Case Studies: Diseases

Aging (including Alzheimer's disease)

C Rundel, Genes, aging, and the future of longevity. Engineering & Science LXV #4, 12/02, p 36. A delightful essay on some issues of aging, written by a Caltech undergraduate as part of a science writing class -- and then published in the Caltech magazine. The article is available online at http://eands.caltech.edu/articles/LXV4/longevity.html. The article discusses some genes that are known to affect aging in simple model organisms, and even a drug which seems to extend the life of fruit flies.

An intriguing result has recently been published: A team at Scripps Research Institute (La Jolla, California) has engineered mice to have a slightly lower core body temperature (by about 0.5 degree Celsius). These mice lived longer (by about 15%) than the "normal" mice. How did they lower the body temperature? By engineering the mice to make a heat-producing protein (uncoupling protein) in the hypothalamus -- where the body senses and regulates its temperature. The cooler mice ate and exercised normally, had somewhat higher weight (since they were producing less heat from the same food) -- and lived longer. Interestingly, one effect of severe caloric restriction, which is known to increase lifespan, is lowering the body temperature. So this work may give us one more piece of a complex puzzle. Its practical significance for now is purely speculative: there is no known way to reduce human body temperature, and of course we know nothing about what the side effects might be. The paper is B Conti et al, Transgenic mice with a reduced core body temperature have an increased life span. Science 314:825, 11/3/06. The paper is accompanied by a "perspective" article: C B Saper, Biomedicine: Life, the universe, and body temperature. Science 314:773, 11/3/06. These are online at http://www.sciencemag.org/content/314/5800/773.summary (perspective, probably the best place to start) and http://www.sciencemag.org/content/314/5800/825.abstract (article).

SAGE KE, the Science of Aging Knowledge Environment Archive Site, from Science magazine. "From October 2001 to
June 2006, Science's SAGE KE provided news, reviews, commentaries, disease case studies, databases, and other resources pertaining to aging-related research. Although SAGE KE has now ceased publication, we invite you to search and browse the article content on this archive site. [http://sageke.sciencemag.org/](http://sageke.sciencemag.org/).

Nature web focus sites on aging:

- [http://www.nature.com/nature/focus/s...nce/index.html](http://www.nature.com/nature/focus/s...nce/index.html). Senescence: Cells, ageing and cancer. (August 2005)
- [http://www.nature.com/nature/focus/l...pan/index.html](http://www.nature.com/nature/focus/l...pan/index.html). Determining lifespan. (September 2003)


Book. Lenny Guarente, Ageless Quest - One scientist's search for genes that prolong youth. Cold Spring Harbor Lab Press, 2003. ISBN 0-87969-652-4. Available in UC Berkeley Library. Guarente is a biologist at MIT. In this short book, he talks about finding a gene that extends the life of simple yeast -- and of worms. The question, then, is whether it is relevant to aging in higher organisms, including humans. He discusses evidence that it may be, though conclusive evidence is not yet available. This story is a good testimonial to the importance of basic research -- how studying simple model systems leads to insights that guide work in more complex systems. It is also a good story of how scientists develop and pursue leads -- some of which work out and some of which do not; that is how science works. It is an optimistic book -- perhaps too optimistic, since the gap between what has been shown and what is needed is still quite large. Enjoy the story, and Guarante’s enthusiasm. But be careful to distinguish what turns out to work from the exciting discussions of what might be.

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**Anthrax**

Anthrax vaccine immunization program. One place where the anthrax vaccine is actually used with high frequency is in the US military. This is their site about the vaccine and the program. Be alert for bias (as with any source!), but there is actually a lot of good info here. [www.anthrax.osd.mil](http://www.anthrax.osd.mil).

Researchers, including a group from UC Berkeley, have explored the tricks that the anthrax bacteria use to get the iron they need for growth. They found that these bacteria make two chemicals designed to steal iron from their host; such chemicals are generically called siderophores. One of these is attacked by the human immune system; however, the other -- the more novel one -- avoids it, and actually succeeds in supplying iron to the bacteria. They suggest that this novel siderophore might be a good target for anti-anthrax drugs, or simply a marker for detection of this pathogen. The work was featured in the student newspaper, December 8, 2006: Researchers Find Possible Way to Block Anthrax, [http://archive.dailycal.org/article/22576/](http://archive.dailycal.org/article/22576/). It was also discussed in a nice article in the student publication BSR: N Keith, Double Trouble - Anthrax has two tricks for stealing iron. Berkeley Science Review, Issue 12, p 15, Spring 2007. BSR is free online; this item is at sciencereview.berkeley.edu/article=briefs_5. The work was published as R J Abergel et al, Anthrax pathogen evades the mammalian immune system through stealth siderophore production. PNAS 103:18499, 12/5/06. Online at [http://www.pnas.org/content/103/](http://www.pnas.org/content/103/).
Antibiotics

Bacterial 'battle for survival' leads to new antibiotic -- Holds promise for treating stomach ulcers. A press release from MIT, Feb 2008, on a new approach for discovering new antibiotics. Briefly, they force bacteria not known to make antibiotics to compete with other bacteria. One possible response is for them to develop the ability to make antibiotics. This should be considered interesting lab work at this point. The potential of the new antibiotics is unknown. web.mit.edu/newsoffice/2008/a...tics-0226.html.

