in which infectious diseases once again reign supreme."

**3-D Molecular Syringes: Scientists Solve Structure of Infection Tool Used by Yersinia Bacterium**

July 31, 2013 — Abdominal pain, fever, diarrhea—these symptoms could point to an infection with the bacterium *Yersinia*. The bacterium's pathogenic potential is based on a syringe-like injection apparatus called injectisome. For the first time, an international team of researchers including scientists at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany, has unraveled this molecular syringe's spatial conformation. The researchers were able to demonstrate that the length of *Yersinia's* injectisome's basal body, which crosses the bacterial cell wall, is adjustable—very likely an adaptation to physical stress.

The rod-shaped bacterium *Yersinia enterocolitica*, which is transmitted through contaminated food, causes gastrointestinal diseases. In Germany alone, several thousand cases are reported annually. *Yersinia* uses a rather sophisticated tool—its injection apparatus—to infect humans. Not only does the apparatus look like a syringe, it actually serves a similar purpose. A molecular "needle," which sticks out from the bacterium's surface, extends across the bacterial membranes to the host cell. It is through this needle that the bacterium "injects" substances that facilitate infection of the host. Now, for the first time, an interdisciplinary team of HZI scientists together with their colleagues at the Biozentrum of the University of Basel and at the Ecole Polytechnique Fédérale de Lausanne in Switzerland, has presented the structure of *Yersinia enterocolitica*’s injectisome in high-resolution and 3D. They published their results in the digital scientific magazine eLife.

Their innovative approach has yielded surprising results. Previous studies had been concerned with isolating the molecular syringe from the bacterium and studying it under the electron microscope. "We, however, actually studied the injectisome in situ, in other words, on the bacterial surface, right where it normally occurs," explains Prof. Henning Stahlberg, University of Basel. To this end, the researchers cooled the bacteria to minus 193 degrees Celsius and used cryo-electron microscopy to take pictures of the syringe from various angles. They then computed a spatial structure from a set of two-dimensional images—a highly effective method for examining large molecular complexes. The syringe, which consists of some 30 different proteins, definitely falls into that category.

When comparing over 2000 single syringes from over 300 bacteria, the researchers made a surprising discovery: "There is a range of different lengths of each injection apparatus' base—in some cases, it's on the order of ten nanometers, or ten millionth of a millimeter. It can be stretched or compressed—just like a spring," explains Dr. Stefan Schmelz of the HZI, one of the study's first authors. As much as we consider
such dimensions to be miniscule—to a bacterium, which itself is but a hundred times that size, they are substantial. "Bacteria are exposed to considerable forces, be it during contact with other cells or upon changes in environmental salinity," explains Prof. Dirk Heinz, the HZI's scientific director and former head of the HZI Department of Molecular Structural Biology. "If the injectisomes were rigidly constructed, bacteria would most likely be unable to resist these forces. Their cell walls would simply rupture."

Insights into the structure of Yersinia's attack tool offer clues as to ways in which the molecular syringe may be therapeutically inhibited. Without this apparatus, the bacteria are practically harmless. "Also other pathogenic bacteria make use of this principle during infection, for example Salmonella that cause food poisoning," confirms Dr. Mikhail Kudryashev, another of the study's primary authors and a researcher at the University of Basel. The team was already able to document this same flexibility in Shigella, the causative agent behind bacillary dysentery. The "molecular building kit," as Schmelz calls it, is highly similar, suggesting that insights from this current study can potentially also be applied to other pathogenic bacteria.

**Journal Reference:**

**'HCC-4 risk score' IDs hepatitis C patients likely to develop HCC**

By: Mary Ann Moon, Family Practice News Digital Network

A risk score derived from four simple test results readily obtained during routine care may help identify the patients with chronic hepatitis C who are most at risk for developing hepatocellular carcinoma, according to a retrospective study published online July 12 in the European Journal of Internal Medicine.

The score could enable physicians to target only the highest-risk patients for annual surveillance for malignant hepatic nodules, which is crucial because current screening methods are too invasive, too expensive, and too low-yield to be applied broadly across all risk groups.

The new risk score also may help identify patients with chronic hepatitis C who are at lowest risk for developing HCC, who can then be reassured that they can safely forgo invasive and expensive surveillance, reported Dr. Juan Carlos Gavilan and his associates at University Hospital Virgin de la Victoria, Malaga (Spain).

The investigators reviewed data from a 17-year longitudinal cohort study involving 829 patients with chronic hepatitis C. These subjects were assessed every 6 months for the development of HCC using serum alpha-fetoprotein (AFP) levels and ultrasound imaging to detect new focal hepatic lesions.

A total of 58 subjects (7%) developed HCC during follow-up.

An initial univariate analysis identified numerous clinical and epidemiologic factors associated with elevated risk for HCC. The researchers constructed a formula for predicting risk using the four independent factors that were most predictive of HCC in this cohort: patient age, platelet count, gamma-globulin level, and AFP level at baseline.

By dividing the study population into tertiles, Dr. Gavilan and his colleagues established cutoff ranges for low, medium, and high risk. They then classified each study participant as belonging to one of these three categories, to see how well this risk score correlated with the actual rates of HCC.

The annual incidence of HCC was 0.06% in the group designated as low risk, 0.5% in the group designated as medium risk, and 2.6% in the group designated as high risk, indicating that this "HCC-4 risk score" was indeed highly predictive, Dr. Gavilan and his associates said (Eur. J. Intern. Med. 2013 July 12 [**doi: 10.1016/j.ejim.2013.06.010**]).

In fact, the score was more accurate at predicting HCC than was the commonly used fibrosis index, they noted.

According to recently published recommendations, surveillance is only justified in populations with an HCC incidence of 1.5% or more per year. Thus, patients found to be high risk using this HCC-4 risk score would be appropriate for such surveillance, while those at medium or low risk would not be.

"These results must be confirmed in other studies," the investigators said.

There was no external funding source for this study, and no financial conflicts of interest were reported.
Sex, drugs and health inequalities: gay men and the public health system
By: Information Daily Staff Writer
Published: Friday, August 2, 2013—09:33 GMT

'Are gay and bisexual men getting a bum deal from public health?’ asks Monty Moncrieff, Chief Executive of London Friend, the UK’s oldest LGBT charity.

Last week we saw the second report in 6 months in leading medical journal The Lancet on the link between new HIV infections and the use of ‘party’ drugs. New HIV infections amongst men who have sex with men (MSM) in London are up more than 20% on last year, a trend we’ve feared based on the gay and bisexual men accessing our specialist support service Antidote for support around their drug use.

It’s another example of health inequalities for people of different sexual orientations and/or gender identities. Are we on the verge of a new public health crisis for the gay community?

Antidote has provided support around drug and alcohol concerns to lesbian, gay, bisexual and transgender people for over a decade, based first with Turning Point in Westminster and since 2011 with the LGBT health charity London Friend. During this time we’ve seen a dramatic shift in the issues clients bring to our service. We used to work primarily with alcohol and powder cocaine users, with some problematic use of ecstasy and ketamine thrown in. Even then this was distinct from the drugs seen in most substance misuse services where heroin and crack dominated, but now the difference is even more pronounced.

Three drugs have dominated our work since around 2010: crystal methamphetamine (a drug that has caused significant concern globally but hasn’t yet hit the UK mainstream); G (shorthand for GHB or GBL, both former “legal highs” and now controlled substances); and mephedrone (the tabloid journalists’ now infamous “meow-meow”). The latter of these has been well-documented across a diverse range of users but we’re seeing the other two disproportionately used by MSM, with crystal barely making a dent outside of these groups.

These drugs are bringing a new set of harms to the doors of treatment agencies like ours, and the NHS partnership we provide with the Club Drug Clinic. We hear alarming rates of injecting – from a community who traditionally found the idea taboo and who consider themselves a world removed from the IV heroin ‘junkie’. We’ve found that regular use of G causes physical dependence, in much the same way as daily alcohol use, and men have had to be admitted to detoxification programmes, sometimes as in-patients, for a medically complex withdrawal.

Oh, and let’s just talk about sex... The vast majority of men seeking support tell us they are using during sex. Of course, sex and drugs have gone hand in hand for many years (inextricably linked to rock & roll) but something’s changed. The pattern used to be to go out for a night on the town, a few drinks, perhaps some ‘recreational’ drugs, a nightclub and then a tumble into bed at the end of the night if you’d got lucky. Our guys tell us now they’re actively seeking sexual encounters specifically to use drugs, often missing the bars and clubs entirely by using social media and smartphone apps to hook-up.

A new vocabulary has emerged to help them find exactly what they’re after: they seek ‘chem-sex’ or ask to P&P (party – or pipe, to indicate the smoking of crystal—and play). The trend is to ‘play’ for several hours, sometimes a few days, and many like to eschew condoms in favour of ‘raw’ or ‘bareback’ sex. Shocking? For those of us who remember the portentous AIDS adverts of the 80s then yes, it can be; the condom message was hammered home whilst gay men died at a frightening rate. But today there’s a different climate around HIV with some people less fearful of the virus, or unaware of the consequences of becoming positive.

Unsurprisingly this all makes for, quite literally, a toxic mix. We see the impact of prolonged or heavy use on our clients’ physical and mental well-being. When we talk to them about their feelings we hear time and again a sense of having felt different growing up; some expecting to be judged for their sexual identity as gay or bi men; some being told their identity was wrong within their religious or socially conservative upbringing; some fearing exploring who they were at all; and many feeling a sense of anxiety about forming relationships, being intimate with partners, or performing to the standards (they think are) expected having learned about gay sex from watching porn.

Using drugs has often been the escape, the permission, the disinhibition they found gave them some emotional freedom to seek closeness through sex. But all too often they tell us they didn’t find what they thought they were looking for.

This complex set of issues poses new questions for an integrated public health response, at a time when public health itself has undergone a major structural overhaul. As new local teams find their feet these issues are likely to fall outside of their experience, a common enough situation for minority health in
general with sensitivities around addressing need relating to sexual and gender identity. With the focus of local responses potentially open to political sensitivities we’re going to need all the might of the Public Sector Equality Duty, already under Government review before it’s even had a chance to have an impact.

We already know that lesbian, gay, bisexual and transgender people can be reluctant to access mainstream services, or feel excluded from generic health promotion messages. In drug services the focus on opiate and crack use can leave practitioners feeling ill-equipped to treat these new and different drugs. From years providing training I find health and social care staff have rarely, if ever, had an opportunity to discuss supporting LGBT clients in a professional setting.

The drive for localism too risks dealing LGBT people a duff hand as budgets are ever squeezed and services restricted by local geography; economies of scale could be found by pooling scant resources, commissioning specialist services to support a larger population, commissioning across local authority boundaries and commissioning across issues to bring substance misuse, sexual and mental health support together.

To boost uptake of services, Directors of Public Health can invest in centres of excellence where experienced voluntary and community sector organisations can ensure not only LGBT inclusion, but also LGBT competence. (The LGBT third sector receives only 0.03% of all VCO funding, a massive under-investment in a population that even the most conservative estimates place at around three million people in the UK.) Their generic providers can be tasked to demonstrate outcomes for LGBT people and performance managed by LGBT-relevant KPIs. To do this will require improved and routine demographic monitoring of sexual orientation and gender identity.

Resources such as the LGBT Companion to the Public Health Outcomes Framework, endorsed by Public Health England and the Department of Health, provide information on key areas of health inequalities experienced by LGBT people, with pointers to evidence – and the lack of it. It should be a vital tool for anyone involved in a Joint Strategic Needs Assessment.

And, don’t forget the importance of engaging with your target audience: service providers, commissioners and policy makers can hear directly from LGBT people and groups about their health experiences, the barriers they may have faced and what kind of services they would like to use. But remember – our resource is limited and often stretched to capacity; you might want to formally contract us to ensure we can professionally and meaningfully inform your engagement and needs assessment activities.

**FDA to Scrutinize HPV Test Linked to False Readings**

*USA Today*, (07.31.2013) By Bob Ortega

The US Food and Drug Administration (FDA) issued a warning more than six months ago that BD SurePath test kits used to screen women for human papillomavirus (HPV) could give incorrect false-negative results. However, laboratories continued to use the BD SurePath test, prompting a dispute between FDA and the American Clinical Laboratory Association (ACLA).

Becton Dickinson and Co. originally developed the BD SurePath kit for Pap testing; laboratory use of the kit for HPV testing was not FDA-approved. Laboratories used SurePath for approximately 3 million Pap/HPV tests annually, despite national cervical cancer screening guidelines that specified use of FDA-approved tests for HPV screening.

ACLA argued that FDA had no jurisdiction under federal law because the SurePath test was not a medical device. Current law specifies that a laboratory can develop clinical tests or use existing tests for non-FDA-approved purposes, if the laboratory conducted studies to establish the “test’s accuracy and sensitivity.” At present, the Centers for Medicare and Medicaid Services (CMS) exercises oversight of lab-developed tests under the Clinical Laboratory Improvement Amendment (CLIA). Developers can outsource review of laboratory-developed tests to auditors, such as the College of American Pathologists, but are not required to provide results of validation studies to CMS.

Because of concerns about SurePath and other laboratory-developed tests, FDA has submitted new draft guidance to the Obama Administration. The College of American Pathologists agreed with the FDA proposal to regulate “high-risk laboratory-developed tests” and recommended that CLIA regulations continue to govern the development of “low- and moderate-risk laboratory-developed tests.”
Plant-Based Compound May Inhibit HIV

Science Daily, (07.29.2013)

Researchers at George Mason University (GMU) in Fairfax County, Va. are in the early stages of experimenting with genistein, a compound in soybeans and other plants, as an effective HIV treatment.

Genistein is a tyrosine kinase inhibitor, which blocks cell communication. Normally, sensors on the cell’s surface communicate with the cell’s interior as well as with other cells. HIV tricks the surface sensors into sending signals to the interior that change the cell’s structure and allow the virus to enter and infect it. According to Yuntao Wu, a professor with the GMU-based National Center for Biodefense and Infectious Diseases and the Department of Molecular and Microbiology, genistein disrupts this cellular deception that allows the virus to infect cells. This approach differs from that of antiretrovirals, which attack the virus itself. The researchers believe that manipulating the cell rather than the virus might be more successful in preventing drug resistance.

Wu noted that the research is in an early stage, but if genistein proves to be effective, it could be used along with current HIV treatment. Wu also believes that the plant-based approach could reduce the common side effect of drug toxicity caused by the frequency and lifelong duration of multidrug treatments to which HIV-infected individuals must adhere. The researchers are working to determine the amount of genistein needed to inhibit HIV and whether the level of genistein found naturally in plants would be enough or if they would need to develop drugs.

Due to sequestration-based budget cuts, the lab has had to locate new ways to fund its research, including the “NYC DC AIDS Research Ride” cycling fundraiser, which previously raised money for the lab.


New findings could influence the development of therapies to treat dengue disease

New research into the fight against Dengue, an insect-borne tropical disease that infects up to 390 million people worldwide annually, may influence the development of anti-viral therapies that are effective against all four types of the virus.

The findings, led by researchers at the University of Bristol and published in the Journal of Biological Chemistry today [2 August], show for the first time that there may be significant differences in specific properties of the viral proteins for the four dengue virus types.

Due to the effects of globalisation, including increased travel and urbanisation of human populations and the expanded geographical distribution of the mosquito vector that is responsible for the transmission of viral infections to millions of people, the number of individuals afflicted with dengue is rising.

Infection with any one of the four types of dengue virus (DENV types 1 – 4) may result in a spectrum of illnesses ranging from dengue fever, a mild flu like illness which causes high fever and joint pains, to the potentially fatal dengue haemorrhagic fever. Despite intensive research, dengue disease is not wholly understood, and there are no vaccines or anti-viral treatments available that can safely or effectively control the disease.

Dr Andrew Davidson, Senior Virologist and lead researcher from the University of Bristol, and colleagues examined the nuclear localisation properties of the NS5 protein of all four DENV types and found that there are major differences in the cellular localisation of the viral NS5 protein for the four DENV types. The four types of DENV are genetically distinct. Although they can all cause dengue disease, little is known about how the genetic differences between them may translate into differences in virus replication and pathogenesis.

Previous studies by the team focusing on DENV-2, have shown that the viral NS5 protein is essential for DENV genome replication and is able to modulate the host immune response. As such, the NS5 protein is a key target for the development of anti-viral agents. Importantly, the team also showed that the DENV-2 NS5 protein accumulates in the nucleus during infection which is believed to effect host cell function.

Dr Davidson, Senior Lecturer in Virology, School of Cellular and Molecular Medicine at the University of Bristol, said: "The study shows for the first time that there may be significant differences in specific
properties of the viral proteins for the four DENV types. This is important as it impacts on our understanding of viral replication and pathogenesis and the design of anti-viral therapies that are effective against all DENV types.

Present studies in the laboratory are focused on comprehensively comparing the effects of different DENV types on the host cell, using the state-of-the-art proteomics facilities at the University of Bristol.

**Paper**

**As Climate, Disease Links Become Clearer, Study Highlights Need to Forecast Future Shifts**

Aug. 1, 2013 — Climate change is affecting the spread of infectious diseases worldwide, according to an international team of leading disease ecologists, with serious impacts to human health and biodiversity conservation. Writing in the journal *Science*, they propose that modeling the way disease systems respond to climate variables could help public health officials and environmental managers predict and mitigate the spread of lethal diseases.

The issue of climate change and disease has provoked intense debate over the past decade, particularly in the case of diseases that affect humans, according to the University of Georgia's Sonia Altizer, who is the study's lead author.

"For a lot of human diseases, responses to climate change depend on the wealth of nations, healthcare infrastructure and the ability to take mitigating measures against disease," said Altizer, an associate professor in the UGA Odum School of Ecology. "The climate signal, in many cases, is hard to tease apart from other factors like vector control and vaccine and drug availability."

Climate warming already is causing changes in diseases affecting wildlife and agricultural ecosystems, she said. "In many cases, we’re seeing an increase in disease and parasitism. But the impact of climate change on these disease relationships depends on the physiology of the organisms involved, the location on the globe and the structure of ecological communities."

At the organism level, climate change can alter the physiology of both hosts and parasites. Some of the clearest examples are found in the Arctic, where temperatures are rising rapidly, resulting in faster developing parasites. A lungworm that affects muskoxen, for instance, can now be transmitted over a longer period each summer, making it a serious problem for the populations it infects.

"The Arctic is like a 'canary in the global coal mine,'" said co-author Susan Kutz of the University of Calgary and Canadian Cooperative Wildlife Health Centre.

"Climate warming in the Arctic is occurring more rapidly than elsewhere, threatening the health and sustainability of Arctic plants and animals, which are adapted to a harsh and highly seasonal environment and are vulnerable to invasions by 'southern' species—both animals and parasites."

A changing climate also is affecting entire plant and animal communities. This is particularly evident in tropical marine environments such as the world’s coral reef ecosystems. In places like the Caribbean, warmer water temperatures have stressed corals and facilitated infections by pathogenic fungi and bacteria. When corals—the framework builders of the ecosystem—succumb, the myriad of species that depend on them are also at risk.

"Biodiversity loss is a well-established consequence of climate change," said coauthor Richard Ostfeld of the Cary Institute of Ecosystem Studies. "In a number of infectious disease systems, such as Lyme disease and West Nile virus, biodiversity loss is tied to greater pathogen transmission and increased human risk. Moving forward, we need models that are sensitive to both direct and indirect effects of climate change on infectious disease."

Where human health is concerned, there is not only the direct risk from pathogens like dengue, malaria and cholera, all of which are linked to warmer temperatures, but indirect risks from threats to agricultural systems and game species crucial for subsistence and cultural activities.

"Earth’s changing climate and the global spread of infectious diseases are threatening human health, agriculture and wildlife. Solving these problems requires a comprehensive approach that unites scientists from biology, the geosciences and the social sciences," said Sam Scheiner, National Science Foundation program director for the joint NSF-National Institutes of Health Ecology and Evolution of Infectious Diseases Program.

The study was funded in part by the National Science Foundation.
"We need to transcend simple arguments about which is more important—climate change or socioeconomics—and ask just how much harder will it be to control diseases as the climate warms?" Ostfeld said. "Will it be possible at all in developing countries?"

To respond to that challenge, Altizer and her colleagues—Kutz, Ostfeld, Pieter T. J. Johnson of the University of Colorado Boulder and C. Drew Harvell of Cornell University—laid out an agenda for future research and action.

One recommendation is to expand data about the physiological responses hosts and parasites have to temperature changes to help develop early warning systems.

"We’d like to be able to predict, for example, that if the climate warms by a certain amount, then in a particular host-parasite system we might see an increase from one to two transmission cycles per year," Altizer said. "But we’d also like to try to tie these predictions to actions that might be taken."

Such forecasting is well established in crop disease management and has been used to both preventatively close coral reefs and target areas at risk of malaria outbreaks.

"We face a tough task in the oceans, where disease outbreaks can be out of sight and undetected," Harvell said. "Because some coral disease outbreaks are predictable from warming events, we are developing forecasting programs to help us respond before the outbreak begins."

The researchers also pointed out that certain human communities, such as those of indigenous peoples in the Arctic, could be disproportionately impacted by climate-disease interactions.

"A better understanding of the impacts of parasitism on wildlife health, and an ability to make accurate predictions of future wildlife sustainability, is particularly important to aboriginal people across the Arctic who depend on wildlife as a source of food, income and a focus of cultural activities," Kutz said.

Johnson continued, "Because disease represents the product of multiple interacting species, including hosts, pathogens and other members of the food web, forecasting responses to ongoing climate shifts is a tremendous challenge," he said. "Given the rising importance of infectious diseases not only for human health but also wildlife conservation, it’s also a challenge for which we are in sore need of a solution. We hope our work contributes to that."

**Journal Reference:**

How 'Junk DNA' Can Control Cell Development
Aug. 2, 2013 — Researchers from the Gene and Stem Cell Therapy Program at Sydney's Centenary Institute have confirmed that, far from being "junk," the 97 per cent of human DNA that does not encode instructions for making proteins can play a significant role in controlling cell development.

And in doing so, the researchers have unravelled a previously unknown mechanism for regulating the activity of genes, increasing our understanding of the way cells develop and opening the way to new possibilities for therapy.

Using the latest gene sequencing techniques and sophisticated computer analysis, a research group led by Professor John Rasko AO and including Centenary's Head of Bioinformatics, Dr William Ritchie, has shown how particular white blood cells use non-coding DNA to regulate the activity of a group of genes that determines their shape and function. The work is published today in the scientific journal *Cell*.

"This discovery, involving what was previously referred to as "junk," opens up a new level of gene expression control that could also play a role in the development of many other tissue types," Rasko says. "Our observations were quite surprising and they open entirely new avenues for potential treatments in diverse diseases including cancers and leukemias."

The researchers reached their conclusions through studying introns—non-coding sequences which are located inside genes.

As part of the normal process of generating proteins from DNA, the code for constructing a particular protein is printed off as a strip of genetic material known as messenger RNA (mRNA). It is this strip of mRNA which carries the instructions for making the protein from the gene in the nucleus to the protein factories or ribosomes in the body of the cell.

But these mRNA strips need to be processed before they can be used as protein blueprints. Typically, any non-coding introns must be cut out to produce the final sequence for a functional protein. Many of the introns also include a short sequence—known as the stop codon—which, if left in, stops protein construction altogether. Retention of the intron can also stimulate a cellular mechanism which breaks up the mRNA containing it.
Dr Ritchie was able to develop a computer program to sort out mRNA strips retaining introns from those which did not. Using this technique the lead molecular biologist of the team, Dr Justin Wong, found that mRNA strips from many dozens of genes involved in white blood cell function were prone to intron retention and consequent breakdown. This was related to the levels of the enzymes needed to chop out the intron. Unless the intron is excised, functional protein products are never produced from these genes. Dr Jeff Holst in the team went a step further to show how this mechanism works in living bone marrow.

So the researchers propose intron retention as an efficient means of controlling the activity of many genes. "In fact, it takes less energy to break up strips of mRNA, than to control gene activity in other ways," says Rasko. "This may well be a previously-overlooked general mechanism for gene regulation with implications for disease causation and possible therapies in the future."

**Journal Reference:**

**Trials challenging HIV drug doses could usher in huge cost cuts**
Monica Heger
06 August 2013

When researchers say they are trying to do more with less in the fight against HIV, they mean it. At last month’s International AIDS Society (IAS) conference in Kuala Lumpur, Malaysia, researchers presented preliminary results from a clinical trial that showed a lower dose of the commonly used antiretroviral drug efavirenz was just as effective as the approved higher dose and seemed to cause fewer side effects in study participants.

"It’s going to have a big impact," Keith Crawford, assistant chief of public health research at the US Military HIV Research Program in Bethesda, Maryland, says of the study. "The fact that this very useful drug can be used in a reduced dose is a big deal. This is a money saver that will allow us to treat more patients."

Finding the right dose for an HIV drug is tricky. The virus mutates rapidly, so if patients take too low a dose the pathogen will quickly develop resistance. However, the drugs are so powerful that too high a dose causes toxic side effects in patients. “Infectious diseases are challenging because we want to give a dose that is efficacious and has a high enough barrier against resistance,” Crawford explains. As a result, when drug companies run clinical trials with their drugs, they often do so with the highest tolerable dose, even if there is not a demonstrable difference in efficacy compared to a lower dose.

The dose optimization trial of efavirenz, known as the ENCORE1 trial, is taking place across 13 countries and includes 630 HIV-positive individuals who had never received treatment before. Over the course of 96 weeks, the participants receive either 600 milligrams of efavirenz each day, the standard dosage regimen currently approved by the US Food and Drug Administration (FDA), or 400 milligrams. All of the study subjects also take a fixed-dose pill containing two antiretrovirals—tenofovir and emtricitabine—which is often given in combination with efavirenz, a pill marketed by New York’s Bristol-Myers Squibb as Sustiva.

Four months into the trial, the researchers found no statistical difference between the two groups in terms of the amount of circulating HIV in the blood. Moreover, 278 patients receiving the higher dose reported a drug-related adverse event compared to 203 receiving the lower dose, a statistically significant 10% difference. Further analyses over the entire two-year study period—set to conclude in July 2014—will analyze safety, tolerability and quality of life.

**Think twice:** Two 200-milligram pills of efavirenz might be just as effective as three.

“The results are extremely positive,” says Sean Emery, principal investigator of the ENCORE1 study, who is also head of the therapeutic and vaccine research program at the Kirby Institute, near Sydney, Australia. “The trial has really illustrated in a robust way that in terms of potency, 400 milligrams for all intents and purposes is identical to 600 milligrams.”

**Access agenda**
According to UNAIDS, out of the 34 million people infected with HIV worldwide in 2012, only 10 million, or 29%, were receiving antiretroviral treatment. UNAIDS has set a goal of increasing that number to 15 million by 2015 and to add an additional million each subsequent year, a task that will be challenging under current financial conditions.
The ENCORE1 trial is only one of several dose optimization trials being pursued in an effort to increase access to drugs in a cost-effective manner while also reducing toxicity from the drugs. Another dose optimization trial is the LASA trial, which is comparing 200 milligrams of the antiretroviral drug atazanavir in combination with 100 milligrams of ritonavir to the standard 300/100 milligram combination dose. The lower dose of efavirenz envisioned by the ENCORE1 trial could save an estimated $16 per person, or $192 million per year, assuming 15 million people per year are treated, whereas a successful LASA trial could result in savings of $501 million per year (Curr. Opin. HIV AIDS. 8, 34–40, 2013).

There’s a precedent for this type of dose optimization. Zidovudine, a second-line HIV treatment, has already been reduced from its original dosage of 300 milligrams every four hours to between 250 milligrams and 300 mg twice daily after the reduced version as shown to be just as effective (N. Engl. J. Med. 322, 941–949, 1990). Now, a phase 2 study is evaluating 200 milligrams versus 300 milligrams twice daily of zidovudine over 48 weeks in 136 treatment-naive patients. The primary goal of the study is to evaluate the reduction of anemia, not efficacy of the reduced dose. So, the trial will not provide enough evidence to gain regulatory approval, but it could act as a starting point for future investigations.