Alliance for the Prudent Use of Antibiotics. www.tufts.edu/med/apua/. This site has "an agenda" -- trying to reduce "inappropriate" use of antibiotics. A particular concern is the use of vast amounts of antibiotics with farm animals, sometimes with minimal justification. The site also contains a lot of general information about antibiotics, aimed at the consumer and at doctors.

A local angle. The July 24, 2003, issue of the Berkeleyan (a campus newspaper for staff) published part of an interview with science writer and UCB journalism professor Michael Pollan on the subject of antibiotics in beef farming, with a focus on McDonald's announcement of favoring suppliers that use less antibiotics. The article title is Prof has a beef with McDonald's antibiotics announcement. The entire interview is online at http://www.berkeley.edu/news/media/releases/2003/07/01_pollan.shtml. Very readable, with a useful general overview of why antibiotics are used in commercial production of animals. Pollan also expresses reservations about how significant the policy announcement will be.

Art

The DNA double helix has become a popular icon, known well beyond the circles of those who know anything about biology. And of course, some artists are attracted to social issues. Thus it should not be surprising that DNA and genes and genomes and related issues have become the subject of artistic efforts.

John Sulston was the head of the British lab working on the human genome. Provocatively and/or appropriately, artist Marc Quinn did a "portrait" of Sulston -- using his DNA. For a news article on this, which includes the "portrait", see http://www.guardian.co.uk/culture/2001/sep/22/art. If you have access to Nature, see Martin Kemp's article about the portrait in the October 25, 2001, issue (413:778). (The printed article and the online PDF file contain the "portrait"; however the online HTML file does not.) This article is part of Nature's regular series, Science and Culture; art historian Kemp is a regular contributor.
Sulston shared the 2002 Nobel prize for his work on development in the worm Caenorhabditis elegans. In the course of that work, he played a key role in discovering the phenomenon of programmed cell death, now called apoptosis. [http://www.nobelprize.org/nobel_priz...aureates/2002/]

England issued a coin to commemorate the 50th anniversary of the DNA structure (which was developed at Cambridge Univ in England); it shows a DNA double helix on one side. (The other side shows the Queen, who coincidentally is celebrating her 50th anniversary as monarch.) For pictures of the coin, plus some information: [http://www.taxfreegold.co.uk/2003two...dsdnagold.html].

Also see L Gamwell, Science in culture: Art after DNA. Nature 422:817, 4/24/03. [http://www.nature.com/nature/journal...l/422817a.html]. The subtitle notes "The double helix has inspired scientists and artists alike."

Bio-inspiration (biomimetics)

Book. Peter Forbes, The Gecko's Foot - Bio-inspiration: Engineering new materials from nature. Norton, 2005. The lotus leaf is easily rinsed clean; the gecko can climb a glass wall. Why? And, can we make use of the principles that Nature has used to achieve these remarkable accomplishments? Those are just two of the topics in this delightful book -- one of which is reflected in its title. The theme is bio-inspiration (sometimes called biomimetics), in which we look to Nature for an idea about how to do something. The hook-and-loop fastener, popularly known by the tradename Velcro, is an example of old, but the field has now taken on an identity that reflects a more focused effort to discover and exploit what Nature has already learned. Forbes emphasizes work at the "nano" level, where recent advances in instrumentation, such as the scanning electron microscope (SEM), helped us unlock Nature's secrets. Commercial importance? Well, products based on the self-cleaning lotus leaf and the sticky gecko foot are on the market. They are not yet big successes; perhaps that will take time, or perhaps there is less here of commercial importance than we would like to believe. In any case, the book is delightful biology, delightfully presented. It is suited for the scientific novice, but even biologists are likely to find it rewarding. This book is listed on my Book suggestions page, and as further reading for Intro Chem Ch 15, re intermolecular forces, and for Organic/Biochem Ch 15, re spider silk. In fact, it was reading this book that prompted me to start this BITN section.

From the University of Reading:

- Centre for Biomimetics. www.reading.ac.uk/biomim/home.htm.
- BIONIS: The Biomimetics Network for Industrial Sustainability. www.reading.ac.uk/bionis/.

From University of California, Berkeley

- Biomimetic Millisystems Lab. "The goal of the Biomimetic Millisystems Lab is to harness features of animal manipulation, locomotion, sensing, actuation, mechanics, dynamics, and control strategies to radically improve millirobot capabilities. Research in the lab ranges from fundamental understanding of mechanical principles to novel fabrication techniques to system integration of autonomous millirobots. The lab works closely with biologists to develop models of function which can be tested on engineered and natural systems. The lab's current research is centered on fly-size flapping flight, and all-terrain crawling using nanostructured adhesives." The "Current Research Projects" listed in January 2008 include: Micromechanical Flying Insect, Biologically Inspired Synthetic Gecko
Adhesives, Millirobot Rapid Prototyping, Micro-Robots and Microassembly. [http://robotics.eecs.berkeley.edu/~ronf/Biomimetics.html](http://robotics.eecs.berkeley.edu/~ronf/Biomimetics.html). This page is from Ronald Fearing, in EECS (Electrical engineering and computer science). However, a glance at the people shows that this is a collaboration that also includes the Departments of Integrative Biology and Chemical Engineering.