Additionally, there are several dose-optimization trials evaluating lower drug dosages in children, including a randomized study in 200 Thai children testing a lower dose of lopinavir/ritonavir. A poster presented at July’s IAS meeting in Kuala Lumpur showed that compared to the approved dose, a lower dose demonstrated noninferiority over 96 weeks with less dyslipidemia, a side effect that results in an abnormal amount of fat cells in blood.

“HIV drugs work very well,” says Andrew Hill, a pharmacologist at Liverpool University in the UK, who is not involved with the dose optimization trials, “but you have a spectra of all these problems.” With the verdict of the ENCORE1 trial now in, the study investigators plan to start working with the FDA on regulatory approval as well as with the drug manufacturers to create lower-dose pills, says Emery. He estimates that the lower-dose pills could be widely available within one year.

Dose-optimization strategies have not yet caught on for other diseases, but Crawford thinks that they will, given that other infectious diseases have similar challenges to HIV in terms of cost and access to treatment. “HIV is going to be the model,” he says.

How to achieve a well-balanced gut
Creating an environment that nurtures the trillions of beneficial microbes in our gut and, at the same time, protects us against invasion by food-borne pathogens is a challenge. A study published on August 8 in PLOS Pathogens reveals the role of a key player in this balancing act.

SIGIRR is a protein present at the surface of the cells that line the gut that dampens the innate (non-specific) immune response of these cells to bacteria. The new study, led by Xiaoxia Li (from the Lerner Research Institute in Cleveland, USA) and Bruce Vallance (from BC’s Childrens’ Hospital and the University of British Columbia in Vancouver, Canada), now shows that SIGIRR function in mice (and presumably also in humans) is necessary to protect the gut against "hostile takeover" by bacteria that cause serious food poisoning and bowel inflammation.

The researchers infected mice that were missing the Sigirr gene with bacterial pathogens that cause food poisoning in rodents (either a relative of toxic E. coli or Salmonella Typhimurium). And even though these mice had a much stronger intestinal innate immune response than mice with intact SIGIRR function, they were unable to defend themselves against the pathogens and got much sicker than their normal counterparts.

Examining the underlying mechanism, the researchers looked at the beneficial microbes that normally reside in the gut. Often, these can delay or even prevent pathogens from infecting the gut by competing for space and nutrients, in a process called "colonization resistance". Consistent with this role, the exaggerated antimicrobial responses triggered by the pathogens in the absence of Sigirr caused a rapid and dramatic loss of beneficial microbes from the infected gut. This depletion seems to reduce the ability of the resident good bugs to outcompete the invading bad ones, leaving the gut highly vulnerable to colonization by the toxic pathogens.

SIGIRR function in the gut therefore reflects a balancing strategy that sacrifices maximal immune responsiveness in order to protect the beneficial resident microbe populations which, when healthy, provide a strong barrier against toxic foreign invaders and thus protection for their host through colonization resistance.
The researchers conclude "Our results suggest our immune system really isn’t very good at preventing food-borne infections, and, through evolution, we have come to rely on our gut microbiota to protect us from many pathogens. If we disrupt this mutualistic relationship (for example, with antibiotics), we leave ourselves highly susceptible to infections."

While being gentle with your beneficial gut flora is clearly a good thing, the researchers also speculate that modulating SIGIRR function within the gut might one day offer therapeutic potential for gastrointestinal disorders, such as inflammatory bowel disease.

**Scientific breakthrough reveals how vitamin B12 is made**

A scientific breakthrough by researchers at the University of Kent has revealed how vitamin B12/antipernicious anaemia factor is made – a challenge often referred to as ‘the Mount Everest of biosynthetic problems’.

Vitamin B12 is pieced together as an elaborate molecular jigsaw involving around 30 individual components. It is unique amongst the vitamins in that it is only made by certain bacteria. In the early 1990’s it was realised that there were two pathways to allow its construction – one that requires oxygen and one that occurs in the absence of oxygen. It is this so-called anaerobic pathway, which is the more common pathway, that proved so elusive as the components of the pathway are very unstable and rapidly degrade.

However, as explained in a paper published by PNAS (Proceedings of the National Academy of Sciences of the United States of America), bioscientists at the University of Kent have trained a friendly bacterium called Bacillus megaterium to produce all of the components of the anaerobic B12 pathway. This has helped them acquire the missing molecular pieces of the jigsaw, allowing them to complete the picture of how this remarkable molecule is made.

The team hopes that this newly acquired information can be used to help persuade bacteria to make the vitamin in larger quantities, thereby contributing to its use in medication for people suffering with the blood disorder pernicious anaemia, amongst other things.

Professor Martin Warren, who led the research, said: ‘This is a really exciting time in the biological sciences – one where our knowledge can be applied with the emerging discipline of synthetic biology to produce strains of bacteria that make enough B12, and other vitamins, for use in medicine and other sectors, such as feed for livestock.’

Key academic partners in the research included Dr Rebekka Biedendieck (Braunschweig University of Technology) and Dr Steve Rigby (Manchester Institute of Biotechnology). The Kent team also included Dr Simon Moore and Dr Mark Howard, Reader in Biological NMR Spectroscopy.

‘Elucidation of the anaerobic pathway for the corrin component of cobalamin (vitamin B12)’ can be viewed online at http://www.pnas.org/content/early/2013/08/06/1308098110

**Hormone Receptors May Regulate Effect of Nutrition On Life Expectancy Not Only in Roundworms, but Perhaps Also in Humans**

Aug, 6, 2013 — A reduced caloric intake increases life expectancy in many species. But how diet prolongs the lives of model organisms such as fruit flies and roundworms has remained a mystery until recently. Scientists at the Max Planck Institute for Biology of Ageing in Cologne discovered that a hormone receptor is one of the links between nutrition and life expectancy in the roundworms.

The receptor protein NHR-62 increases the lifespan of the animals by twenty per cent if their calorie intake is reduced. Furthermore, another study showed that the hormone receptor NHR-8 affects development into adulthood as well as the maximum lifespan of the worms. It may be possible that receptors related to these are also responsible for regulating life expectancy in human beings.

The roundworm Caenorhabditis elegans lives only about 20 days. This makes it an ideal research subject, as the complete lifecycle of the worm can be studied in a short time. Also, the worm consists of less than a thousand cells, and its genetic make-up has been extensively analysed, and contains many genes similar to humans. The scientists in Adam Antebi’s team at the Max Planck Institute for Biology of Ageing use Caenorhabditis elegans to find out how hormones influence ageing. They are particularly interested in hormone receptors that reside in the cell nucleus, which regulate the activity of metabolic genes.

Their results indicate that the receptor NHR-62 must be active for reduced dietary intake to fully prolong the life of worms. If NHR-62 is inactive, Caenorhabditis elegans will live 25% longer under dietary restriction than if this receptor is inactive. "It seems that there is an as yet unknown hormone
which regulates lifespan using NHR-62. If we can identify this hormone and administer it to the worm, we may prolong its life without having to change its calorie intake," Antebi explains.

A restricted diet also affects the expression of genes dramatically: out of the approximate 20,000 worm genes, 3,000 change their activity, and 600 of these show a dependence on NHR-62. It follows that there are many other candidates for improving life expectancy. Since humans have receptors similar to NHR-62, so-called HNF-4α, the Max Planck scientists suspect that the hormone receptors may not only control the maximum lifespan of roundworms, but might affect human beings as well.

However, nutrition also affects lifespan in several other ways. Another study by the scientists has shown that worms lacking the hormone receptor NHR-8 will remain longer in a pre-pubertal stage before they reach adulthood. They also die earlier than animals with this receptor. NHR-8 is a nuclear receptor, responsible for the animal's cholesterol balance. "Without it, the worm cannot produce enough steroid hormones from the cholesterol and therefore reaches sexual maturity later on. In addition, its fatty acid metabolism changes and its life expectancy drops," explains Antebi. Receptors similar to NHR-8 can be found in human beings too. Conceivably cholesterol metabolism could therefore regulate physical development and affect life expectancy in humans as well.

**Journal References:**


**Human Epigenomic Map Extended**

Aug. 8, 2013 — Ten years ago, scientists announced the end of the Human Genome Project, the international attempt to learn which combination of four nucleotides—adenine, thymine, cytosine, and guanine—is unique to homo sapien DNA. This biological alphabet helped researchers identify the approximately 25,000 genes coded in the human genome, but as time went on, questions arose about how all of these genes are controlled.

Now, Harvard Stem Cell Institute Principal Faculty member Alexander Meissner, PhD, reports another milestone, this time contributing to the multilayered NIH-funded human Roadmap Epigenomics Project. Epigenetics is the study of how the over 200 human cell types (e.g., muscle cells, nerve cells, liver cells, etc.) can have an identical compliment of genes but express them differently. Part of the answer lies in the way that DNA is packaged, with tight areas silencing genes and open areas allowing for genes to be translated into proteins. Stem cells differentiate into various cell types by marking specific genes that will be open and closed after division.

New research by Meissner, published online as a letter in the journal Nature, describes the dynamics of DNA methylation across a wide range of human cell types. Chemically, these marks are the addition of a methyl group—one carbon atom surrounded by three hydrogen atoms (CH₃)—anywhere a cytosine nucleotide sits next to a guanine nucleotide in the DNA sequence.

Meissner's team, led by graduate student Michael Ziller, at Harvard's Department of Stem Cell and Regenerative Biology mapped nearly all of the 28-million cytosine-guanine pairings among the 3-billion nucleotides that make up human DNA, and then wanted to know which of these 28 million are dynamic or static across all the cell types.

"When we asked, how many of them are changing, the answer was a very small fraction," said Meissner. The researchers found that eighty percent of the 28-million cytosine-guanine pairs are largely unchanged and might not participate in the regulation of the cell types, while the dynamic ones sit at sites that are relevant for gene expression—in particular distal regulatory sites such as enhancers. "Importantly this allows us to improve our current approaches of mapping this important mark through more targeted strategies that still capture most of the dynamics," Meissner said.

The methylation map generated by the Meissner lab is part of a larger National Institutes of Health (NIH) consortium to look at all of the different epigenetic modification that are found across a large number of human cell and tissue types. Earlier this year, the Meissner's lab recorded all of the gene expression and multi-layered epigenetic dynamics that take place in early stem cell differentiation when they prepare to divide into their next fated cell type.

In addition to his roles at Harvard, Meissner is affiliated with the Broad Institute and the New York Stem Cell Foundation. Only a graduate student in 2007, he has quickly established himself as a leader in the epigenetics field. "It just happens to be that we're at the right time and at the right place, both
physically and sort of in time, " he said. "Just five years ago, we would have had the same question, but we wouldn’t have had the same tools to answer the question."

**Journal Reference:**

**Is Sous Vide Cooking Safe?**
Aug. 7, 2013 — The Institute of Food Research (IFR) has been undertaking research for the Food Standards Agency to establish if the cooking technique sous vide is safe. Sous vide uses lower temperatures to improve food quality and could be a step closer to being more widely adopted after Institute of Food Research scientists assessed the steps needed to ensure the process is safe.

Sous vide cooking involves vacuum packing food in a plastic pouch and then heating in a water bath. Chefs are attracted to the precise nature of the temperature control, allowing innovative use of the technology to create new textures and flavours by manipulating the behaviour of food components such as proteins, starches and fats.

In designing new recipes and processes, microbial safety is paramount and much data has been collected on how well food poisoning bacteria grow and survive in different foods at different temperatures. This data has been collected together and made available through ComBase, a BBSRC-supported National Capability based at IFR. Food manufacturers and academics regularly consult ComBase’s extensive database of microbial growth information.

Recently, there has been an increase in the number of sous vide foods being cooked at lower temperatures, e.g. 42°C to 70°C. Most data on microbial growth in food is based on temperatures below 40°C, with studies focusing on how bacteria grow at ambient temperatures, for example during storage. Other studies have looked at the temperatures at which bacteria are killed, usually around 55-60°C and above. Lack of information in the range of about 40 to 60°C makes it very difficult for cooks, manufacturers, regulators and enforcement officers such to calculate the lethality of such low temperature heat treatments and judge the risk of foods containing pathogens.

To address this issue Dr Sandra Stringer and colleagues at the IFR, which is strategically funded by BBSRC, have gathered the information needed to properly assess the hazards associated with lower temperature cooking. The scientists also carried out a feasibility study on extending models in the 'Combase Predictor' database. Specifically they investigated how much work would be needed to upgrade the ComBase database to model the hazards *E. coli*, *Salmonella* and *L. monocytogenes* between around 40 and 60°C. This would help ensure that the safety assessment for sous vide foods is consistent, effective and commensurate with any risk to public health.

This work was carried out as part of a project for the Food Standards Agency (FSA) to provide the best information on this issue and propose a way forward to fill the knowledge gap. For more information, see [http://www.foodbase.org.uk/results.php?f_report_id=800](http://www.foodbase.org.uk/results.php?f_report_id=800)

**FDA approves new drug to treat HIV infection**
The U.S. Food and Drug Administration today approved Tivicay (dolutegravir), a new drug to treat HIV-1 infection.

Tivicay is an integrase strand transfer inhibitor that interferes with one of the enzymes necessary for HIV to multiply. It is a pill taken daily in combination with other antiretroviral drugs.

Tivicay is approved for use in a broad population of HIV-infected patients. It can be used to treat HIV-infected adults who have never taken HIV therapy (treatment-naive) and HIV-infected adults who have previously taken HIV therapy (treatment-experienced), including those who have been treated with other integrase strand transfer inhibitors. Tivicay is also approved for children ages 12 years and older weighing at least 40 kilograms (kg) who are treatment-naive or treatment-experienced but have not previously taken other integrase strand transfer inhibitors.

“HIV-infected individuals require treatment regimens personalized to fit their condition and their needs,” said Edward Cox, M.D., M.P.H., director of the Office of Antimicrobial Products in the FDA’s Center for Drug Evaluation and Research. “The approval of new drugs like Tivicay that add to the existing options remains a priority for the FDA.”

About 50,000 Americans become infected with HIV each year and about 15,500 died from the disease in 2010, according to the Centers for Disease Control and Prevention.
Tivicay’s safety and efficacy in adults was evaluated in 2,539 participants enrolled in four clinical trials. Depending on the trial, participants were randomly assigned to receive Tivicay or Isentress (raltegravir), each in combination with other antiretroviral drugs, or Atripla, a fixed-dose combination of efavirenz, emtricitabine and tenofovir. Results showed Tivicay-containing regimens were effective in reducing viral loads.

A fifth trial established the pharmacokinetics, safety and activity of Tivicay as part of treatment regimens for HIV-infected children ages 12 years and older weighing at least 40 kg who have not previously taken integrase strand transfer inhibitors.

Common side effects observed during clinical studies include difficulty sleeping (insomnia) and headache. Serious side effects include hypersensitivity reactions and abnormal liver function in participants co-infected with hepatitis B and/or C. The Tivicay label gives advice on how to monitor patients for the serious side effects.

Tivicay is marketed by Viiv Healthcare and manufactured by GlaxoSmithKline, both based in Research Triangle Park, N.C. Isentress is marketed by Whitehouse Station, N.J.-based Merck, and Atripla is marketed by San Francisco, Calif.-based Gilead.

**New Hepatitis B vaccine developed**

*Posted: Aug 12, 2013 7:08 PM EST Updated: Aug 12, 2013 8:06 PM EST*

Written by Dominic Trombino, Producer—[email](mailto:email)

Israeli drug company SciVac has developed a third generation vaccine for Hepatitis B that it believes will halt the global growth of the disease.

Nearly 600,000 people die annually from Hepatitis B, according to the World Health Organization. They also say as many as 400 million people are carriers for the disease.

SciVec CEO Michal Ben Attar says they are optimistic the new vaccine will change those numbers. "No more people need to die from this disease," said Ben Attar. "We can eradicate this disease like vaccines did to small pox, diphtheria, tetanus."

The current second generation, yeast-based vaccine has been around for more than 20 years. SciVac however, says that ten percent of newborn babies and 25 percent of adults over 40 do not respond to it. Ben Attar says the new vaccine is 100 percent effective against Hepatitis B.

SciVec has applied to the U.S. FDA for distribution of the vaccine, and if they receive that approval, they plan to seek similar approval in Europe.

**Monkeys Achieve Drug-Free Control of SIV**

August 9, 2013

Adding both an arthritis drug and a chemotherapy drug to a highly intensified antiretroviral regimen appears to have led to a drug-free control of HIV among macaque monkeys. Publishing their findings in the journal Retrovirology, a group of Italian and American researchers added the gold salt auranofin and the chemosensitizing agent buthionine sulfoximine (BSO) to a five-drug antiretroviral regimen given to macaques infected with simian immunodeficiency virus (SIV). In a previous study, the researchers had found that the addition of auranofin succeeded in reducing both the viral reservoir and the post-therapy viral load set point.

Of the seven monkeys in the trial, all received the five-drug ARV cocktail. Two of them also received auranofin, three of them received auranofin and BSO, and two received no additional therapies.

After the researchers stopped the therapy of the three monkeys taking auranofin and BSO, their viral loads initially rebounded. But with time the animals experienced a significant drop of viral RNA and DNA in peripheral blood cells—an indicator of a diminished viral reservoir—as compared with levels seen before the monkeys began ARV treatment. The monkeys ultimately achieved enough control of their infections to prevent the development of AIDS. The researchers found that the presence of CD8 cells as well as an enhanced level of cellular immune response among the monkeys played a key role in this apparently successful therapy.

The researchers wrote, “The level of post-therapy viral set point reduction achieved in this study is the largest reported so far in chronically SIVmac251-infected macaques and may represent a promising strategy to improve over the current ‘ART [antiretroviral treatment] for life’ plight.”

The investigators plan to start a human clinical trial of this therapy in early 2014.
Levels of HIV-Target Macrophages in Rectum May Facilitate Infection
Author: Mark Mascolini
12 August 2013
Rectal tissue contains more than 3 times as many macrophages vulnerable to HIV than does the colon, according to results of an in situ fluorescence study in healthy volunteers. The study also identified other important differences in HIV target cells between colon and rectum.

A large fraction of HIV transmissions occur rectally, especially in men who have sex with men but also in women. More is known about HIV target cells in colon than in rectum, but assuming the two sites have similar cellular environments may be risky. Understanding the cellular milieu of the rectum is critical to vaccine and microbicide development.

To compare rectal and colonic cell populations, researchers at the NIAID HIV Vaccine Trials Network conducted this in situ fluorescence study of HIV target cells 4 cm and 30 cm distant from the anal canal in 29 healthy individuals. The researchers used computerized analysis of digitized combination stains to analyze cell populations at the two sites. They focused on CCR5-expressing T cells, macrophages, and putative dendritic cells.

Compared with the colon, the rectum contained more than 3 times as many CD68+ (activated) macrophages expressing the HIV coreceptor CCR5 ($P = 0.0001$). The researchers surmised that “rectal macrophages seem biologically closer to the HIV-susceptible CCR5high phenotype in the vagina than the mostly HIV-resistant CCR5low phenotype in the colon.”

In contrast, putative CD209+ dendritic cells, another HIV target, populated the colon more than the rectum ($P = 0.0004$), although CCR5 expression levels in these cells were similar in colon and rectum.

CD3+ T-cell densities and CCR5 expression were comparable in colon and rectum.

The researchers believe their findings demonstrate “in general terms that the colon and rectum are immunologically distinct anatomical compartments” and “emphasize that caution should be exercised when extrapolating data obtained from colon tissues to the rectum.”

“Greater expression of CCR5 on rectal macrophages,” the authors note, “suggests that the most distal sections of the gut may be especially vulnerable to HIV infection.”


As US FDA approves promising new HIV drug dolutegravir, MSF asks when people in developing countries will have access
Geneva/New York, 13 August 2013 — As the US Food and Drug Administration approved the new HIV drug dolutegravir late yesterday, international medical humanitarian organisation Médecins Sans Frontières/Doctors Without Borders (MSF) questioned when people in developing countries would be able to access this promising new drug.

Studies have shown dolutegravir, a drug from the potent new integrase inhibitor class of drugs, to be well tolerated and extremely effective in stopping replication of the HIV virus, with a high barrier to HIV resistance.

Given its advantages over drugs in the same class and those widely used today, dolutegravir will likely become part of first-line therapy in wealthy countries. However, it is still unclear whether people across the developing world will have access to dolutegravir, as initial indications from the drug’s producer ViiV (Pfizer + GlaxoSmithKline + Shionogi) to enable affordable access have not been encouraging.

“Based on studies to date, dolutegravir holds important advantages for use in developing countries, but as treatment providers, our biggest concern is what the price will be,” said Dr Manica Balasegaram, Executive Director of MSF’s Access Campaign. “A promising new drug will only translate into more lives saved if it is affordable, so that people who need it have access.”

But ViiV’s position on access to dolutegravir in developing countries is concerning, with the company indicating it would pursue a ‘tiered-pricing’ strategy that will keep the drug out of reach for people who need it, limiting the use and sale of generic versions to only 67 countries, excluding many low- and middle-income countries where millions of people with HIV live.

“We are deeply concerned that ViiV’s business strategy will result in dolutegravir being priced out of reach in countries excluded from ViiV’s licensing deals”, said Rohit Malpani, director of Policy and
Analysis at MSF’s Access Campaign. “We have seen in the past that excluded countries are left paying exorbitant prices.”

ViV should take proactive steps to make sure dolutegravir will be available and affordable for people in need, especially through registration of the product and by allowing the availability of generic versions in low- and middle-income countries. One way to improve access to more affordable dolutegravir could be through a licence agreement with the Medicines Patent Pool, which would need to include all low- and middle-income countries and have no restrictions on where the drug can be manufactured or active pharmaceutical ingredients can be sourced.

“Where dolutegravir is priced out of reach, the onus will be on countries to overcome patent barriers by making full use of public health safeguards and flexibilities in international trade rules, which allow for more affordable versions to be produced or imported”, said Malpani.

The availability of affordable HIV medicines has been crucial to making the scale-up of antiretroviral therapy to nearly ten million people in developing countries possible. Competition among generic producers of HIV medicines, primarily in India, is what caused the price of treatment to drop by a dramatic 99% over the last decade, from more than US$10,000 per person per year to roughly $120 today. However, patents blocking generic production have resulted in newer drugs remaining priced out of reach, with a possible salvage regimen today costing, at best, more than $2,000 per person, even in the poorest countries, nearly 15 times the price of today’s first-line therapy. Middle-income countries face prices that are far higher.

**Rapid HIV Test Approved by FDA**

*Medical News Today*, (08.12.2013) By Nick Valentine

The US Food and Drug Administration (FDA) has approved the Alere Determine HIV-1/2 AF/Ab Combo test that can detect an HIV infection and distinguish between an early infection and an established HIV infection from “human serum, plasma, and venous or fingerstick whole-blood specimens.” Developed by Alere's Israel-based Orgenics subsidiary, the Alere Determine rapid HIV test not only would provide faster HIV diagnosis, but also would be relatively simple to use in remote high-incidence areas such as sub-Saharan Africa.

The Alere Determine rapid test is able to detect simultaneously the HIV-1 p24 antigen, a signal of HIV-1 infection, and the presence of HIV-1 and HIV-2 antibodies usually present in established infections. Most worldwide AIDS cases developed from HIV-1 infections, and HIV-2 infections have occurred mostly in West Africa. The Alere Determine test is not useful for screening blood donors because it does not distinguish between HIV-1 antibodies and HIV-2 antibodies.

FDA's Center for Biologics Evaluation and Research Director Karen Midthun predicted the test could help in identifying HIV earlier in “outreach settings.” Early detection could help newly infected people receive medical care sooner and potentially could prevent HIV transmission.

CDC estimated that more than a million US residents are HIV-positive, although approximately 20 percent are unaware of their infection. The United States records approximately 50,000 new HIV infections annually.

**MRSA strain in humans originally came from cattle**

A strain of bacteria that causes skin and soft tissue infections in humans originally came from cattle, according to a study to be published in *mBio*®, the online open-access journal of the American Society for Microbiology. The researchers who conducted the genetic analysis of strains of *Staphylococcus aureus* known as CC97 say these strains developed resistance to methicillin after they crossed over into humans around forty years ago. Today, methicillin-resistant *S. aureus* (MRSA) strain CC97 is an emerging human pathogen in Europe, North and South America, Africa, and Asia. The findings highlight the potential for cows to serve as a reservoir for bacteria with the capacity for pandemic spread in humans.

The researchers sequenced the genomes of 43 different CC97 isolates from humans, cattle, and other animals, and plotted their genetic relationships in a phylogenetic tree. Corresponding author Ross Fitzgerald of the Roslin Institute and the University of Edinburgh in Scotland says strains of CC97 found in cows appear to be the ancestors of CC97 strains from humans.

"Bovine strains seemed to occupy deeper parts of the phylogenetic tree—they were closer to the root than the human strains. This led us to conclude that the strains infecting humans originated in cows and that they had evolved from bovine to human host jumps," says Fitzgerald.
Although the CC97 strains from animals were quite genetically diverse, the human isolates cluster together in two tight, distinct "clades", or relatedness groups, indicating that *S. aureus* CC97 in cattle crossed over into humans on two separate occasions. Using mutation rates as a molecular clock, the authors determined that the ancestor of clade A jumped from a bovine host to humans between 1894 and 1977 and clade B made the jump between 1938 and 1966.

After they made the jump, the human CC97 strains acquired some new capabilities, says Fitzgerald, thanks to genes encoded on portable pieces of DNA called mobile genetic elements. "It seems like these elements, such as pathogenicity islands, phages, and plasmids, are important in order for the bacterium to adapt to different host species," says Fitzgerald. "The reverse is true as well: the bovine strains have their own mobile genetic elements."

Perhaps the most problematic new capability the human strains acquired is the ability to resist methicillin, an important antibiotic for fighting staphylococcal infections. Only human strains of CC97 were able to resist the drug, which indicates that the bacteria acquired resistance after they crossed over into humans, presumably through exposure to antibiotics prescribed for treating human infections. This sequence of events contrasts with the case of a *S. aureus* strain from pigs, Fitzgerald points out, since a study in 2012 revealed that MRSA ST398 strains evolved the ability to resist methicillin before they crossed over into humans [http://mbio.asm.org/content/3/1/e00305-11]. Any number of factors could create these differences, making pigs—but not cattle—a source of a drug-resistant bacterium. At this point, though, there isn’t enough information to say whether differences in the *S. aureus* strains, differences between pigs and cattle, or differences between swine and dairy farming practices might be responsible.

Moving forward, Fitzgerald says he and his colleagues plan to widen the investigation. "We have a relatively small sample size, and the findings are robust, but we want to extend the study now to include a greater number of clones to get a bigger picture of what’s going on across the *S. aureus* species," says Fitzgerald.

A wider variety of *S. aureus* strains, Fitzgerald says, from a wider variety of locations and hosts and a wider range of time, will allow them to better pinpoint the timing and circumstances of the host jump events. Understanding how and when MRSA has crossed over from other species in the past can help us to put the brakes on these crossovers in the future and hopefully prevent the birth of the next pandemic *S. aureus* strain.

**Breaking up the superbugs’ party**

The fight against antibiotic-resistant superbugs has taken a step forward thanks to a new discovery by scientists at The University of Nottingham. A multi-disciplinary research team at the University's Centre for Biomolecular Sciences has uncovered a new way of inhibiting the toxicity and virulence of the notorious superbug, *Pseudomonas aeruginosa*.

This bacteria produces an armoury of virulence factors and is resistant to many conventional antibiotics. It is almost impossible to eradicate *P. aeruginosa* from the lungs of people with cystic fibrosis and is therefore a leading cause of death among sufferers. The bug also causes a wide range of infections particularly among hospital patients.

The new discovery concerns the bacterial cells' ability to ‘talk’ to each other by producing and sensing small chemical signal molecules. This is called ‘quorum sensing’ (QS) and enables a population of individual bacteria to act socially rather than as individuals. QS allows a population of bacteria to assess their numerical strength and make a decision only when the population is 'quorate'.

The mechanism through which QS signals work is by activating gene expression upon interaction of a QS signal molecule with a receptor protein. In many disease-causing bacteria, QS controls genes which are essential for infection. These genes code for virulence factors such as toxins which cause damage to host tissues and the immune system. Interfering with the QS signalling process blocks bacterial virulence and renders bacteria unable to cause infection. Consequently QS systems are molecular targets for the development of new anti-infective drugs which do not kill bacteria but instead block their ability to cause disease.