- CIBER. The Center for Interdisciplinary Bio-inspiration in Education & Research. A new center at Berkeley, headed by Dr Robert Full, of Integrative Biology. [http://ciber.berkeley.edu](http://ciber.berkeley.edu). From "Objectives": CIBER "will innovate methods to extract principles in biology that inspire novel design in engineering and train the next generation of scientists and engineers to collaborate in mutually beneficial relationships. ... Biologists working with engineers, computer scientists and mathematicians are discovering general principles of nature from the level of molecules to behavior at an ever-increasing pace. Now more than ever before, nature can instruct us on how to best use new materials and manufacturing processes discovered by engineers, because these human technologies have more of the characteristics of life. This effort will require unprecedented integration among disciplines that include biology, psychology, engineering, physics, chemistry, computer science and mathematics." Choose Publications & Journals for good information on the work going on.

* News story in the Daily Cal, the student newspaper, February 12, 2008. Mimicking the geckos' ability to defy gravity - From geckos to humans to robots: new adhesive tape makes the vertical horizontal. [http://archive.dailycal.org/article/100353/mimicking_the_geckos_ability_to_defy_gravity](http://archive.dailycal.org/article/100353/mimicking_the_geckos_ability_to_defy_gravity).
* News release: Engineers create gecko-inspired high-friction micro-fibers, August 2006. [http://www.berkeley.edu/news/media/releases/2006/08/22_microfiber.shtml](http://www.berkeley.edu/news/media/releases/2006/08/22_microfiber.shtml). As you read the item, note that they are not making synthetic gecko feet, but rather using some of what they learned about gecko feet to help them design a new material.

'Gecko foot' band-aids could promote healing. A news story in New Scientist, February 19, 2008, about the development of a new type of adhesive tape, which may be suitable for not only band-aids but also sutures. It is based in part on the structure of the gecko foot. Importantly, the work does not simply mimic the gecko foot, but builds on it, to develop a material suitable for the intended use. The story is online at [http://www.newscientist.com/article/dn13347](http://www.newscientist.com/article/dn13347). The work referred to is published as: A Mahdavi et al, A biodegradable and biocompatible gecko-inspired tissue adhesive. PNAS 105:2307, 2/19/08. There is a link to the article at the end of the news story.

Posts on my Musings pages on biomimetics include...
* New, February 27, 2011. [Robots should learn to crawl first, then walk (February 27, 2011)](http://www.berkeley.edu/news/media/releases/2006/08/22_microfiber.shtml).

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**Brain (autism, schizophrenia)**

There is evidence to suggest that infection of the mother during pregnancy may increase the chances of some brain diseases, including autism and schizophrenia. The effects seem to be due not to the infectious agent per se, but to the host response. Now, work with a mouse model system points to one specific component, the cytokine IL-6, as promoting the brain mis-development. Remember, this is with mice; the work generates some leads that must be followed up to see if they are relevant to humans. A press release about this work: "Researchers discover link between schizophrenia, autism and maternal flu", Oct 1, 2007: media.caltech.edu/press_releases/13039. The paper is: S E P Smith et al, Maternal immune activation alters fetal brain development through interleukin-6. Journal of Neuroscience, 27:10695-10702, 10/3/07.
Cancer

Some general educational resources...

New, November 29, 2010. Inside Cancer. Educational materials, for the general public. Sections include: hallmarks, causes and prevention, diagnosis and treatment, pathways. Some materials are specifically for teachers. www.insidecancer.org. This is from the Dolan DNA Learning Center, Cold Spring Harbor Laboratory: http://www.dnalc.org/websites/. Other parts of the Dolan DNA Learning Center are referred to under BITN Resources: DNA and the genome and Molecular Biology Internet Resources: Methods.


Cancer Quest, a broad informational resource, largely organized as a tutorial, from G Orloff, Emory Univ. Topics range from the basic underlying biology to clinical issues. Special pages offer guidance to patients, educators, students, and health professionals. http://www.cancerquest.org. Also available in Chinese, Italian, Russian, Spanish.

Other...

Personalized cancer vaccine made in plants. This work deals with a cancer of the immune system, called follicular B cell lymphoma. An important characteristic of this cancer is that each case expresses a unique antigen, reflecting its development from a single immune system cell. The goal is to make a vaccine that targets this particular antigen. Here, they show that they can do this in a plant system -- which is both faster and cheaper than animal systems previously tried. The resulting vaccines do elicit an immune response in [most of] the patients, though no therapeutic benefit was seen in this small early study. The work is of note both for the special approach of making a personalized vaccine, and for the broader issue of making vaccines in plants. News story, from Stanford: Plants can be factories making vaccine to treat cancer, July 23, 2008. http://news.stanford.edu/news/2008/july23/med-plants-072308.html. The paper: A A McCormick et al, Plant-produced idiotype vaccines for the treatment of non-Hodgkin's lymphoma: Safety and immunogenicity in a phase I clinical study. PNAS 105:10131, 7/22/08. Free online: http://www.pnas.org/content/105/29/10131.

Drug targeting. A group from UC Berkeley and San Francisco reported making a new drug delivery system. The active drug is attached to a large molecule called a dendrimer. Because the blood system in tumors tends to be leaky, the large drug complex is taken up by the tumor selectively, and then hydrolyzed. They report promising results in a mouse model system. Both the article and the story about it discuss some of the logic of the system. There is a good news story about the work in BSR, a student publication: N Parghi, Right on target - Reducing chemotherapy’s collateral damage. Berkeley Science Review, issue 12, p 12, Spring 2007. Free online: sciencereview.berkeley.edu/ar...ticle=briefs_3. The paper: C C Lee et al, A single dose of doxorubicin-functionalized bow-tie dendrimer cures mice bearing C-26 colon carcinomas. PNAS 103:16649, 11/7/06. Free online: http://www.pnas.org/content/103/45/16649.

Irreversible electroporation. UC Berkeley scientists, led by B Rubinsky, are working on a new approach to treating solid tumors. A new paper is on the use of the method with pigs, the first large animal tests. The method is a variation of the common electroporation used in laboratory work to make transient membrane pores that can allow uptake of drugs or even DNA. The key difference is that the conditions are chosen so that the pores do not quickly reseal; thus the cells

The Carcinogenic Potency Database (CPDB). A database of carcinogens, based on testing in animals. From Lois Swirsky Gold, Bruce Ames, and colleagues at UC Berkeley. potency.berkeley.edu/.

Book. J Michael Bishop, How to win the Nobel prize - An unexpected life in science. Harvard Univ Press, 2003. ISBN 0-674-00880-4. Bishop is a local story -- long time scientist at UCSF, now Chancellor there. Bishop’s work on cellular genes that become cancer genes earned the Nobel Prize for him and his UCSF colleague Harold Varmus. (And a few days after the Nobel announcement he was at Candlestick Park for the World Series game that did not happen.) The book is based on a series of lectures, and has the informal breezy style of talks for a general audience. It is more generally about the nature of science, and about baseball, music and the human Michael Bishop, than about cancer in particular. One chapter does indeed give a good, not-too-technical introduction to the nature of cancer -- and his own contributions. The final chapter is about the future of science, and its role in society. All-in-all, a fairly light but interesting read.

Diabetes

J Diamond, The double puzzle of diabetes. Nature 423:599, 6/5/03. Feature. Nature's blurb for this article: "Why is the prevalence of type 2 diabetes now exploding in most populations, but not in Europeans? The genetic and evolutionary consequences of geographical differences in food history may provide the answer." The article gives an overview of the types of diabetes, and their incidence. The main purpose is to propose an explanation of why diabetes is not rampant among Europeans. As you read this, remember that he is proposing a hypothesis -- and some tests of it; be careful about remembering his "answer" as if it were true. Reading the article for its background information can be good. Online at http://www.nature.com/nature/journal...l/423599a.html.

Ebola and Marburg

Ebola and Marburg are related viruses. Ebola has been observed to emerge "from the jungle" from time to time. A major -- and important -- mystery is where is it "hiding". That is, what is the "reservoir" (likely an animal) from which the virus emerges? Now there is evidence that bats may be the culprit.; the bats carrying the virus show no symptoms. It is important to emphasize that this is a new finding, subject to further work. Even if correct, it only shows that the bats are a part of the story; there may be more to it. The article is: E M Leroy et al, Fruit bats as reservoirs of Ebola virus. Nature 438:575, 12/1/05. The abstract is at http://www.nature.com/nature/journal...s/438575a.html. Here are two news stories on this finding: http://www.innovations-report.com/ht...ort-53574.html and http://news.bbc.co.uk/2/hi/health/4484494.stm.
Now there is a report of Marburg virus being detected in bats. The work is published: J S Towner et al, Marburg virus infection detected in a common African bat. PLoS ONE 2(8):e764, 8/22/07. There is a news story, August 2007: Scientists detect presence of Marburg virus in African fruit bats, at: http://www.eurekalert.org/pub_releases...-sdp082107.php. This has a link to the article, which is freely available.

Progress with efforts to control Ebola, Marburg viruses. Microbe 1:217, 5/06. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at forms.asm.org/microbe/index.asp?bid=42381. Discusses both vaccines and drugs.

Emerging diseases (general)

In the Spring of 2003, as I started to put together a BITN web site, one dominant news story was a new illness, called SARS (severe acute respiratory syndrome). Our fears of SARS are enhanced by our ignorance. And that is not just the ignorance of the general public, but also the ignorance of the medical and scientific communities. SARS is a new disease. At least at the start, we do not know what causes it, how it is transmitted, how to contain or treat it -- even how to diagnose or define it, or what its risks are. Of course, over time, answers to some of these questions are developed. It is actually quite amazing how fast some of the answers come in. On the other hand, not all the answers we hear are correct. (For example, three different organisms were quickly "identified" as the cause of SARS. Obviously, two of those were likely to be incorrect.)

By mid-summer, we may have the disease under control. Yet, we still have little idea how the disease started -- and if/when it may return.

SARS is an example of an emerging disease -- a new disease. Other diseases that have emerged over the last 30 years include Legionnaire's diseases, AIDS, toxic shock syndrome, Ebola, West Nile Virus -- and perhaps a new strain of Influenza each year. Both SARS and the broader topic raise lots of questions about how we deal with a disease that has emerged, and how we might predict or prevent new emerging diseases.


J L Fox, Cats with MRSA, elephants with TB are parts of a "microbial storm". Microbe 3:451, 10/08. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at microbemagazine.org/images/st...1008000448.pdf (scroll down to page 4 of the file for this item -- or just look for the elephants). "Emerging diseases" is a two-way street. Diseases may pass from humans to other animals, too. This news story discusses some examples and concerns.

The following sites track emerging diseases

- Center for Infectious Disease Research and Policy (Univ Minnesota). http://www.cidrap.umn.edu. I list specific
CIDRAP sections on my pages for Influenza (Bird flu) and Prions (BSE, CJD, etc). Other topic areas here include: Bioterrorism, Biosecurity (e.g., food), Food safety (foodborne illnesses, irradiation), and a miscellaneous section that includes SARS, West Nile, Monkeypox, Chemical Terrorism. Useful for the general audience.