In a study published in the journal, *PLOS Pathogens*, the Nottingham team has described how they solved the 3D structure of a receptor protein called PqsR used by *P. aeruginosa* to sense alkyl quinolone QS signal molecules so that they could visualize the shape of the QS signal molecule-binding site within the PqsR protein.
Professor of Molecular Microbiology, Paul Williams, said: "We were able to synthesize and screen a library of chemical compounds which could fit within the PqsR binding site and block receptor activation by the QS signal molecules. The active compounds were screened for their ability to inhibit QS and through a process of chemical refinement some novel potent QS inhibitors were discovered which were tested biologically on P. aeruginosa and shown to block virulence gene expression."

Professor of Macromolecular Crystallography, Jonas Emsley, added: "This ground-breaking work establishes a platform for the future evaluation and further development of these new QS inhibitor compounds as potential drugs for the treatment of P. aeruginosa infections."

High-Angle Helix Helps Bacteria Swim
Aug. 13, 2013 — It’s counterintuitive but true: Some microorganisms that use flagella for locomotion are able to swim faster in gel-like fluids such as mucus. Research engineers at Brown University have figured out why. It’s the angle of the coil that matters.

Findings are reported in Physical Review Letters.

A high-angle helix helps microorganisms like sperm and bacteria swim through mucus and other viscoelastic fluids, according to a new study by researchers from Brown University and the University of Wisconsin. The findings help clear up some seemingly conflicting findings about how microorganisms swim using flagella, helical appendages that provide propulsion as they rotate.

Simple as single-celled creatures may be, understanding how they get around requires some complex science. The physics of helical swimming turns out to be "a really interesting fluid dynamics problem," said Thomas Powers, a professor of engineering and physics at Brown and one of the new study's authors.

At the scale of a single cell, fluids become much more viscous than on larger scales. A bacterium swimming through water "would be like us trying to swim in tar," Powers said. That means swimming at the micron scale is a completely different enterprise than it is for fish or people. Counterintuitive as it may sound, tiny helical swimmers rely exclusively on drag to move forward. The turning flagellum creates an apparent wave that propagates out from behind the creature. The drag force against that wave pushes the creature in the opposite direction.

In recent years, there has been some theoretical work aimed at fully understanding the physics of this kind of swimming, much of it done by modeling how helical swimmers behave in water. But bacteria and sperm spend a lot of time in fluids like mucus and cervical fluid—fluids that are not only more viscous than water, but also elastic since they are full of springy polymers. Because a rotating helix might be able to push against the polymers, it could be that a viscoelastic fluid makes swimming easier.

"It’s a fairly simple question," Powers said. "Does viscoelasticity make microorganisms swim faster or slower?" Finding the right answer, however, hasn’t been so simple.

Early theoretical work suggested viscoelastic fluids should slow helical swimmers down. But some experimental work in the Brown School of Engineering by Powers, postdoctoral associate Bin Liu, and Kenneth Breuer, professor of engineering, suggested that viscoelastic fluids should actually help helical swimmers move faster.

This latest study, published in the journal Physical Review Letters, helps to bridge that apparent gap. Powers and Liu worked with Saverio Spagnolie, a professor of mathematics at the University of Wisconsin and a former postdoctoral researcher at Brown. Using what Powers described as "some clever numerical methods and a lot of hard work," Spagnolie was able to show computationally that the pitch angle of the helix—the degree to which the helix is coiled—matters in how well it performs in viscoelastic fluids. At a
low pitch angle (think of a stretched phone cord), helices move more slowly in viscoelastic fluids. When the pitch angle increases, performance improves.

The findings reconcile the experimental and earlier theoretical work. Much of the theoretical work, which suggested more viscosity would cause slower swimming, assumed a small pitch angle for the sake of keeping the computations manageable. The experimental work, which showed viscosity sped swimming, involved higher pitch angles. By showing numerically that a higher pitch angle increases speed, the researchers were able to explain that apparent discrepancy. "This work shows how you can connect that prior work," Powers said.

While this work was extremely valuable in linking theory and experiment, there's still much more work to be done on this problem, Powers says. "We don't really understand the result because it is so hard to visualize the three-dimensional configuration of all the forces involved. It's actually very frustrating. We're still trying to get an intuitive picture."

That, at this point, is still an upstream swim.

Ultimately, the researchers say, a better understanding how tiny swimmers get around could inform studies of bacterial infection and fertility. It could also help scientists develop artificial swimmers that could deliver medicine inside the body.

**Journal Reference:**

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**What If HIV Had Never Happened?**
By Dave R.
August 14, 2013

'What if's ...' are a glass half empty, late night go-to for many a positive person but of course each 'what if' is really only a salve for the soul, it doesn't provide answers. They're essentially self-pity mechanisms but end up only reminding you of wrong turnings and mistakes made. We've all been there though and many people will have asked themselves at least once; *what if HIV never existed? How would my life look now?* Irrespective of its relevance to your personal situation, it's an interesting conundrum and one which can certainly make you think.

So, what if ... HIV really had never happened?

To begin with, you have to look back to the last point in time before you were diagnosed. I suppose that really depends on whether you are 'PH' or 'PrH' (well, they're giving acronyms to everything else: Post-Highly Active Retroviral Therapy (HAART) or Pre-HAART). Then again, if you are Post-HAART and HIV has never happened then you disappear from the time-space continuum anyway; so maybe it's better to concentrate on people who were infected before HAART came along.

Then you have to ask the question; would the party have just continued deep into the 21st Century because make no mistake, there was a no-holds barred, all you can eat party, from the late 60s until HIV came along and spoiled the fun.

"Life is not a journey to the grave with the intention of arriving safely in a pretty and well preserved body, but rather to skid in broadside, thoroughly used up, totally worn out, and loudly proclaiming—WOW—What a Ride!"

Attributed to Bill McKenna (motorcycle rider), Anonymous and a Nissan ad. There are less polite versions!

The above is a proclamation that appears on so many internet profiles. It reflects both the pre-HIV joy in gay sexual liberation and the post-HIV determination to live life to the full anyway. It reeks of bravado rather than reality.

Of course, the reason why LGBT people were partying to excess was due to the social and sexual revolutions begun in the 1960's. It was the newly-grown up, post-war generation who, sickened by wars and the ever present threat of nuclear extinction, created women's lib, women's contraception (the Pill), gay lib and black power amongst other forms of emancipation for minorities. People had had enough of the sexual repression and dourness of the 50's and spontaneously spoke out for the freedom to do what you wanted with your own body. It was a liberating feeling and you felt immortal.

I was 18 in 1968 and believe me, although not everybody enjoyed sexual freedom (my theory being that those who were cramped by convention, now run the political and corporate worlds), millions did, myself included. Parents, puritans and Popes were shocked rigid but nobody really believed Pandora's Box could be closed again. It was plus/minus a decade where sexuality was explored and re-invented and
the morals and social restrictions of previous generations were discarded. Nothing new in this really; if you look back through human history, it has happened again and again before repression returned to spoil the fun.

However, not repression but HIV/AIDS arrived and parents, preachers and politicians did their, 'I told you so' dances right down the aisles.

Conspiracy theorists point to the arrival of HIV as being anything but accidental and it's wickedly tempting to think that the plague was brought about by deliberate 'intervention' but of course until a new Edward Snowden pops up with shocking revelations, there's not a shred of evidence. Politicians, church leaders and traditionalists may have wanted to invent a means of stopping the LGBT sexual revolution in its tracks but even a born cynic like me, can't imagine that the men in grey suits actually employed chemical warfare to root us out; they wouldn't ... right?

So looking at that point in history before patient zero; what would have happened if HIV had never emerged? Would something else equally devastating have taken its place?

To evaluate that possibility, you really have to look back at the history of sexually transmitted diseases. If humanity has a record of deadly, sexual viruses or bacterial infection, then you might reasonably assume that if it hadn't been HIV then it would have been something else. The thing is, that HIV is actually the first known deadly virus to be transmitted sexually and other viral STDs (Hepatitis A, B, C; Herpes, HPV and HTLV 1 (Human T-lymphotropic virus Type I linked to simian HIV strains) are also relatively modern. That's not to say that they definitely haven't appeared earlier in human history; only modern diagnostic techniques have been able to identify viruses with any degree of certainty, so they just may not have been recognised as viral infections in the past. We also know that HIV isn't the first deadly STD. Syphilis often proved to be a slow killer before the discovery of antibiotics and what's more, it was easily passed on from parent to child. Syphilis however, is caused by the bacterium Treponema pallidum and is not a virus.

Looking back at the sexual medical history of mankind; it can be divided roughly into three sections:

- In ancient times, if sexual diseases existed and were treated, any knowledge has been lost or was never recorded.
- Then for 500 or more years, sexual diseases were recognised but as nothing could be done about them, they were feared and treated ad hoc often with some degree of unpleasantness and a definite social stigma attached. Syphilis was widely reported in Europe when there seemed to be a continent-wide epidemic in the early 1500s. It was widely referred to as the Pox. However, even in ancient times, cultures from around the world reported the incidence of syphilis but where and how it emerged is not known. Syphilis and gonorrhoea were even thought to be one disease. It was only in the early 20th century, when the different microorganisms were identified under microscopes and reliable diagnostic tests were developed that progress began in treating the two separately. One slightly amusing fact about syphilis, or 'the great pox' is that every country blamed each other for its arrival. In the middle Ages, the English called it names like; like 'French pox'. The French blamed the Italians and called it the 'Neapolitan itch'. The Italians blamed the Portuguese; the Portuguese accused the Spanish; the Germans fingered the Poles. Since then, prostitutes from Africa, East Europeans, Mexicans, and of course, homosexuals have all shouldered the blame for the spread of syphilis and then HIV.
- The 20th Century brought definite medical breakthroughs, largely thanks to the discovery of antibiotics and accurate diagnosis. However, despite the advances of the last century, we can cure STDs caused by bacteria, parasites and fungi but we can't cure STDs caused by viruses! Some bacteria though, can kill you if left untreated and some complications of other STDs can be very serious. Making sure that there is universal antibiotic treatment available, especially in the Third world, will help prevent the emergence of new and resistant strains.

The other main viral STD problems we face today are Hepatitis, Herpes and HPV (human papilloma virus). Herpes simplex which is responsible for genital herpes has only really been a widespread problem since the 1960's. Again, that's as far as is known: it's perfectly possible that it has existed for hundreds of years but was identified with other sexual diseases. It was certainly mentioned by a French doctor in 1736 and in the 19th century, it was often seen as a side effect of syphilis or gonorrhoea.

Similarly, it's difficult to imagine that HPV, (responsible for genital warts and now linked to genital cancers) has only emerged in the 20th century. It seems logical to assume that advances in science have resulted in its identification as a separate viral sexual problem. HPV also has various different forms and only the most modern techniques can diagnose them and their consequences.
Once again, modern science has been able to identify the different strains of hepatitis and diagnose them as viral, although hepatitis as a disease has long been recognised. Certainly the consequences and potential threats of hepatitis are now much better appreciated than a century ago.

**So for the fun of it, let’s take HIV out of the picture; imagine it never happened, where would we stand both medically and socially?**

The medical world without HIV would be a much simpler place. Sexual diseases are actually quite straightforward and limited in number. They’re either bacterial, viral, or fungal and haven’t seemingly changed that much over the centuries; they’ve just been identified much better in the last hundred years. It’s not as if STD’s have mutated hundreds of times and caused worldwide sexual plagues along the way. Syphilis 500 years ago is still the syphilis we know today; it’s just that we can cure it now so it’s not nearly as lethal as it used to be.

**What is worrying is the emerging resistance to known antibiotics.**

Bacterial STDs should be able to be defeated by antibiotics but the farming and agricultural industries across the world have fed the demand for cheap meats and dairy products by dosing their animals with constant antibiotics to keep them disease-free. This means that antibiotics are being taken by humans indirectly and resistance builds up. It’s inevitable and logical but the unstoppable force that is consumerism means that while the demand for cheap meat rises, so does the use of antibiotics in animal foods. The development of new antibiotics can’t keep up with the growing resistance to the current ones. Consequently, we’re seeing pockets of resistant forms of gonorrhoea and syphilis springing up across the world. If they can’t be cured, what happens then?

Similarly, hepatitis C is a growing problem amongst sexually active, LGBT people. Also a virus, there’s no vaccine and its treatment can be brutal for the patient to say the least. It attacks the liver and can cause cirrhosis, liver cancer and eventually liver failure.

The implications of HPV and the herpes viruses are just beginning to be understood as more and more links are being found to other conditions, especially a growing number of cancers (throat and anal being especially relevant). HPV vaccines exist (Cervarix and Gardasil) but seem only to be effective if given to young people, preferably before their first sexual contact.

With herpes, the virus remains in the body for life; there’s no vaccine and it can recur with alarming regularity and is above all, extremely infectious. It travels through the body via the nervous system (hence awful conditions like Shingles) but perhaps more alarmingly, scientists are beginning to see links with other STDs and health problems. The herpes virus may act as a piggy-back conduit for other viral conditions. Certainly many people on HIV immunosuppressants are well aware that herpes reappears much more easily if the immune system is compromised wither by HIV or the medication. The herpes virus that attacks the brain (herpes viral meningitis) is especially worrying and recent, contagious outbreaks in gay circles may yet prove to be a worldwide and potentially fatal problem.

So if HIV had never existed, there’s absolutely no guarantee that nothing else would have taken its place. We need to be as alert for sexually transmitted viruses, as those surrounding various sorts of Flu that have scared us silly recently (Spanish flu (killed 19 million people just after the 1st World War), Mexican flu, Bird flu and SARS to name but three). Science is continually trying to stay on top of viral developments but human history has shown again and again that viruses are extremely difficult to predict or control.

Similarly, we need to be much more aware that our antibiotic resources are limited. Finding new ones takes decades and the bio-industry’s insistence on force feeding its animal stock with ‘preventative’ antibiotics is a sure fire route to resistance. If that happens and bacterial STDs become incurable, it will start a chain reaction that would be potentially as devastating as HIV has been.

**What about the social effects on a world without HIV?**

It’s safe to assume that the heterosexual world would be facing different challenges if the millions of people lost to AIDS were still here. Humanity is used to plagues decimating populations and recovering but the 20th Century has seen the fastest growth of technological and scientific development since the beginning of time. Where would Africa be now for instance, if AIDS hadn’t existed? Would it be a continent even more prone to poverty and starvation thanks to a burgeoning population, or would it have flourished with the input of healthy generations that have been otherwise lost?

You could certainly argue that lost LGBT generations would have had a significant influence on the world today. There would be a much larger ‘senior’ LGBT presence, with all its skills, creativity and experience to make a significant impact on society. This brings us back to one of the original questions of this piece: if the Pre-HIV party had continued, what would the impact on society be now?

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Page 22 of 67
In 2013, we have a snowballing, LGBT social integration taking place. Same-sex marriage and adoption; same-sex presences everywhere in TV, film and entertainment; majorities of nations’ populations all over the world approving LGBT acceptance and so on. It's patchy and has setbacks but there’s no denying its impetus. Would all that have been possible if the sexual revolution had been allowed to run its course and hadn't been stopped in its tracks by HIV? Or would it all have happened much sooner? Personally, I have a feeling that the general population was already feeling uncomfortable about the explosion in sexual freedoms in the late 70s and while some took the opportunity to see AIDS as a natural punishment for excess, many more changed their opinion of LGBT people as they saw the extent of the suffering. Yes HIV was/is frightening and yes people's noses were rubbed in the fact that it was sexually transmitted and had to visualise things they’d never imagined but tragedy is tragedy and a sea-swell of sympathy may have helped LGBT rights to get where they are today.

If the hedonism hadn't been ‘reined in’, you have to wonder what the eventual consequences might have been. Maybe nowadays, we would be far less accepted by society as a whole. Historically, all societies that have given themselves over to sexual freedom and excess have collapsed eventually (look at the ancient Romans) mainly because the majority of the population are not actually part of the fun...living and surviving gets in the way.

Maybe LGBT societies themselves would have turned against the excesses going on around them and demanded moderation and more standard relationships, including marriage. There's only so much sexual fun you can have before it gets boring, though HIV made sure we never found out. That said, there are signs that hedonism is taking root yet again amongst both heterosexual and LGBT youth. Modern society is based on the technological pleasure principle: get as much money as you can, buy as many gadgets as you can and party like it's 2099!

Finally, you have to wonder if HIV is actually only a blip on the human timeline. Societies tend to develop in ever-repeating circles and freedoms are like snakes and ladders; they blossom and decline. That's the way it's been throughout history. Just because the 21st century is more technologically advanced than any other before doesn’t mean that people will intrinsically change their basic behaviours. HIV is a plague that has changed human history within the space of 30 years. Whether it has led to social improvements or decline for the groups it has affected, is maybe less important than the fact that it is only 30 years old and after 50 years may be gone completely. Will it even be remembered in the history books of the 30th century? Now that's a worrying thought!

**Why ACT UP Has Declared War on the New HIV Pandemic**

ACT UP is attempting to tackle the emerging HIV crisis, which threatens to infect more than half of all young gay and bi men and trans women soon.

**BY David Artavia**

**August 14 2013 4:00 AM ET**

In a monumental statement, ACT UP New York has declared war on what it calls the new HIV epidemic, AIDS 2.0, which members say threatens to infect half of all young gay and bisexual men and transgender women by the time they reach 50.

According to the statement, ACT UP plans to demonstrate in the streets; work with government agencies to improve HIV prevention programs; protest federal, state, and city cuts to HIV prevention funding; research and distribute the latest safe sex and medical information in schools; and call out ineffective sex education programs.

Such a major call to action is reminiscent of ACT UP's work in the 1980s. It has shaken up the world before, and with an equally strong message and a new group of young activists, the organization intends to do it again. Matthew Rodriguez, editorial project manager at TheBody.com, is among its newest members.

"My activism is and always has been fueled by the idea of love," Rodriguez says. "That I could love myself enough to fight for my health and that I could love young gay men of color like me enough to fight for us to live. ACT UP was one of the few organizations I walked into where I felt like my life was of the utmost value, as valuable as anyone else’s, and that those around me were willing to go out of their way to keep people like me healthy. That’s really rare."

ACT UP promoted its effort at the New York City Pride parade on June 30, where more than 100 activists marched with the group, chanting "One in two, could be you." The prediction of one in two young gay and bi men and trans women becoming HIV-positive by age 50 comes from projections based on the latest data from the Centers for Disease Control and Prevention.
Since 1987, ACT UP NY has been one of the loudest voices in the fight against HIV and AIDS. It assured that the disease received attention during '80s and '90s, helping jump-start the production of AIDS drugs, and became a prime example of how grassroots activists can bring about change.

Activism around the disease is still needed, says Jim Eigo, who has been involved with ACT UP since the 1980s and was featured in the Oscar-nominated documentary How to Survive a Plague. He says New York City still fails to provide adequately for HIV-positive people.

"New York City spends almost nothing on HIV prevention beyond the funds it gets from the federal government," Eigo says. "When those funds are cut, as they have been over the past several years, the city, instead of securing alternative funding, cuts prevention services."

In the past 15 years, new HIV infection rates among young queer men and trans women have risen steadily, but ACT UP members media and the U.S. school system have done little in the way of education about the virus. And in 2010, only 3.3% of the CDC's discretionary AIDS budget went to services targeting these groups, even though they account for nearly two thirds of new infections.

At the New York Pride event, the organization distributed condoms and lube along with its "Fuck Smarter" fact sheet, which offers information about how to have safer sex even without condoms, with the help of drugs that can help reduce transmission. Today, HIV prevention takes more than just promoting condom use, says Eigo.

"New York City has to conduct research into what behavioral HIV prevention programs might be effective in 2013," Eigo states, "working with communities at risk to develop sex-positive, queer-friendly strategies that build on the early success of safer sex programs but recognize new prevention tools for a very different world."

Infections among young gay men have risen 22% recently, and over 50% of young gay men who are infected with HIV don't know it, the ACT UP statement notes. Fifty percent of young gay black men are expected to be infected by the time they reach 35. Transgender women are being infected at 36 times the rate of men and 78 times the rate of other women, and approximately 15,000 AIDS-related deaths still occur every year in the U.S. More than 696,000 people in America have died of AIDS so far — more than the number of U.S. deaths in the wars in Iraq, Afghanistan, Vietnam, Korea, and World War II combined.

ACT UP's next target is the New York City's Department of Health and Mental Hygiene, which the group says does little HIV prevention, even though gay, bi, and trans New Yorkers have been seroconverting at double the national rate, according to the department's own figures. If young gay men living in New York City continue to be infected at this rate, the city's HIV caseload will increase drastically. ACT UP has pushed for the department to start an information campaign about post-exposure prophylaxis, or PEP, the use of medications that can prevent HIV infection after exposure, and pre-exposure prophylaxis, or PrEP, the administration of drugs that can help decrease the likelihood of transmitting HIV during sex. The group is also calling for the agency to spend more on HIV prevention and update the data it uses on HIV and AIDS rates in the city.

ACT UP will demonstrate Thursday August 15 at 1 p.m. at the department's Gotham Center, 42-09 28th St., Long Island City, in the borough of Queens. Find more information here.

Neutron studies of HIV inhibitors reveal new areas for improvement

The first study of interactions between a common clinical inhibitor and the HIV-1 protease enzyme has been carried out by an international team with members from the US, Britain and France using neutrons at the Institut Laue-Langevin in Grenoble, France. It provides medical science with the first true picture of how an antiviral drug used to block virus replication actually works, and critically how its performance could be improved. The findings, reported in the Journal for Medicinal Chemistry, and the neutron techniques demonstrated at the ILL, will provide the basis for the design of a new generation of more effective pharmaceuticals to address issues such as drug resistance.

HIV-1 protease is essential in the life-cycle of HIV where it breaks polypeptide chains to create proteins used for replication and producing new infectious virus particles. Its key role makes it one of the most studied enzymes in the world. For the past 20 years scientists have used highly intense X-rays to investigate the best way to target and block the protease's role in spreading the virus.

However, this form of analysis has limitations. The strongest bonds between the enzyme and an inhibitor are usually relatively weak hydrogen bonds, yet hydrogen atoms are virtually invisible to X-ray analysis, leaving scientists to speculate as to how this binding takes place.
To address this uncertainty, scientists from Georgia State University, Purdue University and Oak Ridge National Laboratory in the USA and Harwell Oxford in Great Britain used neutrons at the Institut Laue-Langevin to analyse this binding. Neutrons are highly sensitive to lighter elements, allowing the team to identify the positions of every hydrogen atom involved in the system for the first time, and see which were involved in bonding. The inhibitor studied was Amprenavir (APV), first approved for clinical use in 1999, and experiments were carried out on the LADI-III (quasi-Laue neutron diffractometer) instrument at the ILL.

The neutron studies revealed a very different picture to that inferred from the X-ray studies which had overplayed the importance of many of the hydrogen bonds. In fact the team found only two really strong hydrogen bonds between the drug and the HIV enzyme. Whilst this might seem concerning, it actually presents drug designers with a set of new potential sites for the improvement of the drug’s surface chemistry to significantly strengthen the binding, thereby increasing the effectiveness of the drugs and reducing the necessary dosages.

Based on their new understanding the team proposed a number of next steps to make these improvements, including:

- Replacing weaker bonds with a greater number of stronger hydrogen bonds—Now it is known that many of the bonds are actually weak and water-mediated, drug designers should look to replace these with stronger hydrogen bonds. This could be done by changing certain functional groups in the drug chemical structure in order to expel water currently filling the holes.
- Improving the strength of the existing hydrogen bonds—For example lowering the pKa (the ability or tendency of a compound to lose its hydrogen atoms) of certain chemical groups of the drug to make it more similar to that of the enzyme would make the hydrogen atoms in the bond equidistant between the two compounds, resulting in a stronger interaction.

The findings in this latest paper may also help address one of the biggest issues in combating HIV infection—drug resistance. The natural evolution of the virus over time can weaken the binding, a process which is actually sped up by the introduction of the drugs themselves. One way round this would be to improve the binding of the inhibitor with the main-chain atoms of the virus’s protease (rather than its side chains). Before this latest study it was thought the potential for advances in this area was limited because the hydrogen bond interactions with the main-chain atoms were already considered strong. However, this has been shown not to be the case, creating a new avenue for the development of HIV pharmaceuticals much less affected by virus evolution and resistance.

**Quotes**

Dr Matthew Blakeley, Institut Laue-Langevin said: "This study perfectly illustrates the benefits of neutrons in drug design due to their unique sensitivity to hydrogen atoms. Until recently high-resolution neutron studies of large biological systems were restricted due to the size of crystals that needed to be grown and the length of time it took for the results to be collected. However, significant technical developments, led by pioneering work here at the ILL, have greatly extended the range of experiments that can be performed providing the pharma industry with a powerful new tool to improve the performance of their products."

Andrey Kovalevsky, Oak Ridge National Laboratory said: "X-ray crystallography has been playing a crucial role in the structure-guided drug design for over two decades. It provides us with a picture of how a drug molecule binds to its macromolecular target, which is usually achieved through non-covalent interactions between these two molecules. The majority of such weak intermolecular interactions involve hydrogen atoms that normally remain invisible in X-ray structures. If one knows where hydrogen atoms are located it gives a researcher a much better idea about the nature and strength of the interactions. By applying neutron crystallography we have effectively increased the clarity of this picture, because hydrogen atoms become visible in the neutron structures. It is fair to say that by using neutrons we are now able to see every atom in a protein/drug complex, all the way to the smallest atom in nature. We are confident that by combining the two crystallographic techniques it will be possible to significantly improve the method of structure-guided drug design, which will provide patients with newer more effective medicines to not only battle HIV infection, but for other diseases as well."

Professor Irene Weber, Georgia State University said: "This neutron crystal structure provides important new insights into the chemistry of how drugs bind HIV protease."
Scripps Research Institute scientists reveal how deadly Ebola virus assembles

Study published in Cell challenges conventional wisdom, demonstrates protein morphs from one shape to another, offering multiple drug targets

LA JOLLA, CA – August 15, 2013 – Scientists at The Scripps Research Institute (TSRI) have discovered the molecular mechanism by which the deadly Ebola virus assembles, providing potential new drug targets. Surprisingly, the study showed that the same molecule that assembles and releases new viruses also rearranges itself into different shapes, with each shape controlling a different step of the virus's life cycle.

"Like a 'Transformer', this protein of the Ebola virus adopts different shapes for different functions," said Erica Ollmann Saphire, Ph.D., professor in the Department of Immunology and Microbial Science at TSRI. "It revises a central dogma of molecular biology—that a protein molecule has one shape that predestines one biological function."

The research was published today in the peer-reviewed journal Cell.

"These findings open doors to developing new drugs against Ebola," added Zachary Bornholdt, Ph.D., senior staff scientist and first author of the study. "Drugs to block viral replication could target any of the structures themselves or the intermediate steps in the structural transformation process."

Ebola hemorrhagic fever is one of the most virulent diseases known to humankind. Very few pathogens prove more dangerous than Ebola virus once a person is infected. There is no cure, and the case-fatality rate can be up to 90 percent, depending on which strain is involved.

Ebola virus and its cousin Marburg virus are spread when people come into contact with the bodily fluids of a person or animal who is already infected. Infection causes rapidly progressing high fever, hemorrhage and shock. No drugs or vaccines are yet available for human use. Currently, the standard treatment consists of administering fluids and taking protective measures to ensure containment, such as isolating the patient and washing sheets with bleach.

Once rare, the viruses are now reemerging with increasing frequency, and have caused at least four outbreaks among humans in the last two years. Although the viruses are found most often in Africa, they have been unintentionally imported into the United States and Europe several times, and in recent years a version of the Ebola virus has been found replicating in swine raised for human consumption in Asia.

To conduct the study, Dr. Saphire and her group at TSRI collaborated with Yoshihiro Kawaoka, Ph.D., D.V.M., who holds joint appointments at the University of Wisconsin and University of Tokyo. Dr. Kawaoka's group provided cellular microscopy and critical replication experiments to complement the TSRI team's expertise in x-ray crystallography and protein biochemistry.