- ProMED-mail is aimed at medical professionals, informing them about emerging diseases; it is one of the major primary sources underlying the sites listed above. Includes announcements and maps of outbreaks, as well as general information. From the International Society for Infectious Diseases. [http://www.promedmail.org](http://www.promedmail.org). Parts of the site are also available in Chinese, Japanese, Portuguese, Russian, Spanish.

- US government sites with information on emerging diseases:
  - CDC. [www.cdc.gov/ncidod/diseases/e...ease_sites.htm](http://www.cdc.gov/ncidod/diseases/e...ease_sites.htm).


- Posts on my Musings pages on emerging diseases include...
  - Added April 9, 2011. One health (November 15, 2010).

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**Ethical and social issues**

As noted in the introductory materials, I intend the main emphasis here to be the scientific issues. Of course, other issues are important parts of the overall story. Some of the topic-specific resources listed include ethical and social issues. But occasionally, I may want to list a site that focuses on these matters.

Bloodlines: Technology Hits Home. The web site [http://www.pbs.org/bloodlines/](http://www.pbs.org/bloodlines/) was written to accompany a PBS show. It broadly deals with issues arising from reproductive and genetic technologies, and includes interactive questions which you can try to evaluate for yourself.

Bioethics Web. "BioethicsWeb is a gateway to evaluated, high quality Internet resources relating to biomedical ethics, including ethical, social, legal and public policy questions arising from advances in medicine and biology, issues relating to the conduct of biomedical research and approaches to bioethics." Subtopics include: Biomedicine, Clinical practice, Environment/agriculture/foods, Ethics: theory and concepts, Research conduct, Society/policy/law, and more.

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**HIV (AIDS)**

[aidsinfo.nih.gov](http://aidsinfo.nih.gov). A broad source of HIV information, from NIH. It includes a section on vaccine trials, as well as drug treatments and other research areas.

The 2008 Nobel prize in Physiology or Medicine was awarded to Harald zur Hausen, “for his discovery of human papilloma viruses causing cervical cancer” and Francoise Barre-Sinoussi and Luc Montagnier, “for their discovery of human immunodeficiency virus”. See the Nobel site: [http://www.nobelprize.org/nobel_priz...aureates/2008/](http://www.nobelprize.org/nobel_priz...aureates/2008/). This item is
listed on this page for HIV and HPV.

Hormone replacement therapy

A major and continuing news story for 2002-3 was based on some long term studies of the use of replacement hormones by post-menopausal women. The results were not at all what had been commonly expected. One important general point from the story is the problem of knowing what long term effects of a treatment are, especially the smaller effects -- without doing long term studies with large numbers of patients. Lots of info, with regular updates, is available at the home page for the Women's Health Initiative: http://www.whi.org. "The Women's Health Initiative (WHI) is a long-term national health study that focuses on strategies for preventing heart disease, breast and colorectal cancer and fracture in postmenopausal women. This 15-year project involves over 161,000 women ages 50-79, and is one of the most definitive, far reaching programs of research on women's health ever undertaken in the U.S. The purpose of this site is to provide WHI participants [and] others interested in the WHI findings a way of obtaining information about research results directly from the study."

And now, after five more years of data, the advice changes again. It is more detailed, more nuanced. This is common, and emphasizes that we must be cautious about over-interpreting any data set. News story, June 21, 2007, from Brigham and Women's Hospital and Harvard Medical School: "Estrogen Therapy and Coronary Artery Calcification. Women aged 50-59 who took estrogen show a reduced risk of coronary plaque buildup." www.brighamandwomens.org/about...b=0&PageID=272.

For an introduction to the use of testosterone supplements in men, see a page from the US National Institute on Aging: Frequently Asked Questions About Testosterone and the IOM Report, 11/12/03. www.nia.nih.gov/NewsAndEvents...elOMReport.htm.

HPV (Human papillomavirus)

A new vaccine was announced recently. It is widely known by its trade name, Gardasil. It acts to prevent infection by some strains of the human papillomavirus, which cause cervical cancer and genital warts. The vaccine itself is indeed a product of modern biotechnology: it contains only viral proteins (produced in yeast), with no viral genome; thus it cannot grow at all. Here are some materials from the CDC about this vaccine:

* "Questions and Answers about HPV Vaccine Safety". www.cdc.gov/vaccinesafety/Vacc.../hpv_faqs.html

Notes...

There are many strains of HPV. Only some of them cause cancer or warts. The vaccine is effective against four of these strains. Data so far suggests that the vaccine is extremely effective against those four strains, but it is important to realize that strains other than those in the vaccine are responsible for some cancer. One might be confused by hearing that the virus is "100%" effective or "70%" effective. The former number refers to the apparent effectiveness against the strains included in the vaccine; the latter number refers to the overall effectiveness against cervical cancer, given that the current vaccine works against only some of the relevant strains.

Long term issues about this new vaccine are, of course, not known. For example, how long is it effective?

The May 10, 2007, issue of the New England Journal of Medicine contains several articles on this new vaccine -- with more data and perspectives. I suggest that readers start with two editorials, with differing views. Both are freely available online.


Here is another approach to making an HPV vaccine. This one seeks to treat a person who is infected; it is thus a therapeutic vaccine. It targets a protein that is part of the viral life cycle in an infected cell -- and which is actually responsible for causing and maintaining cancer. This vaccine is still in testing. News story: Experimental HPV Vaccine Helps in Treating Mice with Cervical Cancer, Microbe 3:318, 7/08. Free online: microbemagazine.org/images/st...0708000314.pdf. Scroll down to page 5 of the file for this item.