The results, five years in the making, revealed the Ebola VP40 protein exists as a dimer, not as a monomer as previously thought, and it rearranges its structure to assemble filaments to build the virus shell or "matrix" to release countless new viruses from infected cells. The study showed the protein also rearranges itself into rings in order to bind RNA and control the internal components of the virus copied inside infected cells.

This "shape-shifting" or "transformer" behavior explains how the Ebola virus can control a multi-step viral lifecycle using only a very limited number of genes.

Tufts scientists develop new early warning system for cholera epidemics

Remote satellite methodology predicts outbreaks months in advance with greater accuracy

Medford/Somerville, Mass. – In two recently published papers, Tufts University School of Engineering researchers have established new techniques for predicting the severity of seasonal cholera epidemics months before they occur and with a greater degree of accuracy than other methods based on remote satellite imaging. Taken together, findings from these two papers may provide the essential lead time to strengthen intervention efforts before the outbreak of cholera in endemic regions.

Cholera is an acute diarrheal disease caused by the bacterium Vibrio cholerae. It occurs in the spring and fall in the Bengal delta. In past research, scientists have used chlorophyll, a surrogate for phytoplankton, as a measuring stick for cholera. The cholera bacteria lives and thrives among phytoplankton and zooplankton.

In the June issue of Remote Sensing Letters, Antarpreet Jutla, then a doctoral student at Tufts School of Engineering and now on the faculty at West Virginia University, was lead author on a study that measured chlorophyll and other organic matter.
The team, which was led by Shafiqul Islam, Ph.D., professor of civil and environmental engineering at Tufts School of Engineering, used satellite data to measure chlorophyll and algae, organic substances, and flora that also support growth of the cholera bacteria.

Using satellite images, the researchers created a "satellite water marker" (SWM) index to estimate the presence of organic matter including chlorophyll and plankton based on wavelength measurements.

A predominance of green, plankton-rich water— which is measured at 555 nanometers—indicated the degree to which the waters contained chlorophyll, plankton, and other impurities. Clear, blue water—measured at 412 nanometers—indicated low levels of these impurities, according to the researchers.

The researchers targeted the spring epidemic, which is a coastal phenomenon caused by water flow into the delta from three principal rivers – the Brahmaputra, Ganges, and Meghna. Unlike the spring outbreak, the fall epidemic is linked to flooding which follows the monsoons and subsequent breakdown of sanitary conditions rather than costal conditions.

In their study, the researchers correlated cholera incidence from the International Center for Diarrheal Disease Research, Bangladesh from 1997 to 2010 with satellite imaging data from the National Aeronautics and Space Administration for the same time period.

They discovered a relationship between SWM index measurements taken in early winter—from October to December—and the severity of cholera epidemics in the following spring. "In short, the index for chlorophyll along with readings for other biological matter in early winter indicated severity of cholera incidences in the spring," says Jutla.

The SWM is a more accurate predictor of cholera than the algorithm that measures strictly chlorophyll levels because it also measures a broader range of organic matter, says Islam.

"The probability for error in this index-based estimate is less than 10 percent while the error in using the chlorophyll-based algorithm is about 30 percent," says Islam. To validate their hypothesis that the index can be used in coastal areas outside of the Bengal Delta, the team applied the SWM to coastal waters around Mozambique's capital city, Maputo.

Additional authors on this paper are Abu Syed Golam Faruque, and Rita Colwell of the Center for Bioinformatics and Computational Biology at the University of Maryland, and Anwar Huq of the Maryland Pathogenic Research Institute at the University of Maryland. Another member of the team, Ali Shafqat Akanda, was with the Center for Bioinformatics and Computational Biology at UM and is now on the faculty at the University of Rhode Island. He was a doctoral student at Tufts during the research.

In a separate paper that was published online in the journal Environmental Modeling and Software, ahead of the September 1 print edition, Jutla, Islam, and Akanda showed that air temperature in the Himalayan foothills can also be a factor in predicting spring cholera.

The researchers collected air temperature data during the early winter months (October–December) in the foothills. In seasons of warm temperature, the foothills experienced higher than normal precipitation and early snow melt. This caused higher than normal water flow in the Ganges, Brahmaputra and Meghna Rivers and eventually into the Bay of Bengal during the drought period. Higher river flow into the delta impedes plankton-carrying seawater from moving inland.

When correlated with satellite data on chlorophyll levels, the researchers found that air temperatures could lessen the extent of cholera even when chlorophyll levels were high.


Answering crucial questions about anthrax exposure

Information derived through mathematical model can help guide responses to attacks

(SALT LAKE CITY)—If terrorists targeted the United States with an anthrax attack, health care providers and policy makers would need key information – such as knowing the likelihood of an individual becoming infected, how many cases to expect and in what pattern, and how long to give antibiotics – to protect people from the deadly bacteria.

Those questions gained urgency when anthrax-laced letters killed five people and infected 17 others in the wake of the terror attacks of September 2001. Now, using information from prior animal studies and data from a deadly anthrax exposure accident in Russia in the late 1970s, University of Utah and George E. Wahlen Department of Veterans Affairs Medical Center researchers have developed a mathematical model to help answer critical questions and guide the response to a large-scale anthrax exposure.

In an Aug. 15, 2013, study in PLOS Pathogens online, the researchers use their model to estimate that for an individual to have a 50 percent chance of becoming infected with anthrax (known as ID50), he or
she would have to inhale 11,000 spores of the bacteria. A 10 percent chance of being infected would require inhaling 1,700 spores and a 1 percent chance of infection would occur by inhaling 160 spores. The researchers also found that at ID50, the median time for anthrax symptoms to appear is 9.9 days and that the optimal time to take antibiotics is 60 days.

"Anthrax is a well-studied disease and experimental animal data exist, but there is no real good information on dose response for the disease in humans," says Adi V. Gundlapalli, M.D., Ph.D., an infectious diseases specialist and epidemiologist, associate professor of internal medicine at the U of U School of Medicine and staff physician at the Salt Lake City George E. Wahlen Department of Veterans Affairs Medical Center. "We don't want to be overly fearful, but we need to be prepared in the event of a bioterrorism attack with anthrax."

Although studies with animals at other institutions have looked at anthrax, the data are limited and usually involved vaccine testing and not exposure amounts for infection. Gleaning information from accidental exposures in isolated cases is difficult and not often helpful. So, Toth and Gundlapalli gathered what useful information from animal studies reported in the medical literature and then combined it with data from an accidental exposure at a Soviet Union bioterrorism plant that occurred in the city of Sverdlovsk, Russia, in 1979.

Gundlapalli, who as a post-doctoral fellow at the U of U helped build a bioterrorism surveillance system for the 2002 Winter Olympics in Salt Lake City, and Damon J.A. Toth, Ph.D., a mathematician and assistant professor of internal medicine at the U of U, are co-first authors on the study.

Anthrax is found on the skin of dead animals and its spores can live thousands of years. People can become infected when they are in close proximity to anthrax, such as a farmworker who might be exposed to a dead animal and inhales spores of the bacteria. But it also can be manufactured in laboratories and spread in other ways, such as when people opened letters containing anthrax or when the spores are put into an aerosol and dispersed over large areas by wind currents.

Previous studies at other institutions had provided widely varying estimates of the chance of becoming infected with anthrax with low dose exposure. For example, one model based on animal data estimated a 1 percent chance of becoming infected from inhaling one spore, while another study estimated that healthy humans would have virtually no chance of becoming infected after inhaling up to 600 spores. But analyzing the results from a better documented, non-human primate study at another institution, in combination with a carefully constructed mathematical model appropriate for humans, Toth estimated that the number of spores required for a 1 percent chance of infection is 160. These estimates were derived by developing and refining a competing-risks model in which the inhaled bacteria is trying to set up an infection in the lungs and the human body is trying to expel or control the bacteria. Toth then used available experimental animal data to optimize the working of the model to produce results that matched the timing of cases at Sverdlovsk.

"Our study, for the first time, takes all the best data and modeling techniques available on dose response and evaluates them critically," Toth says. "No one study satisfied all our criteria to be the best model, so we refined the available information to develop our model."

"When the Institute of Medicine was asked to look at the effectiveness and costs of different strategies to respond to an anthrax in 2012, the Committee identified a critical need for accurate information on the time from exposure until people became ill and how this would change depending on the dose," said Andrew Pavia, M.D., professor and chief of pediatric infectious diseases at the University of Utah and a member of the IOM committee that wrote the report, "Prepositioning antibiotics for Anthrax," and a consultant to CDC on anthrax. "The time between exposure and when symptoms develop is the most effective time to administer antibiotics to prevent illness. This study adds a thoughtful approach to using all of the available data to improve these estimates, but considerable uncertainty will remain." Pavia was not involved in the study.

Along with existing animal studies, data gathered from the accident at Sverdlovsk proved invaluable. Up to 100 people died when a filter was accidently left off a piece of equipment at a plant that was developing anthrax as a bioterrorism weapon. Spores of the bacteria were released into the air near the town of Sverdlovsk. The Soviets eventually let outside experts in to study the accident. From publicly available accounts, despite limited records and a substantial delay before the investigation, it would appear that scientists were able to estimate when the release happened, plot where people were in the surrounding area when it occurred and then look at weather records to identify wind currents. With that information, they plotted how the spores were scattered in relation to people who became infected.

The timing and geographic pattern of the best documented cases from Sverdlovsk were consistent with both the shape of the dose-response curve and the distribution of incubation periods produced by the
new model. The model also sheds light on how long antibiotics should be given after an exposure to decrease the chances of infection. The model’s predictions match so well with publicly available Sverdlovsk data that Gundlapalli and Toth believe they can use the model to reasonably estimate how exposures to anthrax would unfold, especially at low doses of the bacteria.

"By combining the data from Sverdlovsk and prior studies, we can make defensible estimates on how scenarios might play out if anthrax were released in a terrorist attack," Gundlapalli says. "How many cases could we expect? When would we expect to see the cases? How long should we treat those exposed with preventive antibiotics? Our model provides real answers to help policy makers when they need that information."

More Than 28 Cups of Coffee a Week May Endanger Health in Under 55s
Aug. 15, 2013 — Nearly 400 million cups of coffee are consumed every day in America. Drinking large amounts of coffee may be bad for under-55s, according to a new study published in Mayo Clinic Proceedings. A study of more than 40,000 individuals found a statistically significant 21% increased mortality in those drinking more than 28 cups of coffee a week and death from all causes, with a greater than 50% increased mortality risk in both men and women younger than 55 years of age. Investigators warn that younger people in particular may need to avoid heavy coffee consumption. No adverse effects were found in heavy coffee drinkers aged over 55.

Drinking coffee has become a normal daily routine for large numbers of people worldwide. According to the latest National Coffee Drinking Study from the National Coffee Association, more than 60% of American adults drink coffee every day, consuming on average just over three cups a day.

Coffee has long been suspected to contribute to a variety of chronic health conditions, although earlier studies on coffee consumption in relation to deaths from all causes and deaths from coronary heart disease are limited, and the results are often controversial.

A multicenter research team investigated the effect of coffee consumption on death from all causes and deaths from cardiovascular disease in the Aerobics Center Longitudinal Study (ACLS) cohort, with an average follow-up period of 16 years and a relatively large sample size of over 40,000 men and women. Between 1979 and 1998, nearly 45,000 individuals aged between 20 and 87 years old participated and returned a medical history questionnaire assessing lifestyle habits (including coffee consumption) and personal and family medical history. The investigators examined a total of 43,727 participants (33,900 men and 9,827 women) in their final analysis.

During the 17-year median follow-up period there were 2,512 deaths (men: 87.5%; women: 12.5%), 32% of these caused by cardiovascular disease. Those who consumed higher amounts of coffee (both men and women) were more likely to smoke and had lower levels of cardiorespiratory fitness.

All participants were followed from the baseline examination to date of death or until December 31, 2003. Deaths from all causes and deaths from cardiovascular disease were identified through the National Death Index or by accessing death certificates.

Younger men had a trend towards higher mortality even at lower consumption, but this became significant at about 28 cups per week where there was a 56% increase in mortality from all causes. Younger women who consumed more than 28 cups of coffee per week also had a greater than 2-fold higher risk of all-cause mortality than those who did not drink coffee.

Senior investigator Steven H. Blair, PED, of the Department of Biostatistics and Epidemiology, Arnold School of Public Health, University of South Carolina, emphasizes that "Significantly, the results did not demonstrate any association between coffee consumption and all-cause mortality among older men and women. It is also important to note that none of the doses of coffee in either men or women whether younger or older had any significant effects on cardiovascular mortality."

Coffee is a complex mixture of chemicals consisting of thousands of components. Recent research has found that coffee is one of the major sources of antioxidants in the diet and has potential beneficial effects on inflammation and cognitive function. However, it is also well-known that coffee has potential adverse effects because of caffeine's potential to stimulate the release of epinephrine, inhibit insulin activity, and increase blood pressure and levels of homocysteine.

"Thus, all of these mechanisms could counterbalance one another. Research also suggests that heavy coffee drinkers may experience additional risk through potential genetic mechanisms or because of confounding through the deleterious effects of other risk factors with which coffee drinking is associated," say lead authors, Junxiu Liu, MD, Department of Biostatistics and Epidemiology, and Xue mei Sui, MD, MPH, PhD, Department of Exercise Science, both at the Arnold School of Public Health, University of
South Carolina, "Therefore, we hypothesize that the positive association between coffee and mortality may be due to the interaction of age and coffee consumption, combined with a component of genetic coffee addiction."

The investigators suggest that younger people in particular should avoid heavy coffee consumption of more than 28 cups a week or four cups in a typical day. However, they emphasize that further studies are needed in different populations to assess details regarding the effects of long-term coffee consumption and changes in coffee consumption over time on all-cause and cardiovascular disease mortality.

Leading expert Carl J. Lavie, MD, of the Department of Cardiovascular Diseases, Ochsner Medical Center, New Orleans, and a co-author of this study, explains that "There continues to be considerable debate about the health effects of caffeine, and coffee specifically, with some reports suggesting toxicity and some even suggesting beneficial effects."

**Journal Reference:**

### Researchers Debunk Myth of 'Right-Brained' and 'Left-Brained' Personality Traits

![Significant lateralization of gray matter density. Show more Colored regions included ROIs that showed significantly greater left-](image-url)
or right-lateralization of gray matter density across 1011 subjects, correcting for multiple comparisons using a false discovery rate correction of q<0.05 across 7266 ROIs. Color bars show t-statistics for the left and right hemispheres, respectively. Images are in radiologic format with subject left on image right. (Credit: Nielsen JA, Zielinski, Ferguson, Lainhart, Anderson. An Evaluation of the Left-Brain vs. Right-Brain Hypothesis with Resting State Functional Connectivity Magnetic Resonance Imaging. PLoS ONE, 2013 DOI: 10.1371/journal.pone.0071275

Aug. 14, 2013 — Chances are, you’ve heard the label of being a "right-brained" or "left-brained" thinker. Logical, detail-oriented and analytical? That's left-brained behavior. Creative, thoughtful and subjective? Your brain's right side functions stronger—or so long-held assumptions suggest.

But newly released research findings from University of Utah neuroscientists assert that there is no evidence within brain imaging that indicates some people are right-brained or left-brained.

For years in popular culture, the terms left-brained and right-brained have come to refer to personality types, with an assumption that some people use the right side of their brain more, while some use the left side more.

Following a two-year study, University of Utah researchers have debunked that myth through identifying specific networks in the left and right brain that process lateralized functions. Lateralization of brain function means that there are certain mental processes that are mainly specialized to one of the brain's left or right hemispheres. During the course of the study, researchers analyzed resting brain scans of 1,011 people between the ages of seven and 29. In each person, they studied functional lateralization of the brain measured for thousands of brain regions—finding no relationship that individuals preferentially use their left-brain network or right-brain network more often.

"It's absolutely true that some brain functions occur in one or the other side of the brain. Language tends to be on the left, attention more on the right. But people don't tend to have a stronger left- or right-sided brain network. It seems to be determined more connection by connection," said Jeff Anderson, M.D., Ph.D., lead author of the study, which is formally titled "An Evaluation of the Left–Brain vs. Right–Brain Hypothesis with Resting State Functional Connectivity Magnetic Resonance Imaging." It is published in the journal PLOS ONE this month.

Researchers obtained brain scans for the population they studied from a database called INDI, the International Neuroimaging Data-Sharing Initiative. The participants' scans were taken during a functional connectivity MRI analysis, meaning a participant laid in a scanner for 5 to 10 minutes while their resting brain activity was analyzed.

By viewing brain activity, scientists can correlate brain activity in one region of the brain compared to another. In the study, researchers broke up the brain into 7,000 regions and examined which regions of the brain were more lateralized. They looked for connections—or all of the possible combinations of brain regions—and added up the number of connections for each brain region that was left- lateralized or right-lateralized. They discovered patterns in brain imaging for why a brain connection might be strongly left- or right-lateralized, said Jared Nielsen, a graduate student in neuroscience who carried out the study as part of his coursework.

"If you have a connection that is strongly left- lateralized, it relates to other strongly lateralized connection only if both sets of connections have a brain region in common," said Nielsen.

Results of the study are groundbreaking, as they may change the way people think about the old right-brain versus left-brain theory, he said.

"Everyone should understand the personality types associated with the terminology 'left-brained' and 'right-brained' and how they relate to him or her personally; however, we just don't see patterns where the whole left-brain network is more connected or the whole right-brain network is more connected in some people. It may be that personality types have nothing to do with one hemisphere being more active, stronger, or more connected," said Nielsen.


New Strategy to Disarm the Dengue Virus Brings New Hope for a Universal Dengue Vaccine

Aug. 13, 2013 — A new strategy that cripples the ability of the dengue virus to escape the host immune system has been discovered by A*STAR’s Singapore Immunology Network (SIgN). This breakthrough strategy opens a door of hope to what may become the world’s first universal dengue vaccine candidate that can give full protection from all four serotypes of the dreadful virus.

For years in popular culture, the terms left-brained and right-brained have come to refer to personality types, with an assumption that some people use the right side of their brain more, while some use the left side more.

"Everyone should understand the personality types associated with the terminology 'left-brained' and 'right-brained' and how they relate to him or her personally; however, we just don't see patterns where the whole left-brain network is more connected or the whole right-brain network is more connected in some people. It may be that personality types have nothing to do with one hemisphere being more active, stronger, or more connected," said Nielsen.

This research done in collaboration with Singapore’s Novartis Institute of Tropical Diseases (NITD) and Beijing Institute of Microbiology and Epidemiology is published in the Plos Pathogens journal, and is also supported by Singapore STOP Dengue Translational and Clinical Research (TCR) Programme grant.

Early studies have shown that a sufficiently weakened virus that is still strong enough to generate protective immune response offers the best hope for an effective vaccine. However, over the years of vaccine development, scientists have learnt that the path to finding a virus of appropriate strength is fraught with challenges. This hurdle is compounded by the complexity of the dengue virus. Even though there are only four different serotypes, the fairly high rates of mutation means the virus evolve constantly, and this contributes to the great diversity of the dengue viruses circulating globally. Furthermore, in some cases, the immune response developed following infection by one of the four dengue viruses appears to increase the risk of severe dengue when the same individual is infected with any of the remaining three viruses. With nearly half the world’s population at risk of dengue infection and an estimated 400 million people getting infected each year[2], the need for a safe and long-lasting vaccine has never been greater.

The new strategy uncovered in this study overcomes the prevailing challenges of vaccine development by tackling the virus’ ability to ‘hide’ from the host immune system. Dengue virus requires the enzyme called MTase (also known as 2’-O-methyltransferase) to chemically modify its genetic material to escape detection. In this study, the researchers discovered that by introducing a genetic mutation to deactivate the MTase enzyme of the virus, initial cells infected by the weakened MTase mutant virus is immediately recognised as foreign. As a result, the desired outcome of a strong protective immune response is triggered yet at the same time the mutant virus hardly has a chance to spread in the host.

Animal models immunised with the weakened MTase mutant virus were fully protected from a challenge with the normal dengue virus. The researchers went on to demonstrate that the MTase mutant dengue virus cannot infect Aedes mosquitoes. This means that the mutated virus is unable to replicate in the mosquito, and will not be able to spread through mosquitoes into our natural environment. Taken together, the results confirmed that MTase mutant dengue virus is potentially a safe vaccine approach for developing a universal dengue vaccine that protects from all four serotypes.

The team leader, Dr Katja Fink from SlgN said, "There is still no clinically approved vaccine or specific treatment available for dengue, so we are very encouraged by the positive results with this novel vaccine strategy. Our next step will be to work on a vaccine formulation that will confer full protection from all four serotypes with a single injection. If this proves to be safe in humans, it can be a major breakthrough for the dengue vaccine field."

Associate Professor Leo Yee Sin, Clinical Director of Communicable Diseases Centre and Institute of Infectious Disease and Epidemiology at Tan Tock Seng Hospital who heads the Singapore STOP Dengue Translational and Clinical Research (TCR) Programme said, "We are into the seventh decade of dengue vaccine development, this indeed is an exciting breakthrough that brings us a step closer to an effective vaccine."

Acting Executive Director of SlgN, Associate Professor Laurent Rénia said, "Dengue is a major public health problem in many of the tropical countries. We are very delighted that our collaborative efforts with colleagues in Singapore and China have made a promising step towards a cost-effective and safe dengue vaccine to combat the growing threat of dengue worldwide."

Journal References:

Heat Waves Increase Incidence of Infectious Gastroenteritis and IBD Flares
Aug. 13, 2013 — Swiss researchers report an increase risk of inflammatory bowel disease (IBD) relapse in patients during heat wave periods. The study published in The American Journal of Gastroenterology also found an increase of infectious gastroenteritis during heat waves, with the strongest lag impact following a 7 day lag time after the heat wave.
The authors noted, "There is evidence for an increase of IBD hospital admissions by 4-6 percent for each additional day within a heat wave period. Presence of a heat wave was estimated to increase the risk of infectious gastroenteritis by 4-7 percent for every additional day within a heat wave period. In the control group there was no evidence for a heat wave effect."

Researchers from Zurich, Switzerland studied the data of 738 IBD and 786 IG patients admitted to the University Hospital of Zurich over a 5-year period (2001-2005) and compared data with other non-infectious chronic intestinal inflammations, as the control. The Swiss Federal Office for Meteorology and Climatology provided the climate data. A total of 17 heat waves were identified during that period.

"The evidence of patients with IBD having a significant increase risk of flare ups compared to the control group shows a cause and effect between the climate and the disease," said lead author Christine N. Manser, MD. "This study ties heat stress to digestive symptoms supporting the observed seasonal variation in the clinical course of inflammatory bowel disease and suggests that microbial infections of the gut might be additionally influenced by climate changes."

Some people with IBD may experience flare ups during significant weather changes. "Heat waves are known to cause physical stress as evident from increased frequencies of other stress dependent health events such as heart attacks. Physical as well as mental stress has been shown to cause flares of IBD, and may explain the increase in IBD hospital admissions during heat waves," commented Dr. Manser. "During a heat wave patients with IBD should be aware that there is an increased risk for a flare and contact their gastroenterologist in cases of an increase of stool frequency or abdominal pain. The public should know that a sudden onset of abdominal pain and diarrhea during or shortly after a heat wave might be symptoms of an infectious gastroenteritis."

**High prevalence of CMV retinitis among HIV-positive patients in Asia and Africa**

Michael Carter
Published: 19 August 2013
Prevalence of CMV retinitis remains high among people living with HIV in resource-limited settings, results of a systematic review of 65 studies published in the online edition of Clinical Infectious Diseases show. Prevalence of this AIDS-defining condition was 14% in Asia and 2% in Africa. Approximately three-quarters of cases involved people with a CD4 cell count below 50 cells/mm$^3$.

"This review found that the prevalence of CMV retinitis in resource-limited settings, notably Asian countries, remains high," write the authors. "Part of the explanation for the enduring high prevalence of CMV retinitis in Asia can be found in the fact that, despite considerable progress in scaling up access to ART [antiretroviral therapy], the proportion of patients who present late for HIV care remains high."

Cytomegalovirus (CMV) is a late-stage opportunistic infection in people with HIV, typically occurring when CD4 cell count falls below 100 cells/mm$^3$. The most frequent manifestation of CMV disease in people living with HIV is CMV retinitis, which is responsible for over 90% of cases of HIV-related blindness.

Largely thanks to antiretroviral therapy, new cases of CMV retinitis are very rare in richer countries. There is also an assumption that CMV retinitis is no longer a major concern in resource-limited settings, especially as access to antiretroviral therapy is increasing.

But an international team of investigators was concerned that access to CMV diagnostic and treatment services is limited in many low- and middle-income countries. Moreover, the researchers noted that studies have reported widely varying rates of the condition.

They therefore conducted a systematic review and meta-analysis of research published between 1996 and early 2013 that reported on the prevalence of CMV retinitis among people living with HIV in resource-limited countries. Studies were included if they assessed the occurrence of CMV retinitis by fundoscopic examination and had a cohort of at least ten adults living with HIV.

A total of 65 studies involving 20,280 people met the investigators’ inclusion criteria. Most of these studies were conducted in Asia (39 studies, 12,931 participants), followed by Africa (18 studies, 4325 participants) and Latin America (five studies, 2836 participants). The age of participants at the time of screening ranged from 21 to 41 years. The majority of studies (50) were conducted in hospital settings. Just under a fifth (18%) were carried out between 1993 and 2002; a third between 2003 and 2005; 24% between 2006 and 2008; and 26% between 2009 and 2013.

The overall quality of the studies was rated as low to moderate. The majority (52) had a prospective design and reported using indirect ophthalmoscopy with dilation of the pupils. In 30 studies an
ophthalmologist conducted the screening. Only 30 studies stratified outcomes according to CD4 cell count.

Prevalence of CMV retinitis ranged from a low of 0.2% in a study conducted in Nigeria, to 72% in a Thai study. Prevalence exceeded 5% in four countries: Thailand, 24% (five studies, 1397 patients); Myanmar, 25% (five studies, 2928 patients); China, 15% (nine studies, 2357 patients); and India, 7% (13 studies, 4305 patients).

By region, the highest prevalence was in Asia (14%) and lowest in Africa (2%). Only 19 studies reported whether disease affected one or both eyes. Their findings showed that 43% of patients had CMV retinitis in both eyes. Almost a third (32%) of patients had lost vision in one or both eyes.

Almost three-quarters (73%) of cases involved people with a CD4 cell count below 50 cells/mm³. A further 16% of patients had a CD4 cell count between 50-100 cells/mm³ at the time of diagnosis.

“This review indicates the important clinical burden of CMV retinitis, predominantly in patients with CD4<100 cells/mm³, and that the disease is commonly bilateral and commonly associated with vision loss,” comment the investigators.

Prevalence did not differ over time, and was similar in studies conducted between 1993 and 2002 (12%) and between 2009 and 2013 (17%).

There was no difference in prevalence according to whether screening was conducted by an ophthalmologist or an HIV clinician trained in retinal examination. “From an operational perspective, this is encouraging, and points towards the potential for integrating routine retinal examination as part of basic care for all late presenters,” the researchers suggest.

They believe their findings have important clinical implications, especially the need to improve the detection of people with CMV retinitis: “routine retinal screening by indirect ophthalmoscopy of all late presenters with CD4 below 100 cells/mm³ should be considered.” The investigators also suggest that CMV prophylaxis may be beneficial for some patients and that pressure needs to be exerted to make oral therapies for CMV retinitis affordable for resource-limited countries.

The Medicines Patent Pool and Roche announced an agreement to provide valganciclovir to treat CMV retinitis at low cost in 138 countries earlier this month.

Reference

Low baseline CD4 cell count associated with greater bone loss after starting HIV therapy
Michael Carter
Published: 21 August 2013
A low baseline CD4 cell count is associated with loss of bone mineral density (BMD) during the early years of HIV therapy, US investigators report in the online edition of Clinical Infectious Diseases. Results of three studies conducted between 1998 and 2007 were included in their analysis. DEXA-scan monitoring showed that immune suppression before starting HIV therapy was a risk factor for loss of BMD during treatment.