The 2008 Nobel prize in Physiology or Medicine was awarded to Harald zur Hausen, “for his discovery of human papilloma viruses causing cervical cancer” and Francoise Barre-Sinoussi and Luc Montagnier, “for their discovery of human immunodeficiency virus”. See the Nobel site: http://www.nobelprize.org/nobel_prizes/aureates/2008/. This item is listed on this page for HIV and HPV. It is also noted in a Musings post: Nobel prizes (October 8, 2008).

The main emphasis with HPV and cancer has been cervical cancer. However, there is increasing evidence that these viruses, probably the same strains, may cause other cancers. Here is one news story on this: HPV-Linked Oral Cancer In Men Increasing, Feb 4, 2008. http://www.medicalnewstoday.com/articles/96053.php.

The traditional method of screening for cervical cancer is the pap smear, which looks for abnormal cells; in poor countries, little or no screening may be done. A new study suggests that it might be better to screen for the virus that causes the cancer. Their extensive testing shows that the test for the viral DNA is more effective than the pap smear. They argue that it is also likely to become inexpensive enough to be practical -- and worthwhile -- in poorer countries. A news story on this work: DNA Test Outperforms Pap Smear; April 6, 2009. www.nytimes.com/2009/04/07/he...virus.html. The paper is: R Sankaranarayanan et al, HPV Screening for Cervical Cancer in Rural India. N Engl J Med 360:1385, April 2, 2009. Freely available at http://www.nejm.org/doi/full/10.1056/NEJMoa0808516. The article is

**Malaria**

Malaria is one of the world's great killers. Recent years have seen the analysis of the genome of both the malaria parasite itself and its mosquito vector. Nature has posted a "web focus" on the diverse aspects of this disease, 2008. http://www.nature.com/nature/focus/malaria/index.html

A UC Berkeley group led by Jay Keasling is working on production of artemisinin, a new type of anti-malarial drug, in microbes (bacteria and yeast).

- Here is a campus news story on the funding of this project by the Gates Foundation: "QB3 + Gates’ millions = a cure? Helped by Microsoft's founder, Jay Keasling and his industry partners hope to create an inexpensive treatment for malaria". January 12, 2005. http://www.berkeley.edu/news/berkeley...keasling.shtml.
- This group of items is also listed for Organic/Biochemistry Internet resources: Alkenes. It is also noted in the Synthetic biology section of this page.

Malaria Vaccine Initiative (MVI). http://malariavaccine.org/. For a short news story on malaria vaccines, including the role of the MVI: Money, Technology, and Fresh Ideas Converge on Malaria. Microbe 3:9, 1/08. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at forms.asm.org/microbe/index.asp?bid=55316.

**Measles**

In some ways measles would seem to be a good target for eradication. It occurs only in humans, so there is no need to worry about animal reservoirs. A good vaccine is available. Yet measles remains a major killer. One key reason is that the virus is highly infectious, thus a very high level of population immunity is needed to block its transmission. The following article is a good readable discussion of the issues of measles, its vaccine, and the difficulty of eradicating this disease. D E Griffin & W J Moss, Can We Eradicate Measles? Microbe 1:409, 9/06. It is at microbemagazine.org/images/st...0906000409.pdf.

**Polio**

Whatever happened to polio?. A history site from the Smithsonian Institution, posted to coincide with the 50th anniversary of the first polio vaccine. http://americanhistory.si.edu/polio/. Includes information on the current effort to eradicate polio.

A report from the Institute of Medicine (IOM)... K Stratton et al, Immunization safety review: SV40 Contamination of Polio Vaccine and Cancer, October 2002. http://www.nap.edu/catalog.php?record_id=10534. Some early batches of the original polio vaccine (the Salk vaccine, with killed virus) were later found to be contaminated with the virus SV40 (which...
was not killed by the treatment used to kill the poliovirus). SV40 may be a cancer-causing virus. So, inadvertently, we have been running a big test on whether it causes cancer in humans. A long enough time has passed that it is rather clear there is no big problem. Some data has suggested increases in certain very rare cancers. This report analyzes what is known. One of the frustrations, inherent in an accidental test, is that the data is not kept very well. This is an interesting story, but I do suggest you read it for the message about how things should be done, and not try to make SV40 into a big problem.

Nature web focus: http://www.nature.com/nature/focus/polio/index.html. End of polio - the final assault. (September 2004)

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**Protein Folding -- and diseases**

This topic was suggested by a student. It was stimulated in part by the Sept 8, 2003, issue of The Scientist, including a feature article by P Hunter, Protein Folding: Theory meets disease, p 24: http://classic.the-scientist.com/art...display/14060/. It is also related to the topic Prions (BSE, CJD, etc.).

There are several issues here. The general topic of how proteins fold has long fascinated -- and frustrated -- biologists. But the topic has taken on greater significance with the increasing recognition of how relevant the protein folding problem is to disease. In fact, a good place to start with the Hunter article, listed above, is the side-bar on p 25, "Miss a fold, prompt a disease." Many cases are now known where we realize that the main effect of a mutation that causes a disease is to interfere with protein folding. For example, the major mutation found in cystic fibrosis is of this type. Once/if the mutant protein manages to fold, it works fine, but the mutation greatly slows the folding process.