“We found a strong and independent association between low baseline CD4+ count and total BMD loss in the first two years of treatment,” write the authors. “We did not find any evidence that the extent of immune reconstitution...was associated with BMD change after controlling for baseline CD4+ count.” The investigators believe their findings underline the importance of early HIV treatment.

HIV infection is associated with loss of bone mineral density and an increased risk of fractures. Loss of bone continues after HIV therapy is started, and decreases in BMD of between 2 and 6% typically occur in the first two years of antiretroviral therapy.

The reasons for this are not clear. To gain a better understanding of the causes, investigators examined BMD in approximately 800 people who underwent whole body DEXA scanning before starting HIV therapy and again after 96 weeks.

The participants in the study had a median age of 39 years and 83% were male. Baseline BMI was 25 kg/m². Median baseline CD4 cell count and viral load were 208 cells/mm³ and 63,000 copies/ml, respectively. Almost two-thirds of participants (62%) started HIV therapy with a regimen based on a protease inhibitor and 27% received tenofovir (Viread, also in Truvada and Atripla). These drugs have been associated with reduced BMD in other research.

The mean loss of total BMD at week 96 was 2%. Baseline CD4 cell count was strongly associated with BMD loss. Participants with a pre-therapy CD4 cell count of below 50 cells/mm³ lost 3% more BMD than
people with a baseline CD4 cell count above 500 cells/mm³ (p < 0.001) and approximately 2% more BMD than people with CD4 counts between 350 and 499 cells/mm³.

A greater relative, but not absolute, CD4 cell count 16 weeks after starting therapy was initially shown to increase BMD loss (-2.3% per tenfold increase, p < 0.001). However, this association disappeared after controlling for baseline CD4 cell count.

After taking into account confounding factors, a low baseline CD4 cell count remained strongly associated with BMD loss at week 96. Individuals with a pre-therapy count below 50 cells/mm³ lost 2.27% more BMD at this follow-up point compared to people with a baseline CD4 count above 500 cells/mm³ (p < 0.001).

“We found that even after controlling for multiple confounders such as BMI that there was a robust relationship between low baseline CD4+ count and greater bone loss after ART [antiretroviral therapy] initiation,” comment the authors. “The underlying reason for the relationship between low baseline CD4+ count and bone loss with ART initiation is not known but suggests a potential role for the immune system in skeletal maintenance.”

Older age (each additional year, p < 0.001), female sex (p = 0.007), low BMI (p < 0.001) and a high HIV viral load (p = 0.002) were also associated with greater bone loss.

Participants whose initial regimen included tenofovir lost on average 1.38% more BMD at week 96 (p < 0.001) compared to people taking an alternative drug. Individuals taking a protease inhibitor lost approximately 1% more BMD at follow-up (p = 0.001) compared to individuals taking an alternative class of drugs.

There was also a significant interaction between lower CD4 cell count and higher viral load and BMD loss (p = 0.043). In patients with a higher viral load, the negative effect of a low CD4 cell count on BMD was greater than in individuals with a lower viral load.

The investigators note that the BMD changes found in their study were relatively “modest” and of unknown clinical significance. They also emphasise that they did not have data on some factors associated with bone loss such as tobacco and alcohol use, testosterone and vitamin D levels, and use of medicines that can affect BMD.

Nevertheless, the authors conclude: “low pre-treatment CD4+ count, but not early CD4+ change with ART was a strong and independent risk factor for bone loss after ART initiation, providing further evidence for the benefits of early initiation of ART.”

Reference

Zimbabwe: Killed for Refusing to Take ARVs
21 August 2013
THE trial of a 28-year-old man from Zezani in Beitbridge who was arrested for fatally assaulting his 12-year-old brother for refusing to take his anti-retroviral tablets has been postponed to August 30. Thuso Ndou, who resides in Chief Stauze’s area was not asked to plead to a murder charge when he appeared before Miss Gloria Takundwa. Prosecutor Mr Jabulani Mberesi told the court that Ndou was staying with the now deceased since their parents are late.

The court heard that on July 31 at around noon, Thuso ordered the boy who was on anti-retroviral therapy to take his medication but he refused resulting in Ndou assaulting him. The boy tried to flee from the barrage of attacks but fell headlong and hit a stone before he collapsed. Ndou tried to resuscitate the boy but he failed.

The boy was later taken to Beitbridge District Hospital and died along the way.

The matter was reported to police resulting in Ndou’s arrest.

Food fungi in developing countries linked to worse HIV infection
24 Jul 2013
Two common fungi found on food in developing countries could be worsening the effects of HIV, say researchers from the University of Alabama, Birmingham.

Their study, published in the World Mycotoxin Journal, found that types of fungus on stored foods such as rice, wheat, nuts and corn, are linked to higher HIV viral loads (higher concentrations of the virus in infected people’s blood).

The researchers say: "Higher viral load translates into higher rates of HIV transmission and the potential for earlier progression to the opportunistic infections of AIDS.”
According to the researchers, foods that are stored in warehouses and barns of developing countries near the equator, such as Asia and Africa, become contaminated by 
*Aspergillus flavus* and *A. parasiticus*. Because these fungi produce aflatoxin, a poisonous substance that has been known to cause cancer and liver damage in humans and animals, the Food and Drug Administration (FDA) has imposed regulations on the levels of the toxin in US food—particularly in animal feeds.

There are no similar restrictions on the levels of this toxin in developing countries, meaning citizens are much more likely to be exposed to high levels of the fungi and aflatoxin.

The researchers say around 4.5 billion people worldwide are exposed to unsafe levels of aflatoxin.

**Aflatoxin ‘taking greater toll’ on people with HIV**

For the study, 314 HIV-positive people were recruited who had not yet started antiretroviral treatment for the infection.

Patients were split into four groups dependent on their levels of exposure to aflatoxin.

**HIV-infected people subjected to the highest exposure of aflatoxin were 2.6 times more likely to develop a higher HIV viral load than those in the lowest-exposure group.**

Pauline Jolly, professor in epidemiology at the University of Alabama’s School of Public Health, says: "Our work suggests that aflatoxin exposure may be taking an even greater toll in areas where millions are infected with HIV, including Africa and Asia, the latter with a fast-growing HIV population and rice storage areas contaminated by fungi."

Prof. Jolly adds that the team conducted previous studies focusing on the link between the progression of HIV and interaction with aflatoxin, but the current study analyzed twice as many patients.

For the first time, this study also eliminated factors such as opportunistic infections and antiviral therapy to determine the relationship between HIV and aflatoxin exposure.

**Aflatoxin levels in developing countries ‘need addressing’**

Prof. Jolly notes that although studies have shown a link between aflatoxin exposure and HIV infection, the issue has not yet been recognized or addressed.

She says: "While this study was larger than our previous study, a fungal contribution to HIV transmission will only be proved once and for all by larger randomized studies for which there is no funding. The scientific and world-health communities need to decide soon whether or not this question is worth answering."

Written by Honor Whiteman

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**References:**


**Bacterial toxins cause deadly heart disease**

**Study shows superantigens produced by staph bacteria are required for deadly effects of infective endocarditis and sepsis**

University of Iowa researchers have discovered what causes the lethal effects of staphylococcal infective endocarditis—a serious bacterial infection of heart valves that kills approximately 20,000 Americans each year.

According to the UI study, the culprits are superantigens—toxins produced in large quantities by *Staphylococcus aureus* (staph) bacteria—which disrupt the immune system, turning it from friend to foe.

"The function of a superantigen is to ‘mess’ with the immune system," says Patrick Schlievert, Ph.D., UI professor and chair of microbiology at the UI Carver College of Medicine. "Our study shows that in endocarditis, a superantigen is over-activating the immune system, and the excessive immune response is actually contributing very significantly to the destructive aspects of the disease, including capillary leakage, low blood pressure, shock, fever, destruction of the heart valves, and strokes that may occur in half of patients."

Other superantigens include toxic shock syndrome toxin-1, which Schlievert identified in 1981 as the cause of toxic shock syndrome.

Staph bacteria is the most significant cause of serious infectious diseases in the United States, according to the Centers for Disease Control and Prevention (CDC), and infective endocarditis is the most serious complication of staph bloodstream infection. This dangerous condition affects approximately
40,000 people annually and has a death rate of about 50 percent. Among patients who survive the infection, approximately half will have a stroke due to the damage from the aggressive infection of the heart valves.

Despite the serious nature of this disease, little progress has been made over the past several decades in treating the deadly condition.

The new study, led Schlievert, and published Aug. 20 in the online open-access journal *mBio*, suggests that blocking the action of superantigens might provide a new approach for treating infective endocarditis.

"We have high affinity molecules that neutralize superantigens and we have previously shown in experimental animals that we can actually prevent strokes associated with endocarditis in animal models. Likewise, we have shown that we can vaccinate against the superantigens and prevent serious disease in animals," Schlievert says.

"The idea is that either therapeutics or vaccination might be a strategy to block the harmful effects of the superantigens, which gives us the chance to do something about the most serious complications of staph infections."

The UI scientists used a strain of methicillin resistant *staph aureus* (MRSA), which is a common cause of endocarditis in humans, in the study. They also tested versions of the bacteria that are unable to produce superantigens. By comparing the outcomes in the animal model of infection with these various bacteria, the team proved that the lethal effects of endocarditis and sepsis are caused by the large quantities of the superantigen staphylococcal enterotoxin C (SEC) produced by the staph bacteria.

The study found that SEC contributes to disease both through disruption of the immune system, causing excessive immune response to the infection and low blood pressure, and direct toxicity to the cells lining the heart.

Low blood flow at the infection site appears to be one of the consequences of the superantigen’s action. Increasing blood pressure by replacing fluids reduced the formation of so-called vegetations – plaque-like meshwork made up of cellular factors from the body and bacterial cells—on the heart valves and significantly protected the infected animals from endocarditis. The researchers speculate that increased blood flow may act to wash away the superantigen molecules or to prevent the bacteria from settling and accumulating on the heart valves.

New explanation for key step in anthrax infection proposed by NIST and USAMRIID

A new hypothesis concerning a crucial step in the anthrax infection process has been advanced by scientists at the National Institute of Standards and Technology (NIST) and the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) at Fort Detrick, Md.

The research teams have explored the behavior of the toxins that rapidly overwhelm the body as the often-fatal disease progresses. Their findings suggest a new possible mechanism by which anthrax bacteria deliver the protein molecules that poison victims. Anthrax is easily weaponized; the findings could help lead to a more effective cure.

Anthrax bacteria kill by releasing three toxins that work in concert to destroy cells. One toxin, called PA, attaches to the cell membrane, where its surface serves as a sort of landing pad for the other two toxins, called LF and EF. Once several molecules of LF and EF have latched onto PA, the cell membrane tries to destroy these unwanted hangers-on by wrapping them up in an "endosome," a small bubble of membrane that gets pinched off and moved into the cell’s interior. There, the cell attempts to destroy its contents by a process that includes making the interior of the endosome more acidic. But before the cell can fully carry out its plan, the LF and EF escape from the endosome and wreak havoc in the cell’s interior. The question is: how do these toxins escape?

"A recent hypothesis is that LF and EF completely unfold and then squeeze through the narrow hole that PA forms in the endosomal membrane," says NIST physical scientist John Kasianowicz. "However,
the studies used to support this concept make use of short segments of the toxins, not their native full-length versions. The results don't show that the complete LF and EF are transported through the pore or whether they refold into functional enzymes once they reach the other side. So, we decided to look at other possible explanations."

The NIST/USAMRIID team explored the behavior of full-length toxins using an artificial membrane that mimics a cell's exterior. They put the toxins mixed in salt water on one side of this barrier and slowly rendered this fluid more acidic, resembling conditions within an endosome. But the change in chemistry apparently altered the physical characteristics of the LF and EF toxins, because it caused them to bind irreversibly to the PA pore, creating a "complex" of multiple toxins. This result alone suggested it would be difficult, if not impossible, for LF and EF to thread through the pore.

In addition, the team discovered that the bound toxins tend to rupture membranes. This finding led them to suggest that perhaps it is complexes of LF or EF bound to PA that gets into cells, and that these complexes are the active toxins inside cells.

Kasianowicz says this new hypothesis could explain previous experimental results, in which the complex was found in the blood of animals that died of anthrax. But he emphasizes that the matter is not yet settled.

"We don't know enough to choose between these theories—and in fact it's possible that the toxins escape the endosome by more than one mechanism," he says. "But it's important that we better understand this step in the process to thwart anthrax more effectively."


Growing share of HIV/AIDS burden shifts to changing group of regions
Despite years of strong progress, burden of AIDS growing in the Caribbean and Southeast Asia and still significant in Eastern, Central, and Southern Africa
August 21, 2013—The HIV/AIDS epidemic is changing in unexpected ways in countries around the world, showing that greater attention and financial investment may be needed in places where the disease has not reached epidemic levels, according to a new study from the Institute for Health Metrics and Evaluation (IHME) at the University of Washington.


In 2005, 68.7% of global HIV/AIDS burden was in countries where HIV/AIDS is the leading or second leading cause of the burden of disease. In 2010, 59.4% of the burden was in countries where HIV/AIDS ranked first or second, meaning countries where the disease ranked lower represented a larger share of the burden.

In 2010, for example, 20% of health loss due to HIV/AIDS was in countries where HIV/AIDS was not in the top 10 causes of disease burden compared to only 15.5% in 2005.

The findings were published August 21st in the study "The Burden of HIV: Insights from the GBD 2010" in the peer-reviewed journal AIDS.

IHME researchers also underscore the achievements that have been made against HIV—in terms of raising public awareness and increasing access to antiretroviral treatment—as well as the unrelenting challenges that AIDS poses to health around the world.

Millions of people, including many in low- and middle-income countries, now receive antiretroviral treatments (ARTs). There has been significant progress made against HIV/AIDS since global mortality due to the disease peaked in 2006; it has been steadily declining at an average annual rate of 4.2% since then.

The epidemic has peaked at different times in different countries, showing different rates of progress. In Botswana deaths are down 74%; in Mexico deaths are down 69.2%; and in Kazakhstan deaths are down 66.6%.

Yet HIV/AIDS remains a global issue; in 2012, 186 countries reported HIV cases or deaths. The disease is among the top five causes – but not the leading cause – of burden in 26 countries ranging from the Ukraine to Myanmar to Guyana.

"We cannot afford to become complacent when HIV/AIDS remains a tremendous threat," said researcher and lead study author Katrina F. Ortblad of IHME. "Countries that bear significant burden
must scale up effective interventions and treatments. In countries where the impact of HIV/AIDS is relatively small but burden is increasing, prevention can help change the course of future epidemics.

IHME’s study examines health loss from HIV/AIDS as measured in DALYs, or disability-adjusted life years. DALYs combine years of life lost to premature death with years lived with disability and allow comparisons among different populations and health conditions.

While the global health landscape is increasingly dominated by the rise of non-communicable diseases, injuries, and disabling conditions, HIV takes a particular toll on young people around the world. It is the number one cause of disease burden for men aged 30 to 44 and women aged 25 to 44.

Globally, there are 78 countries where HIV/AIDS accounts for more than 10% of deaths in people aged 30 to 34.

In South Africa, for example, the picture is even more striking. In 2010, HIV/AIDS caused 75% of deaths among people aged 30 to 34; the figure rose to 84% for women in that age group.

Even in wealthier countries, challenges in addressing HIV/AIDS remain. In the United States, where deaths due to the disease are down 75.6% since its peak, HIV/AIDS still contributes to 0.7% of American health loss, far more than in other high-income countries like the United Kingdom, Canada, and France, and even more than in many developing countries such as Congo, Mongolia and Sri Lanka.

Success in these countries and many others has been largely due to substantial global action, policy changes and funding. Between 2002 and 2010, development assistance for health targeting HIV/AIDS increased from US$1.4 billion to US$6.8 billion – an increase of 385.7% that does not include funds spent by low- and middle-income countries themselves.

Increased access to antiretrovirals has accompanied declines in incidence, and more interventions to prevent mother-to-child transmission.

"The success we have made in combatting HIV/AIDS illustrates what can happen when funders, advocates, governments and health experts commit to a common goal, and dedicate resources to back up the commitment," said Dr. Christopher Murray, IHME director and one of the study’s authors. "By gathering the best evidence on the spread of HIV/AIDS we can ensure continued progress."

The study also notes the challenges in collecting country-level estimates from different sources and calls for improvements in vital registration data that records a population’s births and deaths.

In sub-Saharan Africa, which accounts for 70.9% of the global health loss attributable to HIV/AIDS, progress against the disease is mixed. In Rwanda, Botswana and Zimbabwe, for example, mortality due to HIV/AIDS decreased dramatically from epidemic peak to 2010; 83.1%, 74% and 47.5% respectively. In other sub-Saharan African countries like Democratic Republic of the Congo, Angola and the Central African Republic, progress has been nearly nonexistent.

"AIDS is not just a problem in Africa," explained Dr. Rafael Lozano, IHME’s Director of Latin American and Caribbean Initiatives and one of the paper’s authors. "We see significant mortality numbers from AIDS in countries as varied as Venezuela, Thailand and Jamaica."
A Home for the Microbiome: Biologists Identify How Beneficial Bacteria Reside and Thrive in Gastrointestinal Tract

Aug. 19, 2013 — The human body is full of tiny microorganisms—hundreds to thousands of species of bacteria collectively called the microbiome, which are believed to contribute to a healthy existence. The gastrointestinal (GI) tract—and the colon in particular—is home to the largest concentration and highest diversity of bacterial species. But how do these organisms persist and thrive in a system that is constantly in flux due to foods and fluids moving through it? A team led by California Institute of Technology (Caltech) biologist Sarkis Mazmanian believes it has found the answer, at least in one common group of bacteria: a set of genes that promotes stable microbial colonization of the gut.

A study describing the researchers’ findings was published as an advance online publication of the journal Nature on August 18.

"By understanding how these microbes colonize, we may someday be able to devise ways to correct for abnormal changes in bacterial communities—changes that are thought to be connected to disorders like obesity, inflammatory bowel disease and autism," says Mazmanian, a professor of biology at Caltech whose work explores the link between human gut bacteria and health.

The researchers began their study by running a series of experiments to introduce a genus of microbes called Bacteriodes to sterile, or germ-free, mice. Bacteriodes, a group of bacteria that has several dozen species, was chosen because it is one of the most abundant genuses in the human microbiome, can be cultured in the lab (unlike most gut bacteria), and can be genetically modified to introduce specific mutations.

"Bacteriodes are the only genus in the microbiome that fit these three criteria," Mazmanian says.

Lead author S. Melanie Lee (PhD ’13), who was an MD/PhD student in Mazmanian’s lab at the time of the research, first added a few different species of the bacteria to one mouse to see if they would compete with each other to colonize the gut. They appeared to peacefully coexist. Then, Lee colonized a mouse with one particular species, Bacteroides fragilis, and inoculated the mouse with the same exact species, to see if they would co-colonize the same host. To the researchers’ surprise, the newly introduced bacteria could not maintain residence in the mouse’s gut, despite the fact that the animal was already populated by the identical species.

"We know that this environment can house hundreds of species, so why the competition within the same species?" Lee says. "There certainly isn’t a lack of space or nutrients, but this was an extremely robust and consistent finding when we tried to essentially ‘super-colonize’ the mice with one species."

To explain the results, Lee and the team developed what they called the "saturable niche hypothesis." The idea is that by saturating a specific habitat, the organism will effectively exclude others of the same
species from occupying that niche. It will not, however, prevent other closely related species from colonizing the gut, because they have their own particular niches. A genetic screen revealed a set of previously uncharacterized genes—a system that the researchers dubbed commensal colonization factors (CCF)—that were both required and sufficient for species-specific colonization by B. fragilis.

But what exactly is the saturable niche? The colon, after all, is filled with a flowing mass of food, fecal matter and bacteria, which doesn't offer much for organisms to grab onto and occupy. "Melanie hypothesized that this saturable niche was part of the host tissue"—that is, of the gut itself—Mazmanian says. "When she postulated this three to four years ago, it was absolute heresy, because other researchers in the field believed that all bacteria in our intestines lived in the lumen—the center of the gut—and made zero contact with the host...our bodies. The rationale behind this thinking was if bacteria did make contact, it would cause some sort of immune response."

Nonetheless, when the researchers used advanced imaging approaches to survey colonic tissue in mice colonized with B. fragilis, they found a small population of microbes living in miniscule pockets—or crypts—in the colon. Nestled within the crypts, the bacteria are protected from the constant flow of material that passes through the GI tract. To test whether or not the CCF system regulated bacterial colonization within the crypts, the team injected mutant bacteria—without the CCF system—into the colons of sterile mice. Those bacteria were unable to colonize the crypts.

"There is something in that crypt—and we don't know what it is yet—that normal B. fragilis can use to get a foothold via the CCF system," Mazmanian explains. "Finding the crypts is a huge advance in the field because it shows that bacteria do physically contact the host. And during all of the experiments that Melanie did, homeostasis, or a steady state, was maintained. So, contrary to popular belief, there was no evidence of inflammation as a result of the bacteria contacting the host. In fact, we believe these crypts are the permanent home of Bacteroides, and perhaps other classes of microbes."

He says that by pinpointing the CCF system as a mechanism for bacterial colonization and resilience, in addition to the discovery of crypts in the colon that are species specific, the current paper has solved longstanding mysteries in the field about how microbes establish and maintain long-term colonization.

"We've studied only a handful of organisms, and though they are numerically abundant, they are clearly not representative of all the organisms in the gut," Lee says. "A lot of those other bacteria don't have CCF genes, so the question now is: Do those organisms somehow rely on interactions with Bacteroides for their own colonization, or their replication rates, or their localization?"

Suspecting that Bacteroides are keystone species—a necessary factor for building the gut ecosystem—the researchers next plan to investigate whether or not functional abnormalities, such as the inability to adhere to crypts, could affect the entire microbiome and potentially lead to a diseased state in the body.

"This research highlights the notion that we are not alone. We knew that bacteria are in our gut, but this study shows that specific microbes are very intimately associated with our bodies," Mazmanian says. "They are living in very close proximity to our tissues, and we can't ignore microbial contributions to our biology or our health. They are a part of us."

Funding for the research outlined in the Nature paper, titled "Bacterial colonization factors control specificity and stability of the gut microbiota," was provided by the National Institutes of Health and the Crohn’s and Colitis Foundation of America. Additional coauthors were Gregory Donaldson and Silva Boyajian from Caltech and Zbigniew Mikulski and Klaus Ley from the La Jolla Institute for Allergy and Immunology in La Jolla, California.

Journal Reference:

Ingredient in Turmeric Spice When Combined With Anti-Nausea Drug Kills Cancer Cells

Aug. 20, 2013 — In a laboratory, preclinical study recently published by the journal Organic & Biomolecular Chemistry, Virginia Commonwealth University Massey Cancer Center researchers combined structural features from anti-nausea drug thalidomide with common kitchen spice turmeric to create hybrid molecules that effectively kill multiple myeloma cells.

Thalidomide was first introduced in the 1950s as an anti-nausea medication to help control morning sickness, but was later taken off the shelves in 1962 because it was found to cause birth defects. In the late 1990’s the drug was re-introduced as a stand-alone or combination treatment for multiple myeloma.

Turmeric, an ancient spice grown in India and other tropical regions of Asia, has a long history of use in...
Coffee and Tea May Contribute to a Healthy Liver
Aug. 16, 2013 — Surprise! Your morning cup of tea or coffee may be doing more than just perking you up before work.

An international team of researchers led by Duke-NUS Graduate Medical School (Duke-NUS) and the Duke University School of Medicine suggest that increased caffeine intake may reduce fatty liver in people with non-alcoholic fatty liver disease (NAFLD).

Worldwide, 70 percent of people diagnosed with diabetes and obesity have NAFLD, the major cause of fatty liver not due to excessive alcohol consumption. It is estimated that 30 percent of adults in the United States have this condition, and its prevalence is rising in Singapore. There are no effective treatments for NAFLD except diet and exercise.

Using cell culture and mouse models, the study authors—led by Paul Yen, M.D., associate professor and research fellow, and Rohit Sinha, Ph.D of the Duke-NUS Graduate Medical School's Cardiovascular and Metabolic Disorders Program in Singapore—observed that caffeine stimulates the metabolism of lipids stored in liver cells and decreased the fatty liver of mice that were fed a high-fat diet. These findings suggest that consuming the equivalent caffeine intake of four cups of coffee or tea a day may be beneficial in preventing and protecting against the progression of NAFLD in humans.

The findings will be published in the September issue of the journal Hepatology.

"This is the first detailed study of the mechanism for caffeine action on lipids in liver and the results are very interesting," Yen said. "Coffee and tea are so commonly consumed and the notion that they may be therapeutic, especially since they have a reputation for being "bad" for health, is especially enlightening."

The team said this research could lead to the development of caffeine-like drugs that do not have the usual side effects related to caffeine, but retain its therapeutic effects on the liver. It could serve as a starting point for studies on the full benefits of caffeine and related therapeutics in humans.

In addition to Yen and Sinha, collaborators included Christopher Newgard, PhD, director of the Sarah W. Stedman Nutrition and Metabolism Center at Duke University School of Medicine, where the metabolomics analysis of the data was conducted.

Journal Reference:
Rohit Anthony Sinha, Benjamin L. Farah, Brijesh K. Singh, Monowarul Mobin Siddique, Ying Li, Yajun Wu, Olga R. Ilkayeva, Jessica Gooding, Jianhong Ching, Jin Zhou, Laura Martinez, Sherwin Xie, Boon-Huat Bay, Scott A. Summers, Christopher B. Newgard, Paul...
Panel Eviscerates UK Forensic Science
Turmoil in UK forensic services could threaten the integrity of the country’s criminal justice system, according to a government report.

By Chris Palmer | July 25, 2013

A new report on the state of UK forensic science since the March 2012 closure of the government-run Forensic Science Service (FSS) portrays a system in shambles. According to the report, released Thursday (July 25) by the House of Commons Science and Technology Committee, the lack of a coherent, nationwide forensics strategy may be responsible for major crimes going unsolved and an increasing risk of innocent people being convicted.

The committee’s report cites several failures since the initial decision in December 2010 to shutter the FSS due to its poor economic performance, including improperly archived investigative materials, as well as police laboratories and private firms that are not meeting quality standards in forensic evidence analysis. The report also states that a lack of research funding jeopardizes the future of UK forensic science.

The chairman of the committee’s inquiry, Labour party member Andrew Miller, said in the report, “Forensic science provides vital evidence to the criminal justice system, and if the government wants to continue being able to put the most serious criminals behind bars, it has a duty to protect its health.”

The committee’s most severe criticism focused on the performance of the minister for crime prevention, Jeremy Browne, who gave evidence in the inquiry. The report states that Browne was “not prepared for the evidence session” and demonstrated “little understanding of the subject.”

The committee made a series of recommendations, including relocating the supervision of the forensics system to the office of the minister for policing and criminal justice, encouraging the nation’s research councils to make funding forensic science a priority, and endowing the country’s forensic science regulator position with statutory powers.

Opinion: Statistical Misconceptions
Researchers must be wary of the common mistakes of correlation analysis when drawing conclusions about the nature of their data.

By Vladica M. Veličković | July 31, 2013

Statistics are the basis of scientific data analysis, and with the flood of data coming from new genomics technologies, biostatistics has truly become an inseparable part of modern science. Nevertheless, a fundamental statistical technique—correlation analysis, which measures the relationship between two variables—is often employed incorrectly, leading to erroneous conclusions about the true nature of the relationship between the studied phenomena.

The primary task of correlation analysis is to test for a relationship, or agreement, between two variables of interest—say smoking and higher incidence of lung cancer. Furthermore, provided that the survey was carried out on a sufficiently large sample, a rough assessment of the degree of correlation between the observed phenomena, quantified as the linear correlation coefficient, can be performed.

This coefficient must then be interpreted and critically analyzed, as correlation analysis does not aim at explaining the nature of the quantitative agreement—in other words, the causal relationship between the two variables. In addition to assuming causality, researchers commonly fall victim to two other misconceptions: inferring the nature of the individual based on the group findings, and thinking that a correlation of zero implies independence. Each of these errors in analysis can lead to inadequate conclusions.