Another type of folding-disease connection is illustrated by the prions. Although our understanding of prions is still incomplete, it seems that the prion proteins have two stable forms. One is the normal form of the protein, in your cells, and the other form causes disease. See the Prions (BSE, CJD, etc.) page for more.

A classic experiment in the history of studying protein folding was done by Christian Anfinsen, around 1960. Anfinsen showed that a protein could fold up properly in vitro, without any external source of "information" on how to fold. This established the paradigm that the 3D shape of a protein follows from its amino acid sequence. Although there are some nuances, this still underlies our modern understanding of protein folding. Anfinsen shared the 1972 Nobel prize for Chemistry "for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation". See the Nobel site: http://www.nobelprize.org/nobel_priz...aureates/1972/.

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**RNAi (RNA interference or silencing)**

Natural small RNA molecules act as gene regulators. Similarly, synthetic small RNA molecules may be useful to biologists to probe gene function -- and may be useful as therapeutic agents. This is a new field. Particularly with regard to actual therapeutic use, there is much promise but little information. Two articles in the March 29, 2004, issue of The Scientist provide a good introduction and overview. The articles are A Adams, RNAi inches toward the clinic (p 32), and A Constans, Concocting a knock-out punch for HIV-1 (p 28). http://classic.the-scientist.com/art...display/14559/ & http://classic.the-scientist.com/art...display/14552/.

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https://bio.libretexts.org/Bookshelves/Introductory_and_General_Biology/Supplemental_Modules_(Molecular_Biology)/Case_...
The Scientist for Sept 13, 2004 (Vol 18 #17) has the feature topic of RNAi, with multiple articles: classic.thescientist.com/2004/9/13/. Again, an excellent introduction and overview.


The 2006 Nobel prize for physiology or medicine was awarded to Andrew Z Fire and Craig C Mello for their discovery of "RNA interference - gene silencing by double-stranded RNA". http://www.nobelprize.org/nobel_priz...aureates/2006/.

See the BITN page Prions (BSE, CJD, etc): Treatment for a paper on the possible use of RNAi to treat a prion disease.

See the BITN page Agricultural biotechnology (GM foods): Recent items for a paper on the use of RNAi, targeted to the seeds, to reduce production of a toxic chemical in cotton seeds.

Nature has a web focus site on this topic. Of particular interest may be a set of animations of how the process works: www.nature.com/focus/rnai/ani...ons/index.html.

SARS (Severe acute respiratory syndrome)

See Emerging diseases section, above, for perspective.

The web site of the US Centers for Disease Control (CDC) is a good site to keep abreast of SARS -- and of course of other diseases. The CDC SARS page: www.cdc.gov/ncidod/sars/

The CDC site has links to all local and state public health departments, and also includes travel advisories.

Nature magazine's "web focus" on SARS: http://www.nature.com/nature/focus/sars/index.html. This set seems to be freely available.

In July, Nature published a "news feature" called "SARS - What have we learned?" It is in the form of a series of questions, with answers, about various aspects of the SARS story. Among the questions... Was the fuss overblown? Are we prepared for the next viral threat? Where did the SARS virus come from? What about a vaccine? Very readable overview and update. Nature 424:123, 7/10/03; also available at the top of their web focus page, listed above.

A free online SARS "textbook", maintained by B S Kamps & C Hoffmann: http://www.sarsreference.com. Also available...
in Chinese, French, Greek, Italian, Portuguese, Romanian, Spanish, Vietnamese.

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**Smallpox**

www.bt.cdc.gov/agent/smallpox/index.asp. The site provides a wide range of information, including much history. Some materials are also available here in Spanish.

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**Sudden Oak Death**

http://www.suddenoakdeath.org. A range of information, both for the consumer and the scientist. The site is from UC Berkeley.

Sudden larch death (SLD) is due to the same pathogen. Some information on the spread of SLD in Europe is included at this site. Just search on larch.

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**Synthetic biology**

A nice overview of the field of synthetic biology. M Stone, Life redesigned to suit the engineering crowd. Microbe 1:566, 12/06. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at forms.asm.org/microbe/index.asp?bid=47155 (HTML) or forms.asm.org/ASM/files/ccLib...120600566.pdf (PDF).

Craig Venter, of genome sequencing fame, plans to make new organisms. One key step along the way was to take a small bacterium, and determine how many of its -- already small -- gene set are really needed. This sets the stage for making artificial genomes -- and then for designing new organisms to do specific tasks. News has been coming fast and furious from the Venter lab; I list some of the news coverage and some of their own press releases below.
Good news stories:
* Venter Institute team builds M. genitalium genome from scratch (Microbe magazine, April 2008). microbemagazine.org/images/st...0408000162.pdf.
* Countdown to a synthetic lifeform (7/11/07). http://www.newscientist.com/article/mg19526114.000.
* Tycoon's team finds fewest number of genes needed for life (6/8/07). http://www.guardian.co.uk/science/20...etics.research.

Press releases from the J Craig Venter Institute:
Since the terms "synthetic" or "artificial" cells are ambiguous and subject to hype, we should be clear what is accomplished here. They made a synthetic genome; that is, they assembled a new genome without using any natural DNA. They then transplanted this into an existing cell, and the new genome "took over". In this case, the synthetic genome is (substantially) identical to a known genome. That is, this work is proof of principle that a new genome can be made and used.