Misconception #1: Correlation implies causality
Every scientist knows that “correlation does not imply causation.” Indeed, both variables may incidentally show the same tendency of quantitative variability without any logical and natural relationship between them at all. Alternatively, two variables may trend together since they are under the impact of the same confounding factors that are causing the changes in both. Nevertheless, the inappropriate assumption of causality is the biggest source of error in interpreting the results of correlation analysis.

In 2008, for example, the Journal of Pediatrics published a study in which the authors concluded that eating breakfast can solve the problem of teenage obesity, based simply on the fact that teenagers who do eat breakfast are less likely to be obese. Although the correlation found by the authors indicates a possible causality, it is unlikely that eating breakfast can solve the potential problem of teenage obesity. More
likely, there is a common cause behind these two phenomena (eating breakfast and teenage obesity)—poverty, for example—but no direct relationship between them. Similar examples of authors misinterpreting the correlation coefficient are common in the epidemiological literature. One group of researchers, for example, found a correlation between women taking combined hormone replacement therapy (HRT) and a lower-than-average incidence of coronary heart disease (CHD) and concluded that HRT lowered the risk of CHD. However, randomized controlled trials have found the contrary: HRT caused the increase in risk of CHD. It was later determined that lower-than-average incidence of CHD is caused by the benefits associated with a higher average socioeconomic status of those taking HRT, not by therapy itself.

Studies including this type of error are published even in leading biomedical journals. For example, a 1999 Nature study found a strong association between myopia, or near-sightedness, and night-time ambient light exposure during sleep in children. The authors concluded that it seems prudent that infants and young children sleep at night without artificial lighting in the bedroom. A later study refuted these findings and reported that, in this case, the cause of myopia was genetic, not environmental, as many of the study participants’ parents also suffered from the condition.

Of course, the fact that “correlation does not imply causation” should not lead towards diametrically opposite conclusions that correlation could not point to a possible existence of causality. Correlations, especially the high value of the linear correlation coefficient, may point to the existence of causality, but the conclusion requires systematic examination.

Misconception #2: Individuals follow the group
It is not always possible to make inferences about the nature of individuals from information about the group to which those individuals belong. Many researchers do make such assumptions, however, thereby falling victim to the ecological inference fallacy.

One example of ecological inference fallacy is a 2012 paper in a New England Journal of Medicine: the study author found that there was a close and significant linear correlation between chocolate consumption per capita and the number of Nobel laureates per 10 million persons in a total of 23 countries. On the basis of this finding, he concluded that chocolate consumption enhances cognitive function and closely correlates with the number of Nobel laureates in each country. But without accurate data at the individual level, it is impossible to draw such a conclusion. For example, it was unknown how much and whether Nobel laureates consumed chocolate.

Misconception #3: A correlation of zero implies independence
Based on the previous two examples, it is clear that high values of the linear correlation coefficient cannot by themselves be sufficient to conclude about the relationship between the variables. Conversely, a correlation coefficient of zero does not mean that the variables are independent. That is because the correlation coefficient measures linear association only. A U-shaped, non-monotonic relationship, for example, may have a correlation of zero, such as the dose-response relationship in steroid hormone receptor-mediated gene expression.

Conclusion
Proper, clear, and correct use of biostatistical methods requires not only adequate knowledge in biostatistics but also continuing education in this field. In that regard, biostatisticians trained in these methods should be involved in the research from the very beginning, not after the measurement, observation, or experiments are completed.

Vladica M. Veličković is an assistant in the department of public health at the University of Niš in the Republic of Serbia.

Turmoil for AIDS Conference Organizers
Conflict between former conference organizers has shuttered a website that has come to serve as a resource for the HIV/AIDS community.

By Kate Yandell | July 30, 2013

The website for the annual Conference on Retroviruses and Opportunistic Infections (CROI), a major US HIV/AIDS meeting, is currently offline following a conflict between the two groups that formerly organized the event, ScienceInsider reported.

CROI, which has taken place annually for the past 20 years, has been the site of many important announcements in the history of HIV/AIDS research. The conference website was host to years’ worth of conference abstracts and other resources for AIDS researchers and the public.

The nonprofit CROI Foundation and the for-profit CROI LLC have previously been responsible for organizing the conference each year. But the two groups appear to have had a falling out. “I’m not allowed
by our confidentially agreement to divulge anything,” Constance Benson, CROI Foundation board president and a professor at the University of California, San Diego, told ScienceInsider. “We reached an impasse this past couple of years over several issues and decided we needed to go in a different direction.”

Melissa Sordyl, head of CROI LLC, told ScienceInsider, “CROI LLC is no longer the conference secretariat and that is why the site is no longer active.”

Benson told The Scientist in an email that anyone seeking information on the 2014 conference, which will take place in Boston in March, should go to a new website: www.CROI2014.org. “We have no further update on the old website at this time,” Benson said. She added that Sordyl owned and maintained the old website and that it does not belong to the CROI Foundation.

The CROI Foundation is partnering with the International Antiviral Society-USA to put on the 2014 conference, according to the new website.

Simon Collins, head of HIV i-Base, a website for HIV treatment activism and information, wrote on his site that the loss of the CROI website was a frustrating one: “CROI is established as the most important HIV scientific meeting,” he wrote, adding that “the website is a vital resource not only as a record of previous meetings but as a free open-access research tool.”

Benson told The Scientist that the conference organizers are “working on a solution for the old content from past meetings.”

When function isn’t always ‘function’ for non-coding RNAs

One of the more striking biological discoveries of the past decade has been the extent of transcription from regions of the genome that do not code for proteins. The resulting non-coding (nc)RNA has been the subject of lively debate. Much of this debate has focused on what proportion of this ncRNA is likely to be functional. Two opposing PloS Biology papers from 2011 offer a good starting point, arguing either that ncRNAs probably represent functional transcripts, or that while substantial ncRNA transcription exists, it is often not biologically meaningful, representing either technical artefact or undirected transcriptional ‘noise’. The debate reared its head again last year with the publication of ENCODE, whose inclusion of any biochemical activity in its definition of ‘functional’ was subject to complaint.

The difficulty of arriving at a meaningful definition of function for ncRNAs is highlighted by a review published in BMC Biology from Florian Pauler, Denise Barlow and colleagues at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. While we usually think of transcription as simply a necessary step in the production of RNA, which goes on to either be translated into protein or to perform its own catalytic function, the authors summarise instances where the process of RNA transcription itself regulates nearby genes. This kind of transcription-mediated silencing, termed “transcriptional interference”, has been noted before, but usually involves two protein-coding genes that are themselves functional. Pauler and colleagues highlight cases where the transcribed ncRNA may well be disposable, and the transcription process is the key functional element.

The number of ways transcription can mediate gene regulation is surprisingly high. Gene promoters are the targets of transcriptional interference in many of the cases discussed, albeit through a number of different mechanisms. DNA methylation, nucleosome repositioning and histone modification can all be effected as part of the transcription process and negatively impact promoter activity. Alternatively, transcription through enhancer (and perhaps other) elements can have a positive effect on gene expression, producing a permissive open chromatin environment. It isn’t all chromatin modification, though: Barlow lab favourite Airn gets a look in, and here transcription of Airn through the Igf2r promoter has a silencing effect that is not dependent on chromatin changes – the mechanism is unknown, but may involve physical obstruction of the promoter by RNA polymerase.

Returning to the question of function, it’s with this in mind the authors finish by laying out a number of ways to distinguish function of an ncRNA from function of its transcription – particularly useful as it isn’t yet clear how widely-applicable these kinds of regulatory mechanisms are. With significant and increasing interest in uncovering the ncRNA universe, we can almost certainly look forward to more examples in the future.
Double trouble: Mark Jobling on twin studies and the genetics of uniqueness

Posted by Biome on 15th July 2013—0 Comments

This article was written by Mark Jobling, professor of genetics at the University of Leicester, and originally published in Investigative Genetics.

‘How unique are you?’ – an infuriating question for anyone with a pedant’s ear for linguistic correctness, but one that’s posed many a time in the fervid world of public engagement in genetics. And the expected answer is ‘very’ – pedants notwithstanding. The conventional way to demonstrate this is to ask a series of questions about traits with a supposedly simple genetic basis: tongue-rolling, hitch-hiker’s thumb, direction of hair whorl, cleft chin, attached earlobes... Often a tiny square of innocent-looking paper is proffered, with instructions to place it on the tongue (rolling or otherwise); to some people it’s tasteless, while to others it’s bitter due to its content of phenylthiocarbamide, meriting a sugary antidote in the form of a Polo mint. Sometimes there’s a vase of freesias whose scent fills the air – at least, for those of us whose genes allow us to detect it. Less savoury aspects involve interrogations about the colour or the smell of a subject’s urine following the eating of beetroot or asparagus.

Testing many such traits in a large group demonstrates that few people share the same combination, and emphasises how genetically different we all are. The problem is that, as John H. McDonald’s splendid Myths of Human Genetics website illustrates, many of these traits are continuous rather than discrete, and most do not have a simple genetic basis at all. Tongue-rolling, for example, certainly has some genetic component, with children of tongue-rolling parents more likely to be rollers themselves, but is not a simple dominant phenotype, as is often assumed. Hitch-hiker’s thumb, cleft chin, and attached earlobes are assumed in the ‘human uniqueness’ tests to be binary characteristics, but in fact all show continuous variation.

Apart from family studies, another way to investigate the genetic components of traits is to compare concordance in twins. It was Francis Galton who realized their possible value ‘to weigh in just scales the effects of Nature and Nurture’ (Galton F, Inquiries into Human Faculty and Its Development, 1883, London: J.M. Dent & Company). He sent questionnaires to twins and their relatives, and having built a respectable database was interested to find that ‘similarity and extreme dissimilarity between twins of the same sex are nearly as common as moderate resemblance’. We now refer to the twins who are so alike that ‘the one is sometimes fed, physicked, and whipped by mistake for the other’ as monozygotic (MZ – ‘identical’), since they arise from the division of the same zygote, rather than dizygotic (DZ – ‘fraternal’). MZ twins are certainly very similar, but not identical – traits such as hair whorl, tongue rolling, and the effect of a bowl of borscht on the urine all reveal cases where one twin differs from the other (McDonald JH, Myths of Human Genetics, 2013).

A very simple question, as posed by the Swedish twin registry in 1961 (J Intern Med. 2002, 252, 184–205) sorts out the MZ/DZ issue in 95% of cases: “During childhood, were you and your twin as alike as two peas in a pod, or not more alike than siblings in general?” (to be precise, the Swedes actually asked whether twins were ‘similar as two berries’). With the arrival of DNA fingerprinting, and its descendant technology STR profiling, it became a matter of science to distinguish between twin types. Indeed, in the 1990s Alec Jeffreys analysed the DNA of 11-year-old twin sisters for a popular BBC television programme, ‘Jim’ll Fix It’ (fronted by the now deceased and disgraced Jimmy Saville). The DNA fingerprints, set up behind a curtain, were revealed to be identical, confirming what anyone could tell by the simple double-take of looking at the girls.

The indistinguishable DNA profiles of MZ twins can pose a problem in forensic analysis. One in 300 people has such a twin, and if they leave a DNA sample at a crime scene and other evidence fails to exclude their sibling, then how do we know which is responsible? Naturally enough, witness statements can be very unreliable. In one of Galton’s case studies (again featuring corporal punishment): ‘Two twins were fond of playing tricks, and complaints were frequently made; but the boys would never own which was the guilty one, and the complainants were never certain which of the two he was. One headmaster used to say he would never flog the innocent for the guilty, and another used to flog both.’

There have been a number of real cases in which this difficulty has arisen. One comes from November 1999, when a young woman was raped in the town of Grand Rapids, Michigan; the crime was unsolved until 2004, when Jerome Cooper, in jail at the time for a sex offence, applied for parole, requiring him to provide a DNA sample. His profile was checked against a list of unsolved crimes, and matched DNA recovered from the 1999 rape. Case solved? – not quite, because of the existence of Jerome’s MZ twin brother, Tyrone, who was also in the area at the time of the rape. The practice of the first headmaster had
to be followed – it was impossible to jail both brothers for the crime, so they remained free. Similar cases involved putative jewellery thief Hassan or Abbas O. in Germany, and putative rapist Darrin or Damien Fernandez in Boston.

A more recent French case has been widely reported: police investigating a series of sexual assaults in Marseille arrested a 24-year-old unemployed delivery driver, but the arrestee had a twin brother (with the same non-profession), and a victim could not tell them apart. The DNA left at the crime scenes was of no use, at least as far as a conventional DNA profile was concerned. BBC reports suggested that an ‘ultra-sophisticated genetic test’, might help, and gave the price-tag of this mysterious product as 1 million euros ($1.3 M).

This seems a lot of money – what test can they possibly mean? Differences in copy-number of DNA sequences (Am J Hum Genet. 2008, 82, 763–771), or in epigenetic modifications such as DNA methylation (Mol Biol Rep. 2013, May 7) between MZ twins in matched tissues have been reported, and might in principle help, but neither would be easy to get past a skeptical defence lawyer. As next-generation DNA sequencing continues to fall in cost and rise in power, it’s there we need to look. The tissue of interest in the French case, it’s safe to assume, is sperm. Could we find simple sequence differences between the genomes of the sperm populations of each twin, which had arisen during the development of either of them from the original zygote from which they both derived?

The zygote splits after fertilisation to give two identical single-celled proto-twins, which then undergo on average about seven cell divisions in the first week of development to give embryos each consisting of about 100 cells. In the subsequent week the primordial germ cells, which give rise to the stem cell population of spermatogenesis in each male, become detectable. So let’s take 2 x 7 as a conservative minimum number of cell divisions that clearly separate the primordial stem cell populations of each twin. Any heterozygous somatic mutations that arose during these 14 cell divisions are expected to be present in half the sperm of one twin, but absent from the other. If we carry out high-coverage whole genome sequencing from a donated sperm sample of each twin, with a mutation rate of 0.05 x 10–9 per nucleotide per cell division (Mutat Res. 2012, 729, 1–15), and a diploid genome size of 6 x 109bp, this back-of-an-envelope calculation suggests that we expect to find ~4 such differences between the sperm samples (there will obviously be other, later-occurring variants that exist at lower frequencies). Having identified the variants, they could be confirmed by conventional DNA sequencing, and then typed in the crime-scene samples. Four nucleotide differences seems alarmingly few, but at only ~ $6000 per high-coverage genome sequence it seems worth a try.

All the same, it’s a pity that a simpler and better-established forensic tool was not available in this case, which can answer the ‘how unique are you?’ question in a pedant-satisfying way. The inquisitive Galton (Galton F, Finger prints. London and New York: Macmillan and Co., 1892) noted that the friction ridges on our fingertips (actual, rather than DNA fingerprints), while more similar between twins than non-twins, are nonetheless different enough to allow them to be distinguished every time.

**Cancer-Associated Viruses Overblown?**

**An MD Anderson study calls into question estimates on the percentage of viruses linked to cancer.**

By Tracy Vence | August 7, 2013

Numerous studies have come out in recent years linking certain viruses to cancer, highlighting the immune system’s role in staving off—and at times, succumbing to—potential malignancies. But according to a paper appearing this month in the *Journal of Virology*, researchers may have overestimated the percentage of viruses associated with cancer.

Using samples from The Cancer Genome Atlas, Xiaoping Su and his colleagues at the University of Texas MD Anderson Cancer Center sequenced RNA from 3,775 malignant tumors and used a bioinformatics approach to locate viral transcripts. The researchers also mined the data for viral integration sites within the host genome.

All told, their findings suggest fewer cancers may be associated with DNA viruses than previously estimated. While they did find traces of human papillomavirus in head-and-neck squamous cell carcinoma, uterine endometrioid carcinoma, and squamous cell carcinoma of the lung, and evidence of hepatitis B virus and Epstein-Barr virus in hepatocellular carcinoma and gastric carcinoma tumors, respectively, the researchers found that most of the common cancers they studied did not contain traces of DNA viruses at all.
“The search for virus associations in these malignancies has consumed the efforts of many investigators,” Su said in a statement. Now, he suggested, scientists might consider focusing their efforts elsewhere.

At any rate, he noted that bioinformatics is an important tool for identifying potential convolutions between viruses and cancers. “This study highlights the importance of bioinformatics in defining the landscape of virus integration across cancer subtypes,” said Su.

Q&A: NIH Brokers HeLa Genome Deal

Officials at the government agency hammer out an agreement with the Lacks family to provide restricted access to genomes of their relative’s unwittingly donated cells.

By Bob Grant | August 7, 2013

Through negotiations with the surviving family members of Henrietta Lacks, the National Institutes of Health (NIH) has outlined a framework for sharing the genome sequence of HeLa cells, the progenitors of which were provided without consent more than 60 years ago. The cervical cancer cells were harvested from Lacks at Johns Hopkins University hospital, and became the first cells researchers were able to culture indefinitely. Those original samples would go on to give birth to cell lines that are still replicating in thousands of labs around the world and to shed light on the molecular and genetic mechanics of cancer and myriad other biological phenomena.

The unprecedented agreement—announced yesterday (August 7) in Nature via a commentary written by NIH Director Francis Collins and Kathy Hudson, the agency’s deputy director for science, outreach, and policy—spells out terms that make two sequenced genomes of HeLa cells available only to scientists who apply for access and promise to use the genome data solely for biomedical research purposes. The deal follows the publication and subsequent retraction of one HeLa genome sequence this past March, which ignited debate over the privacy rights of the family. The agreement covers that genome sequence, completed by researchers at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, as well as a second HeLa genome sequenced by NIH-funded researchers at the University of Washington in Seattle.

Researchers who use the genome data in their work are also asked to formally recognize and acknowledge the contribution of Henrietta and her family to science. A board that will include members of the Lacks family will review applications to access the data and will evaluate papers that used the data to ensure that proper acknowledgment was given.

Science journalist Rebecca Skloot was instrumental in bringing Collins, Hudson, and other researchers and bioethicists to the table to hammer out the deal, a process that occurred over three meetings and several months. Though Skloot—who brought the bioethical issues concerning the nonconsensual harvesting and culturing of Henrietta Lacks’s cervical cancer cells to the forefront with her 2010 book The Immortal Life of Henrietta Lacks—is adamant that she did not play an active role in the negotiations that led to the agreement, she was present (via phone) for all of the meetings between NIH officials, scientists, genetic counselors, and the Lacks family, playing what she calls an “observer’s role” in the discussions. She also wrote an OpEd piece in The New York Times after the publication of the EMBL genome that likely played a role in the retraction of the paper.

The Scientist spoke with Skloot—who stressed the fact that the opinions of the Lacks family, and not her own, were the most important determinant of the agreement’s success—to get her perspective on the historic deal announced today.

The Scientist: What role did you play in the negotiations that resulted in this deal between NIH and the Lackses?

Rebecca Skloot: When the first genome was published—the German version that I wrote the OpEd about—I talked to Francis Collins and Kathy Hudson at the NIH as sources when I was writing about the genome. So when I first started talking to them it was to interview them about the fact that this genome had been published without consent. And then we just sort of started talking about what happens next. So I said, “OK, how about we get everybody in a room?”

We get Francis Collins, Kathy Hudson, and then I brought in other people who I knew the Lacks family already knew a bit and trusted. . . . At that point, I said, “This is not my job. You guys go and have the discussions you need, and this is sort of private with family.” I sort of felt like I wasn’t going to be involved. And then the family said, “Oh no you’re not!” So they really wanted me to be there, and I was fine with that.
[Still], I saw my role, if anything, as more translator than moderator or negotiator. So I was basically there, mostly quiet the entire time, just listening, and then occasionally, if the Lacks family had a question, we would talk afterwards.

**TS:** How did the Lacks family approach the discussions?
**RS:** They’re incredibly proud of the HeLa cells and what they’ve done for science. So they were like, “We want that to keep going. We don’t want HeLa cells to stop doing good things. We just want to have a voice in it.”

**TS:** Did anyone voice concerns about the agreement imposing limitations that might impede the progress of science around HeLa cell genomes?
**RS:** Absolutely. It was laid out as one of the important things to consider and to talk about. We talked about each option. And one of those options was: don’t release it. There was a lot of discussion about what would mean for science and why releasing it is good for science and how having it out there widely can lead to good science happening. The basic gist of it is that you have to be a card-carrying scientist. The family wanted the restrictions to not be too limiting on science. But they simply weren’t comfortable at this point just saying, “Sure, throw it up online so anyone can download it, scientist or not.”

**TS:** Did the economic argument ever come up? Did the Lackses ever ask, “How can we be compensated for this?”
**RS:** The topic definitely came up. It’s an important part of their story, historically. So one of the questions was, “What could this mean commercially? Are people going to be patenting this stuff?” Everything that could have been part of this conversation was: consent, privacy, commercialization. They really covered all potential aspects of the topic. . . . And then the Supreme Court ruling on the breast cancer genes happened in the middle of all this. So that changed that conversation quite a bit, because then the answer was, “No. No one can patent any gene that they find and no one can patent the genome.”

I was with the Lacks family as they did an interview the other day, and what they said basically was, “Money is not our big concern in this right now.” Right now they’re thinking about science. They’re thinking about making it so that science can go forward while protecting their family’s privacy.

**TS:** Was privacy their major concern?
**RS:** I don’t know if I could say that there was one [concern] that outweighed them all. . . . But yes, the privacy conversations were extensive, and they had a separate meeting with genetic counselors to understand what of their own information might be in there, what of their parents’ and grandparent’s might be in there.

**TS:** Do you think that this agreement, or at least the way it was brokered, might serve as a blueprint for future issues concerning bioethics?
**RS:** This is a very unique situation. . . . I don’t imagine that with every genome that somebody wants to do research on and publish will there be an entire family sitting around the table for multiple meetings talking about how to handle that. If you apply that to every bit of research, that’s unrealistic. . . . But could this help inform the questions that scientists need to ask before they sequence someone’s genome and publish it? Probably. I imagine it will.

What’s important is that this is a very big statement from the NIH and from the scientific community saying, “It matters to know what the subjects want and to tell them what’s going on.” In that way, yes, this is setting an important precedent. . . . I do think it’s sort of a symbol of where things are headed in the future with science and the public being more comfortable and involved with each other.

**TS:** Do you see this as the pinnacle of the dialogue you started concerning Henrietta Lacks’s case?
**RS:** My hope is that the next pinnacle will involve the Lacks family and scientists and not me. The only reason I was involved in this is because scientists did this without the family’s consent and then it got all of this press coverage, and no one asked the question, “Did the family give consent?” So I sort of waded back in.

That OpEd that I wrote was the first time I’d ever publically expressed an opinion, which was, “Really?? Are we going to continue to not ask the Lacks family questions?” I was kind of shocked in a sense that nobody thought to raise that issue.

[But now] I’m very happy that [the negotiations] happened, and in a sense relieved. Because hopefully this will be the beginning of conversations happening between scientists and non-scientists across the board in a way that might be different.
Cancer-Causing Herbal Remedies
A potent carcinogen lurks within certain traditional Chinese medicines.
By Ruth Williams | August 7, 2013

Plants of the Aristolochia genus have for centuries been used in Chinese herbal remedies, but they contain a naturally carcinogenic compound that causes mutations in the cells of people who consume them, according to two studies published in Science Translational Medicine today (August 7). The papers reveal that the compound, called aristolochic acid, causes more mutations than two of the best-known environmental carcinogens: tobacco smoke and UV light.

“A lot of people in the lay public assume that if something is herbal or natural that it is necessarily healthy,” said Marc Ladanyi, an investigator in the human oncology and pathogenesis program at Memorial Sloan–Kettering Cancer Center in New York who was not involved in the studies. “But this work very clearly shows that this natural plant product is extremely genotoxic and carcinogenic.”

Despite the long history of Aristolochia use in herbal remedies, evidence of the plants’ inherent danger emerged only recently. In the early 1990s, women who had received Aristolochia treatments at a weight loss clinic in Belgium developed kidney problems that progressed to renal failure and, in later years, to abnormal growths in their upper urinary tracts. More recently, Aristolochia contamination of local wheat crops was determined to be the cause of a high incidence of urothelial carcinomas of the upper urinary tract (UTUC) among rural communities on the banks of the Danube river in Europe. And in Taiwan, where recent prescription records reveal that approximately one-third of the population has taken Aristolochia-containing medicines, the incidence of UTUCs is the highest in the world.

Aristolochic acid has been banned in most countries since 2003. But, said Thomas Rosenquist of Stony Brook University in New York, “there are a lot of countries in Asia, like India, that still use it as part of their traditional herbal medicines. And even though it is banned in places like China, it is still readily available.”

The continued use of the plants might be because “[practitioners] may be slow to accept that they are actually hurting people that they are trying to help,” said Rosenquist. “And there may be a 20- to 30-year lag time between exposure to the carcinogen and [developing cancer], so making the connection might be difficult.”

In addition, many people may simply not know about the risk, said Steve Rozen of the Duke-National University of Singapore Graduate Medical School. “I’m eager to make sure this paper gets public press, because I think it’s important that people really understand the dangers.”

Rosenquist, Rozen, and their teams conducted two separate studies to analyze the genome-wide mutations in patients with UTUCs who had known exposure to aristolochic acid. The two reports found that an unusual mutation, called an A-to-T transversion, previously identified in aristolochic acid-exposed tissues, was abundant throughout the genomes of the cancerous cells. And the number of mutations in general was unusually high—far greater than that seen in lung cancers caused by smoking or in melanomas caused by UV exposure.

“The number of mutations identified per megabase of DNA was pretty astounding,” said Elaine Mardis, director of technology development at The Genome Institute at Washington University in St. Louis, who was not involved in the work. “Heretofore we thought that melanoma was the world class leader in terms of mutation number, or rate, but this now looks like it’s above and beyond that.”

The genome-wide analyses also revealed a preference for mutations to occur at particular sequence motifs—CAG or TAG—and to occur on the non-transcribed strand of coding DNA, indicating some mutations were erased as a result of transcription-coupled repair. These patterns, together with the extremely high mutation frequency and the abundance of A-to-T transversions, equated to a genomic signature of aristolochic acid exposure.

Identifying the signature in a patient’s DNA probably wouldn’t change the way they are treated, said Rosenquist. But screening for the signature in individuals thought to have been exposed to aristolochic acid may enable early detection of UTUCs. “We are trying to develop a screen to detect DNA carrying these mutations in plasma and urine . . . and see whether it has the sensitivity to detect those cancers before other routine methods [would],” he said.

In addition to the known risk of developing UTUC, Rozen’s team discovered that certain liver cancer genomes exhibited the telltale signature of aristolochic acid exposure. Thus, more organs might be at risk from exposure to the carcinogen than originally thought.

The sequencing of other cancer genomes will reveal whether this is indeed the case. For now though, perhaps the most important message of the two studies is that consuming these plants can certainly be
dangerous. “As is often the case in cancer research, the biggest successes can be in prevention,” Rozen said.


Tumor-Targeting T Cells Engineered
Scientists genetically modify T cells derived from pluripotent stem cells to attack lymphatic tumors.

By Chris Palmer | August 11, 2013

Scientists have combined the ability to reprogram stem cells into T cells with a recently developed strategy for genetically modifying patients’ own T cells to seek and destroy tumors. The result is the capacity to mass-produce in the laboratory an unlimited quantity of cancer-fighting cells that resemble natural T cells, a type of white blood cell that fights cancer and viruses. In a study published today (August 11) in Nature Biotechnology, researchers show that the genetically engineered cells can effectively wipe out tumors in a mouse model of lymphoma.

“To put these two techniques together is really groundbreaking,” said Pam Ohashi, a cell biologist at the Ontario Cancer Institute, who was not involved in the study. “The idea that you can make unlimited numbers of tumor-killing cells is very exciting.”

Earlier this year, a team led by cancer specialist Michel Sadelain at the Memorial Sloan-Kettering Cancer Center reported Phase 1 clinical trial results showing that treatment with genetically manipulated T cells could quickly eradicate tumors in patients with acute lymphoblastic leukemia, a tenacious cancer that kills more than 60 percent of those afflicted. However, the immunotherapy—one of a number of treatments in which the immune system is trained to attack cancer—requires the extraction, processing, and reintroduction of T cells from each individual patient’s own blood, making the procedure laborious and expensive. Also, because there are many circumstances, such as HIV infection, in which patients have few or none of their own T cells, not all patients can benefit from the treatment.

Now, Sadelain’s team has used cell reprogramming technology to grow in a dish large quantities of precursor T cells that can be can be genetically modified to identify and eliminate tumors, potentially making immunotherapies for certain types of cancer more widely available.

“This is the first proof of principle that it is feasible to use a differentiated-directed process to generate lymphoid T cells endowed with therapeutic properties in vitro,” said Sadelain.

Sadelain’s team isolated T cells from the peripheral blood of a healthy female donor and reprogrammed them into stem cells. The researchers then used disabled retroviruses to transfer to the stem cells the gene that codes for a chimeric antigen receptor (CAR) for the antigen CD19, a protein expressed by a different type of immune cell—B cells—that can turn malignant in some types of cancer, such as leukemia. The receptor for CD19 allows the T cells to track down and kill the rogue B cells. Finally, the researchers induced the CAR-modified stem cells to re-acquire many of their original T cell properties, and then replicated the cells 1,000-fold.

“By combining the CAR technology with the iPS technology, we can make T cells that recognize X, Y, or Z,” said Sadelain. “There’s flexibility here for redirecting their specificity towards anything that you want.”

Yet questions remain about exactly what kind of cell the researchers created. “It’s really an unknown population of cells,” said Ohashi.

Sadelain’s team used gene expression microarrays to compare the mRNA expression profiles of the engineered T cell precursors with several types of natural T cells from the female donor. The analysis revealed that the engineered cells more closely resemble the gd T cell subtype that is involved in an initial broad-spectrum immune response, rather than the αβ subtype, the so-called adaptive subtype, which is slower to respond, but retains a memory of its exposure to various antigens.

Next, the researchers showed that the genetically engineered T cells lysed tumors in an in vitro mouse lymphoma cell line. In addition, precursor T cells injected into tumor-bearing mice were shown to produce a strong anti-tumor response, similar in strength to that of the donor’s natural gd T cells that had been modified to express the CD19 receptor. “They function just as well as T cells we harvested from peripheral blood,” said Sadelain.
“What they’ve shown is that you can engineer these cells into some kind of T cell,” said Michael Kalos, a cancer researcher at the University of Pennsylvania, who was not involved in the study. “You can grow these cells in an antigen-driven manner to large numbers and . . . they have effector functions.”

Sadelain’s group is not the first to derive T cells from stem cells. Last year, two groups in Japan grew T cells from iPSCs, but unlike the current study, the Japanese studies failed to fully compare the derived T cells with natural T cells, nor did they create enough T cells to test in vitro.

Sadelain said that before any treatment based on the new cells is ready for clinical trials, much work is needed to assess the cells’ safety and to understand more about their biological nature.


Eat Less and Live Longer?
Mice on a low-calorie diet harbor a distinct population of gut microorganisms that helps prolong life.

By Debamita Chatterjee | August 13, 2013
Scientists have shown a link between long-living calorie-restricted mice and the types of microbes residing in the guts of those mice. The finding, published last month (July 16) in Nature Communications, suggests a novel mechanism of living longer by establishing the right kind of microbes in our gut through a low-calorie diet.

“The study underlined the effectiveness of the healthy modulation of the gut microbiota along with diet specificities,” Jean-Paul Vernoux, a professor of food toxicology at the University of Caen in France who was not involved with the study, said in an email to The Scientist.

Caloric restriction has been known to extend life span in a variety of organisms, including humans, though the molecular mechanisms of this effect are not known. Recent research has begun to outline the role of the apparently innocuous microbes of the gut in modulating metabolism and immunity of their host. Based on these findings, Liping Zhao of Shanghai Jiao Tong University and his colleagues wondered if caloric restriction may prolong life span by modulating the type and composition of gut microbes.

The team fed groups of mice a high- or low-fat reduced-calorie diet. As expected, mice on a low-fat, calorie-restricted diet lived the longest. Additionally, these mice displayed lowest body weight and fat content coupled with other healthy metabolic parameters such as glucose homoeostasis and a favorable serum lipid profile.

Using high-throughput sequencing, the researchers further showed that these calorie-restricted mice harbored a distinct population of beneficial bacteria such as Lactobacillus, as well as lower counts of harmful bacteria. Moreover, the microbial changes in the gut were concomitant with significantly reduced levels of serum lipopolysaccharide-binding protein (LBP), a soluble inflammatory protein that binds to lipopolysaccharide and other antigens and thus can be used as a blood-based biomarker of inflammatory response. This suggests that animals under calorie restriction can establish an optimal composition of gut microbiota, which in turn may lead to a better health by reducing overall inflammation.

Although more research is needed to translate these findings into humans, the study has far-reaching implications, Zhao noted. The idea of a balanced gut microbiota—with more beneficial microbes and fewer harmful ones—is an advantageous factor of a diet low in calories. However, the gut microbiome is also influenced by an individual’s genetic background and lifestyle, as well as environmental factors, he added, so a tailor-made personalized strategy would be the best approach to figure out how many calories to cut to attain an optimal bacterial community in the gut.

The researchers also suggest that such changes in the gut microbiota could be used as early warning signs of aging and age-related increase in inflammatory responses in the host. “We can analyze the composition of gut bacteria as a biomarker,” Zhao said. “We can also analyze serum LBP and see if that is increased or decreased.”

“There was a significant decrease of the negative to positive bacterial ratio correlated with life span in animals under caloric restriction,” said Vernoux. “It also justified the good positive role of probiotic Lactobacilli. The extrapolation to human is plausible, but it needs a lot of more work.”

Zhao’s team now plans to investigate the molecular mechanisms of how reducing caloric intake leads to changes in the gut microbiota, and would eventually like to run clinical trials to confirm these results.

Mouth Microbe Turns Carcinogenic
Two studies peg down how a bacterium indigenous to the oral cavity can contribute to the development of colorectal cancer.

By Tracy Vence | August 14, 2013

_Fusobacterium nucleatum_ is a Gram-negative oral commensal microbe, but it has the potential to become pathogenic, occasionally causing periodontal disease. In October 2011, two separate teams from Canada’s BC Cancer Agency and the Broad Institute in Cambridge showed that the bacterium could also be found in the gut, where its abundance was associated with colorectal cancer. Now, two new studies present functional evidence to help explain how _F. nucleatum_ spurs the development of cancer.

In papers published in *Cell Host & Microbe* today (August 13), teams led by Harvard Medical School’s Aleksandar Kostic and Case Western Reserve University’s Mara Roxana Rubinstein used a mouse model of intestinal tumorigenesis and human colon cancer cells, respectively, to show that _F. nucleatum_ induces proinflammatory and oncogenic activities that promote the growth of colorectal cancer.

“It is usually impossible to infer whether microbes are causative or opportunistic colonizers without functional studies,” said Robert Holt, who led the BC Cancer Agency team that in 2011 reported an association between _F. nucleatum_ in the gut and colorectal cancer but was not involved in the present studies. “Identifying an infectious origin for disease almost always starts with observing an association between the presence of a microbe and the presence of a particular pathology, but an understanding of causality—or lack thereof—requires the gradual accumulation of experimental and epidemiological evidence,” such as that reported today.

The Washington University School of Medicine’s Gautam Dantas agreed that the new work helps distinguish cause from consequence. “Is an observed altered microbiome state in a diseased individual the cause of the disease, or a symptom?” Dantas, who was not involved in the studies, wrote in an e-mail to *The Scientist*. The papers published today “report on significant strides towards . . . identifying the mechanisms by which a human commensal bacterium, _Fusobacterium nucleatum_, promotes colorectal cancer.”

Oncologist Wendy Garrett, coauthor on the Harvard study, told *The Scientist* in an e-mail that interactions between fusobacteria and immune cells in the tumor microenvironment are what ultimately lead to cancer. “When we fed fusobacteria to mice with a genetic susceptibility for developing intestinal tumors, we found more tumors and more invasive tumors developed . . . as compared to controls,” Garrett said. “This was interesting because the mutation that the mice had is shared with human cancers and precancerous lesions of the GI tract.”

In the mouse model of intestinal tumorigenesis her team used, she added, fusobacteria seemed to cause several kinds of immune cells to associate with the tumor, though none of the type that help the body shrink such malignancies. “The immune cells we found in tumors of mice fed fusobacteria were immune that are well known to promote tumor growth and spread,” Garrett said.

Meantime, Case Western’s Yiping Han and her colleagues pegged down the interactions between _F. nucleatum_ and tumor microenvironment, identifying a specific cell-surface component of the bacterium that enables it to induce inflammation and oncogenesis. This component, an adhesin called FadA, binds E-cadherin on colorectal cancer cells to activate β-catenin signaling within them, differentially regulating inflammatory and oncogenic responses, the team reported.

The researchers also identified the FadA-E-cadherin binding site and designed a synthetic peptide derived from the same region of E-cadherin. When they administered the peptide to human colorectal cancer cells, they found that it abolished cell growth, as well as oncogenic and inflammatory responses. The synthetic peptide, which presumably blocked the binding of _F. nucleatum_’s FadA to E-cadherin, “shut down all the adverse responses,” Han said.

The researchers said their work points to FadA binding as a potential diagnostic and the E-cadherin binding site a potential therapeutic target for colorectal cancer, though much work remains to be done.

For starters, further research is required to fully ascertain _F. nucleatum_’s role in promoting cancer. “_Fusobacterium nucleatum_ is well known to be highly interactive with other bacteria, and it is probably unlikely that it is acting alone in the context of colon cancer,” said Holt. Moreover, he noted that fusobacteria vary. Some strains are more virulent than others, and could therefore be more carcinogenic.

Han, too, was quick to point out that _F. nucleatum_ itself is unlikely to be silver bullet for colorectal cancer. “We have evolved beyond the stage of ‘one bacteria, one disease.’ I think we will still find those keystone pathogens that play a key role in those diseases, [but] with microbiome studies . . . mechanistic studies are very important,” she said.
“Just about every person has fusobacteria in their mouth and thankfully not everyone develops colon cancer,” Garrett said. “We need to develop a well-nuanced understanding of what and how fusobacteria function to potentiate the development of colon tumors.”


**HIV Protein Boosts Cocaine’s Effect**

Mice whose brains express the HIV-1 Tat protein show a heightened response to the drug and appear more vulnerable to relapse.

By Kerry Grens | August 15, 2013

A protein involved in HIV transcription enhances the rewarding effect of cocaine and causes mice to become even more hyperactive when they’re on the drug, researchers report today (August 15) in *Neuropsychopharmacology*. The findings could help explain why people infected with HIV and who use drugs tend to suffer more neurological and cognitive decline than people who don’t have the disease or don’t abuse substances.

The link between HIV, drug abuse, and cognitive decline has “been observed epidemiologically for some time, but the mechanisms of how that interaction might occur have really been very elusive,” said Rosemarie Booze, a professor at the University of South Carolina, who was not part of the study. “I think this paper sheds important information in terms of identifying how those drugs and HIV might interact and affect brain function.”

The ways in which HIV itself might affect drug use have not been well understood, said Jay McLaughlin, an associate member at Torrey Pines Institute for Molecular Studies in Port Saint Lucie, Florida, and one of the study’s authors. Tat, a neurotoxic protein that facilitates the transcription of HIV genes in infected individuals, has been implicated in HIV-related neurological problems. The protein works not only in the host cell, but is thought to travel between cells to prime them for infection.

To see how the protein might alter the effects of a stimulant, McLaughlin and his colleagues gave cocaine to transgenic mice whose astrocytes expressed Tat when the animals were given doxycycline, as well as mice who lacked the Tat gene altogether. Other control mice had the Tat gene, but did not have its expression induced by doxycycline.

All of the mice became hyperactive after the cocaine, but the researchers found that those with Tat expressed ran around much more than mice without the protein. “We interpret that as demonstrating that Tat protein is increasing the effects of cocaine,” McLaughlin told *The Scientist.*

All mice given cocaine also showed a preference for the chamber where the drug was administered by spending more time there. Mice with Tat protein in their brains, however, spent 3- to 5-times as long in the cocaine chamber compared with the other mice. McLaughlin’s team could then extinguish this preference over time, and the mice both with or without Tat would no longer spend more time in any given chamber. But once Tat was induced again—in the absence of cocaine—the mice reinstated their preference for the chamber where the drug had been given weeks earlier. “The conclusion we’re drawing from that experiment was exposure to Tat protein may increase vulnerability not only to the rewarding effects of drugs of abuse, but could increase vulnerability to relapse,” McLaughlin said.

The mechanisms to explain these heightened responses to cocaine are unclear. Tat “is probably affecting the dopamine neurons in the brain,” Booze told *The Scientist.* “Those are thought to underlie many rewarding actions.” Tat, she added, “probably has a direct affect on the dopamine transporter system . . . whereby cocaine and Tat protein facilitate each other’s actions,” though this has yet to be demonstrated, she noted.

“This is a very elegant study in the field as it elegantly demonstrates how HIV Tat potentiates the addictive effects of cocaine in mice,” said Shilpa Buch, a professor at the University of Nebraska Medical Center, in an email to *The Scientist.* “This study also has clinical ramifications as it sheds light on the ability of HIV Tat to increase the possibility of relapse in abstinent subjects with a history of cocaine abuse.” She added that it will be important to next test how this animal model of Tat exposure behaves during studies in which the drug is self-administered.

Tat is a particularly insidious component of HIV infection and is known to be neurotoxic. In humans, the protein persists even despite undetectable viral loads resulting from anti-retroviral therapy. There’s suspicion that Tat is involved in the neurologic damage that can go along with HIV infection, called neuroAIDS, even after the virus is essentially knocked down.
“It’s a serious problem. We can knock the viral content down to immeasurable levels, but it’s still having an influence on the well being of infected patients,” McLaughlin said. He added that some groups are working to develop drugs that could somehow block Tat, or even use it as a vehicle for good, by piggybacking on its ability to travel between cells.


**Sketching out Cell Theory, circa 1837**

How a dinner-table conversation between two biologists led to the formulation of the theory that cells are the building blocks of all living organisms.

By Kate Yandell | August 1, 2013

GREEN SHOOTS: Matthias Schleiden was not satisfied merely with classifying plants; instead, he studied them under his microscope. Those observations prompted Schleiden to theorize about the importance of cells and their nuclei. This picture shows Schleiden’s sketches of an assortment of cells and embryonic structures from a palm, an orchid, the cherry rice-flower, and several other plants.WELLCOME LIBRARY, LONDONIn 1837, Matthias Schleiden and Theodor Schwann were dining together in Berlin when Schleiden mentioned a recent discovery by the Scottish botanist Robert Brown: the nucleus. Brown had shown that it was present in a variety of plant cells.

Schwann, an animal physiologist, and Schleiden, a botanist, were students of Johannes Peter Müller at Berlin’s Humboldt University. When Schwann heard about the nucleus, he realized that he had seen a similar structure in the vertebrate notochord—a rodlike structure in the embryo that develops into the spinal column. Sure enough, when the duo got together to examine notochords under the microscope, they saw cells containing nuclei just like those seen in plants. Such observations might seem ho-hum today, but they were unprecedented at the time.

Robert Hooke had coined the word “cell”—short for cellula, or “small compartment” in Latin—in the mid-17th century, after he’d seen tiny rectangular shapes while studying slices of cork using a rudimentary microscope. But Hooke had not grasped the importance and ubiquity of cells in plants. And by Schwann and Schleiden’s time, though animal physiologists had observed structures that would later be recognized as cells, little evidence had arisen to suggest that these structures had much in common with plants’ boxy, walled compartments.

Based on his microscopic observations of various animal tissues—from notochords and cartilage in tadpoles to the pith of birds’ feathers to the aorta of a pig fetus—Schwann proposed that all animal tissues are composed of cells, and that the cell was the fundamental structural and functional unit of all living organisms. “The real contribution of Schleiden and Schwann was to say [cells] were everywhere,” says Laura Otis, a professor of English at Emory University in Atlanta and author of *Müller’s Lab*, a book about Müller and his students.

In his 1838 article “Contributions to Phytogenesis,” Schleiden had written that cells and their nuclei are the essential building blocks of plants, beginning in the embryo. Schwann published his theories a year later, in a book called *Microscopical Researches into the Accordance in the Structure and Growth of*
Animals and Plants: “[I]t may be asserted that there is one universal principle of development for the elementary parts of organisms, however different, and that this principle is the formation of cells.” That proposition, he explained, “as well as the conclusions which may be drawn from this proposition, may be comprised under the term cell theory.”

Müller’s influential lab was the perfect place from which to disseminate such ideas. Indeed, Müller included cell theory in his widely read *Handbook of Human Physiology*. “From the 1840s to the 1880s it was probably the most important physiology textbook in Europe,” says Otis. “Everyone read Müller.”

Schwann and Schleiden had not understood that cells arise through a process of division, however. Schleiden argued that cells form around nuclei, with cell membranes growing out of nuclear structures. Schwann, meanwhile, thought that animal cells tended to “crystallize” out of the material between previously existing cells, which he called the cytoplasm.

Soon after formulating cell theory, both Schwann and Schleiden took professorships in other cities. Their ideas continued to be refined by Müller’s students, such as Rudolf Virchow, who popularized the idea that all cells arise from cells. That was the final pillar of cell theory, a sketchy set of ideas that, once refined, eventually formed the edifice of modern biological research.

Brain-Based Labels Bunk?
An fMRI study shows speculations that people are “left-brained” versus “right-brained” are not backed by evidence.
By Kate Yandell | August 19, 2013
Creative types have been commonly thought to rely on the right side of their brains, while analytical folk have been considered more “left-brained” thinkers. But people don’t actually show such tendencies toward either left- or right-brained activity, according to a study published last week (August 14) in *PLOS ONE*.

“It’s absolutely true that some brain functions occur in one or the other side of the brain. Language tends to be on the left, attention more on the right,” explained study coauthor Jeff Anderson of the University of Utah in a press release. “But people don’t tend to have a stronger left- or right-sided brain network. It seems to be determined more by connection by connection.”

Anderson and his colleagues analyzed functional magnetic resonance imaging (fMRI) data from the brains of more than 1,000 resting subjects. While the researchers found that various regions of the subjects’ brains were “lateralized,” with certain mental processes occurring on one side of the brain or the other, across whole brains, neither the left nor the right side seemed to dominate.

“It may be that personality types have nothing to do with one hemisphere being more active, stronger, or more connected,” said coauthor Jared Nielsen, a graduate student in neuroscience at Utah, in the press release.

Kerfuffle Over Marijuana Claim
A pro-pot group airs an ad stating marijuana is “less toxic” than alcohol, but a federal science agency disputes the assertion.
By Bob Grant | August 20, 2013
Marijuana law reform has been in the air lately. Last November, Colorado and Washington voted to legalize recreational weed use in their states, and Illinois recently became the latest state to legalize the drug for use as a medicine. In a speech at the American Bar Association’s annual meeting this month, US Attorney General Eric Holder announced that the federal government would no longer seek harsh mandatory minimum sentences for drug offenders that had no ties to gangs, violence, or trafficking—though he drew the ire of medical marijuana proponents for failing to mention the drug specifically once during the speech. Now, the National Institute on Drug Abuse (NIDA) has weighed in on what appears to be a rising tide of pro-marijuana sentiment.

In response to an advertisement sponsored by the pro-pot group Marijuana Policy Project, which called marijuana “less toxic” than alcohol, NIDA wrote in an e-mail to watchdog group *PolitiFact*: "Claiming that marijuana is less toxic than alcohol cannot be substantiated since each possess their own unique set of risks and consequences for a given individual." *PolitiFact*, which fact-checks claims made by politicians, pundits, and special interest groups, surmised the claim that marijuana is less toxic than alcohol was “mostly true,” citing numbers from the Centers for Disease Control’s (CDC) National Center for Health Statistics. According to the CDC, more than 41,000 deaths were tied to alcohol in 2010 (almost 16,000 attributed to alcoholic liver disease and more than 25,000 to alcohol-related accidents and
homicides), while zero were reportedly linked to marijuana. In addition, the CDC lists “1.2 million emergency room visits and 2.7 million physician office visits due to excessive drinking” on its website, as PolitiFact pointed out Thursday (August 15).

Just a few days before PolitiFact’s analysis of the “less toxic” claim ran online, NIDA released a statement on its own website, reaffirming its commitment to studying the effects of marijuana as a drug of abuse and addiction. “NIDA funds a wide range of research on and related to marijuana (cannabis); its main psychoactive ingredient, THC; and chemicals related to THC (cannabinoids),” the statement read. “This includes understanding patterns of use, its effects on the brain and behavior, and developing prevention and treatment interventions.”

Notably absent from the federal government’s marijuana research funding portfolio are studies that look into the supposed medicinal benefits of the smoked form of the drug. As The Scientist reported last year, several researchers who would like to study the medicinal properties of marijuana are stymied by the fact that the US government blocks access to federal stores of the drug and funding to conduct such research.

**Biomarkers Can Predict Suicidal Behaviors**

*Researchers identify six biomarkers related to stress and cell death that can increase the accuracy of predictions about future suicidal behaviors.*

By Chris Palmer | August 20, 2013

do not always seek psychiatric help or discuss these thoughts with friends or loved ones. Therefore, the development of a simple blood test to predict when an individual has a higher risk for self-harm has been a long-term goal of the medical community. Now, a team of researchers at Indiana University in Indianapolis has found a handful of molecular indicators that can increase the accuracy of predictions of future suicide-related hospitalizations. The team reported its findings today (August 20) in *Molecular Psychiatry*.

The team used a four-part approach to search for biomarkers related to suicidal behaviors. They first identified nine men with bipolar disorder who went from having no suicidal thoughts to later scoring high on a test for suicide risk. Blood tests on the men revealed 41 potential molecular markers that may have been involved in the increase in suicidal thoughts. “It works like a Google search ranking,” study lead Alexander Niculescu, a psychiatrist at Indiana University, told *Nature*. “Those that had the most independent lines of evidence got the highest rank.”

Next, the nominal markers were compared to those detected in blood samples from nine bipolar men who had recently committed suicide, narrowing the list down to 13 potential markers. Additional statistical tests left the team with six biomarkers to test. Levels of four of those six were elevated in 42 men with bipolar disorder and 46 men with schizophrenia who had been hospitalized for suicide attempts. In a long-term study, those four markers, along with clinical measures of mood and mental state, boosted the accuracy of predictions about future hospitalizations from 65 percent to more than 80 percent. The strongest predictor of suicidal ideation was a protein encoded by the gene SAT1, whose expression was previously found to be increased in response to exposure to toxins, infection, and lack of oxygen.

Ghanshyam Pandey, a psychiatrist at the University of Illinois at Chicago, told *Nature* that Niculescu’s work is important, but the results must be validated in much larger study before a biomarker test is ready for the clinic. “That’s a big challenge,” Pandey told *Nature*. 
Hidden Treasures
Tiny genes that control fly and human heartbeats hint at a trove of ignored but important sequences.

By Ed Yong | August 22, 2013

The regular heartbeats of humans and fruit flies both depend on tiny genes that have gone unnoticed because of their small size. They encode proteins with just 30 amino acids or fewer, and belong to an enigmatic group of sequences called small open reading frames (smORFs).

The human genome contains thousands of smORFs but their size makes them hard to identify and characterize. With a few exceptions, no one knows what they do. But by showing that the homologous smORFs control human and fly hearts—a role retained over 550 million years of evolution—Juan Pablo Couso from the University of Sussex has made a compelling case that these tiny genes are important players that deserve more attention. His study is published today (22 August) in Science.

“There could be thousands of these things that need to be isolated, described, and studied,” said Couso. “I think it’s amazing that we have missed them until now.”

Most human proteins are around 500 amino acids long, while smORFs, by definition, encode proteins with 100 amino acids or fewer. Using traditional methods, these mini-genes are hard to distinguish from random sequences. “These things have fallen through the cracks of traditional gene-finding algorithms, and most of the ones we know about have been serendipitously discovered,” said Alan Saghatelian, a physiologist at Harvard University, who was not involved in this study.

For example, in 2003, Couso noticed that one of his fruit flies was missing most of its legs. He and others later showed that this deformity is caused by a mutation in tarsal-less, a gene that produces a miniscule peptide of just 11 amino acids. However, tarsal-less is unique to insects and some crustaceans, so the wider relevance of such smORFs remained unclear. “The big thing about our new paper is that we’ve found another smORF in flies that’s also conserved in humans and other animals,” says Couso. Tarsal-less was originally described as a long noncoding RNA (lncRNA)—sequences that may help to control other genes but are supposedly never translated into proteins. By studying similar lncRNAs in fruit flies, Emile Magny, a student in Couso’s lab, identified two more smORFs, made up of 28 and 29 amino acids, respectively. Both were found within a gene called pncr003:2L, which the team later renamed sarcolamban.

Sarcolamban is activated in muscles including heart. When Magny deleted it, the flies’ hearts were more likely to beat erratically—a defect he could fix by adding back the peptide encoded by either smORF.

Within the heart, sarcolamban is active in the sarcoplasmic reticulum—a structure that responds to electrical signals from neurons by releasing a flood of calcium, which makes muscle cells contract. Without sarcolamban, these calcium spikes become larger and briefer, leading to irregular contractions.

The team found that humans have counterparts to sarcolamban—two 30-amino acid proteins called sarcolipin and phospholamban. These also control the movement of calcium in the sarcoplasmic reticulum, and sarcolipin has even been linked to human heart arrhythmias in previous studies. “This gene was well known through clinical research because of its association with arrhythmia, but no one made a fuss of the fact that it was a smORF,” says Couso.

These smORFs all derived from a single ancestral gene and still seem to play the same roles in heart control, despite 550 million years of evolutionary separation. The team confirmed this by showing that human and fly smORFs can stand in for one another. Human sarcolipin and phospholamban will home to the right part of a fly’s cells and partially correct the arrhythmic defects caused by a loss of sarcolamban.

This could be the tip of the iceberg. Several groups have found thousands of smORFs by systematically searching various genomes, but their roles are unclear. “We essentially said they’re there, but we don’t know if they’re functional,” said Saghatelian. “The new work suggests that these elements are not only unknown but also biologically interesting.”
Couso suspects that around a fifth of IncRNAs actually contain smORFs that are used to make proteins. “We don’t know what answers to what problems could be found in this pool of new genes,” he said.


**Study Evaluates Safety and Comparative Immunogenicity of an HIV-1 DNA Vaccine in Combination with a Plasmid IL-12 Vaccine and the Impact of Intramuscular Electroporation for Delivery**

“DNA vaccines have been very poorly immunogenic in humans but have been an effective priming modality in prime-boost regimens. Methods to increase the immunogenicity of DNA vaccines are needed. ... HIV Vaccine Trials Network (HVTN) studies 070 and 080 were multicenter, randomized, clinical trials. The human immunodeficiency virus type 1 (HIV-1) PENNVAX®-B DNA vaccine (PV) is a mixture of 3 expression plasmids encoding HIV-1 Clade B Env, Gag, and Pol. The interleukin 12 (IL-12) DNA plasmid expresses human IL-12 proteins p35 and p40. Study subjects were healthy HIV-1-uninfected adults 18-50 years old. Four intramuscular vaccinations were given in HVTN 070, and 3 intramuscular vaccinations were followed by electroporation in HVTN 080. ... Vaccination was safe and well tolerated. Administration of PV plus IL-12 with electroporation had a significant dose-sparing effect and provided immunogenicity superior to that observed in the trial without electroporation, despite fewer vaccinations. ... Use of electroporation after PV administration provided superior immunogenicity than delivery without electroporation. This study illustrates the power of combined DNA approaches to generate impressive immune responses in humans.”

**Bats a Source of MERS?**

A fragment of viral RNA isolated from an Egyptian tomb bat matches viral RNA isolated from the first human victim of the novel coronavirus.