Jay Keasling's work, at UC Berkeley, to develop a cheaper way to make the anti-malarial drug artemisinin is noted in the Malaria section of this page. The work involves making major changes in the metabolic capabilities of the microbes, and is considered synthetic biology.

TGN1412: The clinical trial disaster

March 2006. The news media carried a story of a clinical trial gone terribly wrong. Within an hour or so of receiving a drug, all recipients were seriously ill. What happened? Was there some mix-up -- perhaps the wrong drug used? Was the trial not properly planned or executed? Or was this just "one of those things" -- showing why we start with a small test in humans? So far, the evidence suggests that the last possibility is correct. Everything seems to have been done properly. However, given the severe result in this case, people are questioning whether "properly" was good enough. Was there reason to have been more cautious in this case -- more cautious than just following standard procedure? Perhaps -- and people are debating this. The drug was of a new type, one about which we know little, and about which some are very concerned -- despite the good data from animal tests. It is clear that even a simple precaution, of giving the drug to one patient at a time, and watching them for an hour or two, would have been much better in this case.

As to the nature of the drug, it is hard to describe briefly. But a simple start would be that it was designed to stimulate the immune system -- and the problem is that it did so inappropriately in the human subjects.

The analysis of the incident is still in progress. However, some information is now appearing in the literature, so it seems appropriate to share that here. I do encourage people to be cautious in reaching conclusions at this point.

The New England Journal of Medicine published three articles in the September 7 issue on this topic. In the order listed...
below: one is a perspective (an overview discussion of the topic), one is the main scientific report, and one is a commentary. All are freely available online. For most people, the first item listed below -- the perspective -- may be the best place to start.


There is also a government report on the incident. I might cynically comment that it reads like a government report. Nevertheless, browsing it may be useful, at least as a guide to the questions that get raised. The final report (December 2006) is at [www.dh.gov.uk/en/Publications...ance/DH_063117](http://www.dh.gov.uk/en/Publications...ance/DH_063117). (The link to the preliminary version of the report at the end of the Drazen article listed above is now a dead link.)

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**Vaccines (general)**

A general comment and caution... Vaccines seem to be the subject of many controversies. But be particularly careful with any arguments that appear to make criticism of vaccines in general. The diseases against which we have vaccines are diverse, and the vaccines are diverse. Most real vaccine issues are specific to a particular vaccine or type of vaccine.

This section is mainly for sources about vaccines in general, or sources with info about many vaccines. Also see sections for individual diseases for info about specific vaccines. For example, the sections on Anthrax, Ebola, HIV (AIDS), HPV (Human papillomavirus), Malaria, Measles, Polio, Smallpox, and West Nile Virus contain info on vaccines for those diseases. An item listed under Cancer deals with making personalized vaccines in plants.

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Making a wimpy virus. One approach to making vaccines is to use an attenuated strain of the infectious agent -- one that can induce an immune response, but not cause disease. Scientists at Stony Brook have developed a new approach to making an attenuated virus for use in a vaccine. They re-code the virus so that it uses codons that are poorly translated. They made a few hundred changes in the poliovirus genome, each one making it harder for the genome to function. The result was a virus that seemed to work well as a vaccine strain in mouse tests. A nice feature of this approach is that it would seem to be of general applicability, though of course it needs to be tested in each case. Press release,

https://bio.libretexts.org/Bookshelves/Introductory_and_General_Biology/Supplemental_Modules_(Molecular_Biology)/Case_...

Thimerosal in vaccines. Thimerosal is an organic mercury compound, used as a preservative -- including in vaccines. As with any mercury compound, it is toxic. Of course, the fact that it is toxic is why it is used as a preservative. The intent is that it is more toxic to bacteria and fungi than to humans. The available information suggests that the risks from exposure to mercury from thimerosal are quite small. (Exposures from eating fish and from coal-fired power plants are likely to be larger.) As a precaution -- in the US and Europe -- thimerosal is now rarely used in vaccines intended for children; the common Influenza vaccine is the one prominent exception. Note points of uncertainty, especially regarding children (which is why extra precautions are taken with children), but also note that there is really no data suggesting any problem with thimerosal as used in vaccines.

* This FDA web page is a good overview of the use of thimerosal. It should serve as a good framework for further discussion. http://www.fda.gov/BiologicsBloodVacc...fety/UCM096228.
* A new study shows that ethyl mercury, the form of mercury from thimerosal, is eliminated from the body much faster than methyl mercury. (Methyl mercury is a more common toxic form of mercury, and has been used as a frame of reference for discussing thimerosal in the absence of more direct information.) Children getting many vaccines containing thimerosal (in Argentina) do not show elevated blood level of mercury. A press release from the University of Rochester accompanying publication of this work: Babies Excrete Vaccine-Mercury Quicker than Originally Thought, January 30, 2008. http://www.urmc.rochester.edu/news/s...ex.cfm?id=1848. The paper is M E Pichichero et al, Mercury Levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines. Pediatrics 121:e208-e214, 2/08. It is freely available at http://pediatrics.aappublications.or...e208.abstract.
* I have posted a page showing the chemical structure of thimerosal and some related compounds, including aspirin: thimerosal.
* This topic is also listed under Introductory Chemistry Internet Resources: Thimerosal and Introduction to Organic and Biochemistry Internet Resources: Alcohols, ethers, sulfur compounds.

Growing vaccines in plants. Oral, Plant-Based Vaccine against Shiga Toxin Effective in Mice. A news story about this new approach, in Microbe 1:311, 7/06. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at forms.asm.org/microbe/index.asp