By Kate Yandell | August 23, 2013

NIAID Researchers may have found a source for the first reported human case of Middle East respiratory syndrome (MERS), which is caused by a coronavirus that has infected more than 100 people in the region and killed 49. A sequence fragment derived from an Egyptian tomb bat matches viral RNA isolated from a Saudi Arabian man who died from the virus in June 2012, according to a report published this week in *Emerging Infectious Diseases.*

The 182-nucleotide fragment was found in a fecal sample from a bat of the species *Taphozous perforatus,* which was captured within 7.5 miles of the victim’s home. The bat-derived sequence was identical to the corresponding section of viral RNA isolated from the victim.

But some researchers note that the short stretch of nucleotides is not enough to establish that the bat- and human-derived viruses are one and the same. Marion Koopmans, an epidemiologist at the National Institute for Public Health and the Environment in the Netherlands, told *ScienceNOW* that the findings indicate that bats are a reservoir of the virus. However, she added, the RNA snippet comes from a relatively non-variable region of the viral genome.

“There’s still potential for it to be relatively distant if we had the complete genome,” Andrew Rambaut, who studies molecular evolution at the University of Edinburgh, told *The Canadian Press.*

The RNA fragment was likely so short because the bat samples thawed after being opened in customs en route to study coauthor Ian Lipkin’s virology lab at Columbia University. Lipkin noted that while bats may play a role in human MERS, there are likely other missing links in the chain of transmission.

“There have been so many cases of MERS described in the Middle East where we cannot make a direct link with bats,” he told *ScienceNOW.* “So there is likely to be an intermediate host.”

Some MERS victims have reported contact with camels, which appear to be susceptible to the virus, implicating the animals as potential disease transmitters.
A fifth of gay men in a relationship with an HIV-negative man have not tested for HIV while in their current relationship

Higher levels of trust associated with not testing

Michael Carter

Published: 26 August 2013

A fifth of gay men in a relationship with an HIV-negative male partner have not had an HIV test while in their present relationship, results of US research published in the online edition of the Journal of Acquired Immune Deficiency Syndromes show. Factors associated with not having a test included younger age, lower levels of education, having a sexually “closed” relationship and greater levels of trust.

“Interventions are urgently needed that not only encourage and assist at-risk HIV-negative partnered MSM [men who have sex with men] to test for HIV, but to also develop and sustain an interval testing plan that accurately reflects the dynamics of their individual risk and relationship profile,” comment the authors.

Previous research suggests that between 33 and 66% of HIV infections among gay and bisexual men in the US are transmitted within the context of a primary relationship. The Centers for Disease Control and Prevention (CDC) recommend that all sexually active gay men should have an HIV test at least annually, and more frequent screening – every three to six months – is recommended for men with known risk factors for HIV infection, for instance multiple or anonymous sexual partners.

However, relatively little is known about patterns of HIV testing among gay men in relationships. Investigators therefore designed a study to ascertain the frequency of HIV testing among gay men in a relationship with another HIV-negative man. They also examined the demographic and relationship characteristics associated with testing.

A total of 275 HIV-negative male couples (550 gay men) were recruited in 2011 via Facebook. All were aged 18 or over, lived in the US and were in a relationship with another man and had had oral or anal sex with their primary partner in the previous three months. Couples where one partner was HIV negative and the other HIV positive were excluded from the study.

Participants completed an online questionnaire. They were prompted to describe their HIV testing history since establishing their current relationship. Demographic data were also collected, and the men were asked to provide information regarding the characteristics of their relationship, including duration, the presence of a sexual agreement (an explicit mutual understanding between the two partners about permitted sexual behaviour), and also levels of trust, communication and commitment.

Almost all the participants identified as gay, and the majority were white, employed and lived in an urban environment.

A fifth of men reported they had never tested for HIV since entering their current relationship; 30% stated that they tested when they thought they were at risk of HIV; 29% had an annual HIV test and 21% stated they tested every three to six months.

Compared to the other testing groups, men who had never tested for HIV were younger (p < 0.000), had a shorter relationship duration (p < 0.000), had lower levels of education (p < 0.000) and were less likely to have an agreement about the sexual parameters of their relationship (p < 0.05). Men who had never tested also reported higher levels of commitment to their relationship (p < 0.05) and a greater degree of trust and faith in their partner (p < 0.05).

The investigators then compared the characteristics of the men who had never tested to those of participants who reported having an HIV test at least every six months. The authors found that the men who had tested frequently were more likely to belong to a racial or ethnic minority (p < 0.05), were more likely to have an “open” relationship and recently had sex with a man other than their main partner (p < 0.001) and were also more likely to concur with their partner about the existence of an agreement that set the permitted sexual parameters of their relationship (p < 0.05). However, men who tested frequently were less likely to report trusting their main partner (p < 0.01).

Comparison between men who never tested and individuals who had an annual HIV screen showed that the men testing for HIV every twelve months were more likely to have a bachelors degree or higher (p < 0.05) and to report that they or their partner had recently had sex outside their relationship (p < 0.01). Men who tested frequently were more likely than the never tested group to have a degree (p < 0.01) and to report that they or their partner had sex outside the relationship (p < 0.05). The at-risk testers also had significantly lower levels of trust in their partners than the never tested group (p < 0.05).
The investigators believe that an important overall finding of their study was that men who had greater levels of trust in their partner were more likely to never test for HIV. They write: “Additional research is warranted to further explore how concepts of trust affect partnered men’s and gay couples’ HIV testing behaviours, including their interval or history to test for HIV while in a primary relationship.”

They authors believe that the current CDC testing recommendations for gay men are not specific enough for those in relationships: “Men who engage in UAI [unprotected anal intercourse] within their relationship and have sex outside of their relationship could benefit by getting tested for HIV and STIs more often than the current recommendation of annually, especially when condoms are not always used for anal sex with casual partners.”

Reference

Gene makes some HIV-infected patients more at risk for fungal disease
HIV-infected people who carry a gene for a specific protein face a 20-fold greater risk of contracting cryptococcal disease, according to a study published in *mBio*, the online open-access journal of the American Society for Microbiology.

*Cryptococcus neoformans* is the most common cause of fungal meningitis among HIV-infected individuals. While the disease is a risk for everyone with HIV who has a very low level of CD4+ T cells, researchers have discovered that those with the gene for the protein FCGR3A 158V have an immune cell receptor that binds tightly to antibody-bound *C. neoformans*. Perversely, this tight binding by a vigilant immune system may mean the patient's own immune system strength becomes a weakness when facing the fungus.

"We found that this high affinity Fc receptor polymorphism was very highly overrepresented in the patients that got cryptococcal disease," says corresponding author Liise-anne Pirofski of the Albert Einstein College of Medicine & Montefiore Medical Center in The Bronx, New York. Patients with two copies of the high affinity Fc receptor gene had an almost 20-fold increased risk of contracting the disease.

"It's surprising that a receptor involved with a higher capacity to bind immune complexes would be associated with susceptibility in patients with HIV," says Pirofski, since phagocytosis of immune complexes is thought of as a mechanism for fighting invading microorganisms.

Differences among Fc gamma receptors (FCGR) have already been linked to cryptococcosis susceptibility among people who are not infected with HIV, but this new information sheds light on how these receptors could influence susceptibility in HIV patients, who are at elevated risk of developing cryptococcosis and are known to have high levels of antibodies to *C. neoformans*. FCGRs are proteins expressed on the outsides of different kinds of immune cells, including B lymphocytes, natural killer cells, macrophages, neutrophils, and mast cells. They bind to antibodies that have grabbed onto invading pathogens, then stimulate the immune cells to destroy the invaders.

The researchers performed PCR-based genotyping on banked samples from 164 men enrolled in the Multicenter AIDS Cohort Study (MACS), including 55 who were HIV-infected and developed cryptococcal disease, a control group of 54 who were HIV-infected and 55 who were HIV-uninfected. After correcting for a number of factors like demographics and T cell counts, they found a strong association between the gene for the high-affinity FCGR3A 158V allele and the risk of cryptococcal disease in HIV-infected men.

To figure out what that meant, they followed up with binding studies and showed that cells that express FCGR3A 158V bind more strongly to antibody-*C. neoformans* complexes. Greater affinity for the antibody-*C. neoformans* complex could increase the attachment of the fungus to monocytes or macrophages, which could in turn increase the numbers of fungi living and replicating inside immune cells. And there’s also the possibility that these infected immune cells could act like a Trojan horse, delivering *C. neoformans* cells across the blood-brain barrier and allowing them to infect the brain. Pirofski says these possibilities are now under investigation.

*C. neoformans* is found all over the environment and studies show that nearly everyone is exposed to the fungus during their lifetime. However, the organism rarely causes disease in healthy people, but strikes most often in people with weakened immune systems. It is the main cause of fungal meningitis in people living with HIV, and causes devastating disease in those with profound CD4+ T cell deficiency.

But not everyone with serious T cell deficiency develops cryptococcosis, and there is currently no way of knowing which patients will develop disease. Pirofski says a test that could distinguish who is most at risk has the potential to save countless lives, particularly in sub-Saharan Africa, which is home to 69% of all people living with HIV.
"This could be the beginning of a predictive test, at least in high-risk people" says Pirofski. "I think that we’re ready to study this receptor further as a risk factor for disease in larger cohorts."

**HPV vaccine wears off quickly in HIV-positive women**

By: M. Alexander Otto, Family Practice News Digital Network

BERNALILLO, N.M. – Women with HIV probably need a booster shot of HPV vaccine within 2 years to maintain efficacy, according to a Canadian study of quadrivalent HPV vaccine (Gardasil) in 136 HIV-positive women.

Antibody response to the vaccine is strong enough at 2 years to protect about 90% of HIV-negative women against HPV [human papillomavirus]. "But in our population, with approximately a year and a half of follow-up, that number decreased to about 63%. There’s a much more rapid decline in antibody levels" among HIV-positive women, "which suggests this population might in fact benefit from a booster," said lead investigator Erin Moses, R.N., a researcher at the Women’s Health Research Institute in Vancouver, B.C.

Cervical specimens from the women were negative for HPV DNA – and their blood was negative for HPV antibodies– both at screening and 3 months later when they received the vaccine. They were then assessed at 6, 12, and 18 months for cervical HPV DNA.

The initial seroconversion rate was high at about 99%, but "we saw nine breakthrough infections" to HPV types targeted by the vaccine "in a short period of follow up. Although we’ve only been monitoring these women for approximately a year and a half, we have already seen five [new] infections of HPV type 18. Of those five, we saw two persistent infections, which means these women had two positive tests 6 months apart for HPV 18," Ms. Moses said at the Infectious Diseases Society for Obstetrics and Gynecology annual meeting.

Women who picked up a new infection had a mean CD4 nadir of 69 cells/mm³; women who did not had a mean nadir of 228 cells/mm³, a significant difference. Women who became infected also were more likely to have a new sexual partner.

"We didn’t see a correlation between viral load" and new infections, "which was odd because typically you would think that if they have an unsuppressed viral load, they would be more at risk, but there was no correlation with that," Ms. Moses said.

The median age in the study was 40 years; about half the women were black, most of the rest were white. The median time since HIV diagnosis was 8 years, and 11% were coinfected with hepatitis C; 92% of the women were on highly active antiretroviral medications, and 69% had undetectable viral loads.

Ms. Moses said she had no relevant financial disclosures. The study was funded by Merck, the maker of Gardasil, and the Canadian Institutes of Health Research.

August 23, 2013

**Woman With HIV Not Guilty of Assault for Oral Sex in Canada**

A judge has found an HIV-positive woman in Ontario, Canada, not guilty of aggravated sexual assault for oral sex, according to a statement by the Canadian HIV/AIDS Legal Network, which opposes HIV criminalization. However, “JM” was convicted of one count of aggravated sexual assault for not disclosing her status before having unprotected vaginal sex. At the time, her viral load was undetectable. She faces potential jail time.

**FDA Puts Strict Limits on Oral Ketoconazole Use**

Published: Jul 26, 2013 | Updated: Jul 29, 2013

By John Gever, Deputy Managing Editor, MedPage Today

SILVER SPRING, Md. – Oral ketoconazole (Nizoral) should never be used as first-line therapy for any type of fungal infection because of the risk of liver toxicity and interactions with other drugs, the FDA said Friday.

The agency ordered a series of label changes and a new medication guide for patients that emphasize the risks, which also include adrenal insufficiency. It noted that the restrictions apply only to the oral formulation, not topical versions.

Late Thursday, the chief advisory body for the FDA’s European counterpart went further. The EU’s Committee on Medicinal Products for Human Use (CHMP) recommended that member nations pull oral ketoconazole from their markets entirely.
Both the FDA and the CHMP cited studies indicating high risks of severe, acute liver injury in patients taking the drug. Studies using the FDA's adverse event reporting system and a similar database in the U.K. indicated that liver toxicity was more common with oral ketoconazole than with other anti-fungals in the azole class.

The FDA also said that oral ketoconazole "is one of the most potent inhibitors" of the CYP3A4 enzyme. This effect can lead to sometimes life-threatening interactions with other drugs metabolized by CYP3A4, and also to adrenal insufficiency, since the enzyme also catalyzes release of adrenal steroid hormones.

"This accounts for clinically important endocrinologic abnormalities observed in some patients (particularly when the drug is administered at high dosages), including gynecomastia in men and menstrual irregularities in women," the FDA said.

The only indication for oral ketoconazole still supported by the FDA is for use in life-threatening mycoses in patients who cannot tolerate other anti-fungal medications or when such medications are unavailable.

In such instances, the FDA said, physicians should assess liver function before starting the drug. It is contraindicated in patients with pre-existing liver disease, and patients should be instructed not to drink alcohol or use other potentially hepatotoxic drugs.

Adrenal function should also be monitored in patients using the drug.

The CHMP also indicated the topical formulations of ketoconazole should stay on the market, but it found no basis for keeping the oral form available for any purpose.

"Taking into account the increased rate of liver injury and the availability of alternative anti-fungal treatments, the CHMP concluded that the benefits did not outweigh the risks," the panel indicated in a statement.

It recommended that physicians stop prescribing oral ketoconazole and that they should review alternatives in patients currently receiving the drug. The committee also said that patients now taking oral ketoconazole "make a non-urgent appointment" with their physicians to discuss their treatment.

**Tuberculosis “Time Bomb” Costs Europe Billions Annually**

*German health economists reported that the projected costs of emerging drug-resistant TB strains in European Union (EU) countries would justify immediate investment in the expensive process required to develop new anti-TB drugs. The report estimated that the annual direct cost of TB to EU countries exceeded 500 million euros. Productivity losses, which are based on disability-adjusted life years (DALYs), could reach approximately 5.3 billion euros. DALYs measure disease burden in terms of years lost to poor health, disability, or early death.

The World Health Organization estimated that 8.7 million people worldwide had TB in 2011, and as many as 2 million people could have drug-resistant strains by 2015. Typical TB patients must take anti-TB drugs for six months, although many fail to complete treatment. Stopping treatment early and misusing or overusing antibiotics has led to development of multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB) strains. The emergence of drug-resistant strains has turned TB into a “time bomb of rising costs” in Europe, according to study authors.

The report summarized TB treatment costs for two groups of EU countries. The direct cost per typical TB case for 15 old EU countries, Cyprus, Malta, and Slovenia was 10,282 euros; the cost to treat MDR TB rose to 57,200 euros; and the cost to treat XDR TB was 170,700 euros. For the remaining EU nations, treating typical TB cases cost 3,427 euros, and treating drug-resistant cases cost approximately 24,100 euros.

The full report, “Costs of Tuberculosis Disease in the EU—A Systematic Analysis and Cost Calculation,” was published online in the European Respiratory Journal (2013; doi: 10.1183/09031936.00079413).**

**Microneedle Patch Could Replace Standard Tuberculosis Skin Test**

*By Michelle Ma*

The standard tuberculin skin test (TST) is done by inserting a needle at a specific angle and depth in the arm to deposit a small amount of solution under the skin. Engineers from the University of Washington and researchers from Seattle’s Infectious Disease Research Institute designed a patch with minute biodegradable needles that pierce the skin and deliver the TB test.

When the researchers tested the patch on guinea pigs, they found skin reactions were similar to those with the standard TST. Marco Rolandi, senior author, considered the microneedle patch test to be simpler
and more reliable than the traditional TST, particularly for children who might be afraid of needles or developing countries with limited medical help. He compared using the patch to applying a bandage. Other advantages included: little room for error, as the microneedle length determined depth of delivery rather than needle angle; less painful; and more successful, as the solution would not be given too deep or too shallow into the skin for the test to fail.

The researchers made the microneedles from chitin, a biodegradable material. Each microneedle is 750 micrometers long, or approximately one-fortieth of an inch. Each needle tip is coated with purified protein derivative, which is used in TB testing. The researchers will continue developing the microneedle TB test and plan to test it on humans next. They also plan to develop additional diagnostic tests using microneedles.


**Digesting milk in Ethiopia: A case of multiple genetic adaptations**

A genetic phenomenon that allows for the selection of multiple genetic mutations that all lead to a similar outcome—for instance the ability to digest milk—has been characterised for the first time in humans.

The phenomenon, known as a 'soft selective sweep', was described in the population of Ethiopia and reveals that individuals from the Eastern African population have adapted to be able to digest milk, but via different mutations in their genetic material.

A team of geneticists from UCL, University of Addis Ababa and Roskilde University have shown that five different alleles are found in the Ethiopian population that cause adult lactase production, one of which is newly confirmed. Their study is published in The American Journal of Human Genetics.

Professor Dallas Swallow, from the Department of Genetics, Evolution and Environment, senior author of the paper said: "Our genetic make-up determines our ability to digest milk into adulthood. Just over a third of the global population have inherited genes that allow us to make lactase, the enzyme that digests milk, as adults.

"This study shows that several different genetic changes that allow our bodies to make lactase have emerged independently. Changes to our lifestyle over the past 10,000 years—including diet, altitude acclimatisation and infectious disease resistance—will likely have caused many genetic adaptations of this kind."

We need lactase when we are babies to digest our mother's milk, so in babies large amounts of lactase enzyme are expressed by our genes. When we are older we no longer rely on our mother's milk for essential nutrients, so in most humans manufacture of the lactase enzyme stops through de-activation of the corresponding gene.

However, subtle mutations in the regulatory region of the gene in some individuals cause lactase to carry on being expressed into adulthood. Different mutations are likely to affect lactase expression using slightly different mechanisms. This parallel selection of different gene mutations that have the same phenotypic effect—in this case lactase persistence—is known as a soft selective sweep.

Soft selective sweeps have not been so clearly described before in humans, one reason being that variations caused by soft selective sweeps are more likely to be caused by genetic mutations in regulatory sequences, rather than mutations found in coding regions of genes.

Most statistical methods that analyse genetic variation assume we are looking for only one variation as the cause of genetic adaptation. But, in soft selective sweep patterns, more than one genetic variation is selected in parallel, which makes them more difficult to detect.

Dr Bryony Jones, also from the UCL Department of Genetics, Evolution and Environment, and lead author of the paper said: "Such variations have so far been very poorly studied and it will be important for them to be better characterised to understand better the relationship between historic adaptation and 21st century disease susceptibility."

Only in the last 5-10,000 years have humans started drinking the milk of other animals, following advances in our ability to herd animals. In times of plenty, being able to drink the milk of other animals would not have given a particular advantage to those with lactase persistence.

However, in situations where food sources became scarce, individuals capable of producing lactase as adults would be able to drink the milk of their animals, increasing their chances of survival.

Ethiopia has been subject to frequent droughts that contribute to famine. Individuals who can digest milk are more likely to increase their chance of survival under these conditions.

Dr Jones explained: "Ethiopia has been a cross-roads of human migrations in the last five thousand years since the lactase persistence genes are likely to have come under selection."
"Our studies on other African and Middle Eastern populations show quite different geographic distributions, with overlap in Ethiopia, suggesting that their origins are all different, but determining where these were and how they spread is likely to be difficult."

Professor Swallow said: "The combination of mutation, large effective population size, migration and selection has been shown to be important in generating this kind of pattern of diversity, namely parallel selection of multiple alleles of similar function, a so-called soft selective sweep."

'Diversity in lactase persistence alleles in Ethiopia; signature of a soft selective sweep' is published online on the 29th of August in The American Journal of Human Genetics.

Intestinal Flora Determines Health of Obese People

Aug. 28, 2013 — New research shows that there is a link between richness of bacterial species in the intestines and the susceptibility to medical complications related to obesity. Researchers demonstrated that people with fewer bacterial species in their intestines are more likely to develop complications, such as cardiovascular diseases and diabetes. A flora with decreased bacterial richness appears to function entirely differently to the healthy variety with greater diversity.

The international consortium MetaHIT, which includes the research group of Jeroen Raes (VIB/Vrije Universiteit Brussel) were involved with the research. Jeroen Raes (VIB/VUB) said, "This is an amazing result with possibly enormous implications for the treatment and even prevention of the greatest public health issue of our time. But we are not there yet, now we need studies in which we can monitor people for a longer period. We want to perform these types of long-term studies together with the "Vlaams Darmflora Project" (Flemish Gut Flora Project), which is only possible thanks to the selfless efforts of thousands of Flemish residents."

Obesity, a health problem

Metabolic conditions have become an epidemic partly due to the modern lifestyle without a lot of exercise and easy access to (a lot of) energy-dense food. It is expected that obesity will increase tremendously all over the world; from 400 million obese people in 2005, to more than 700 million in 2015. A trend that will persist at least until 2030. Some people appear to be more sensitive to obesity than others. Many studies over the years have examined the possible cause of this.

Bacterial richness in your intestines is associated with susceptibility to obesity

Over the last years it has become very clear that there is a link between the bacterial population in our intestines and our health. As a result, scientists also started studying the link between obesity and intestinal flora. An international consortium, including the VIB scientists Falk Hildebrand, Gwen Falony and Jeroen Raes in Brussels, examined the intestinal flora of 169 obese Danes and 123 non-obese Danes.

Jeroen Raes: "We were able to distinguish between two groups based on their intestinal flora: people with a large richness of bacterial species in their intestines and people with a few less bacterial species. A species-rich bacterial flora appeared to function differently compared to the poorer variety. It was surprising to see that obese and non-obese people were found in both groups."

The scientists did see that the group with lower species richness in the intestinal flora was more susceptible to developing obesity-related conditions and chronic inflammation. The obese people in this group are more at risk of cardiovascular conditions than the obese people in the other group. These are important results that suggest that it is not only weight gain and dietary habits that play a role in the development of medical complications in obese people.

The Flemish Gut Flora Project

The question that remains is whether these results also translate to other countries and populations. Therefore, Jeroen Raes has established the Flemish Intestinal Flora Project to follow up on these types of studies on a larger scale. Such efforts are crucial to confirm the insights acquired in smaller studies and to make an effective step towards improved treatments and medicines.

Journal Reference:
Experts urge fast-track of HIV vaccine
Published: 29 Aug 2013 at 20.31

Health experts on Thursday called for trials of an HIV vaccine under development in Thailand to be hastened following recent setbacks in other efforts to end the Aids epidemic.

Initial test results of the RV144 vaccine—jointly developed by US military researchers and the Thai Health Ministry—in 2009 found a 31% protection rate among 16,000 Thai volunteers.

Phase IIb trials could start next year in the kingdom, a major forum in Bangkok heard.

Experts are optimistic a modified version of the vaccine will raise the protection rate to around 50%—the figure needed to obtain regulatory approval for public release.

"After 30 years of this epidemic we’re closer to a vaccine than we ever have been," Mitchell Warren, of US-based AVAC Global Advocacy for HIV Prevention, said at a forum in Bangkok.

"But it’s important we don’t let our efforts slip. The challenge now is to make sure we take the next steps quickly," he said.

He said the next tests would take one or two years. After that comes Phase III, the widest and most exhaustive trial stage.

Experts at the Aids Vaccine Efficacy Consortium in Bangkok said the vaccine could be available by 2020 if tests are expedited in Thailand, as well as in South Africa where parallel research is planned.

Thailand has pledged to establish a public-private company to manufacture the vaccine if trials are successful.

The kingdom became a research hub for the illness after high rates of HIV were detected among army recruits in the 1990s, and has been praised for its proactive approach to prevention, awareness-raising and treatment of the illness.

However the World Health Organisation says Thailand still has more than 520,000 people living with HIV and Aids—the highest number in Southeast Asia.

HIV rates are rising among high-risk groups such as gay men, who saw an increase from 24.5% in 2005 to 29.4% in 2011, according to US and Thai health authorities.

There is currently no vaccine against HIV on the market, and no cure for Aids, which has killed some 35 million people around the globe.

US authorities announced in April they had halted clinical trials of an experimental vaccine called HVTN 505, which was the latest in a series of unsuccessful studies.

Any successful vaccine must be speedily targeted at high-risk communities particularly in the Asia-Pacific region where rates are bucking a global downward trend, according to Luiz Loures of UNAIDS.

"But we can end Aids," he added. "For the first time we've started to see that the end of Aids is a real possibility."

Dueling Infections: Parasitic Worms Limit the Effects of Giardia, and Vice Versa
Aug. 30, 2013 — If the idea of hookworms makes you shudder, consider this: Those pesky intestinal parasites may actually help your body ward off other infections, and perhaps even prevent autoimmune and other diseases.

Studying members of the Tsimane, an indigenous population in the lowlands of Central Bolivia, UC Santa Barbara anthropologists Aaron Blackwell and Michael Gurven found that individuals infected by helminths—parasitic worms—were less likely than their counterparts to suffer from giardia, an intestinal malady caused by a flagellated protozoa. Similarly, those with giardia tended to be less infected by helminths. The researchers' findings appear in the Proceedings of the Royal Society B.

Treatment of one parasite also led to a greater likelihood of having the other later, the researchers found. The study used longitudinal data on 3,275 Tsimane collected over six years, which thereby permitted the authors to make more definitive causal inferences. This represents a distinct improvement over common correlative studies.

"People living in developing countries are often burdened by simultaneous infections," said Blackwell, an assistant professor of anthropology and the paper’s lead author. "The key finding in this study is that worms and giardia have antagonistic effects on one another, such that infection with one limits infection with the other."

The researchers' findings also suggest that treating one infection might allow the other to run rampant, which raises questions about currently accepted protocols for dealing with parasites.
According to Gurven, a professor of anthropology and co-director of the Tsimane Health and Life History Project, a collaboration between UCSB and the University of New Mexico, more than 1.5 billion people in the developing world have soil-transmitted intestinal worms. To determine which particular individuals are infected—and require treatment—however, is a very costly endeavor.

"There are campaigns in many developing countries to give every child under five de-worming medication, but if the basic infrastructure that leads to infection doesn’t change—like sanitation and access to shoes and clean water—re-infection is likely to happen within six months," he said. "And if intestinal worms are protective against giardia, there’s a tradeoff, and then the question is, which of the two is worse?"

Diagnosis and treatment of parasites usually happen on an organism-by-organism basis, continued Gurven, a co-author of the paper. Further, he argues that in the case of hookworm and giardia, the relationship between the parasites needs to be taken into account in order to maintain the overall health of the individual involved.

That one intestinal parasite has the ability to limit the pervasiveness of another also sheds light on the significance of parasites in general. "The community of pathogens in the body are interacting and can have differential effects on each other, and effects that are unanticipated," Gurven said. "Twenty years ago, people wouldn’t have guessed so much that the presence of intestinal worms, gut bacteria, and other ‘old friends’ living in our bodies might have beneficial effects."

Hence the wave of probiotic supplements designed to increase the number of "good microbiota" in the intestines, he noted.

According to both Gurven and Blackwell, a growing number of studies show that helminths have existed for long periods of evolutionary history. They cite the "old friends" hypothesis, which suggests that, in the absence of these physiological compatriots, human immune responses may not behave the way they are supposed to. "We see very minimal autoimmune disorder in the Tsimane," Gurven said.

"Imagine you have a gut parasite. Your body might be able to clear it, but it’s more likely that it won’t," he explained. "But when that’s the case, you can often live with the parasite. The immune system is activated to hold the parasite at bay. Unlike bacteria, which grow in your body, most intestinal worms can't reproduce in the body. So your immune system is humming along, keeping the worms under control. And because your immune system is working on something else, it doesn't act wonky and start attacking itself."

Added Blackwell: "In terms of looking at disease and parasite transmission, it's important to look at the broader disease ecology and other factors that might be impacting the infection. That can be true not only for these particular infections or parasites, but for other diseases as well."

Journal Reference: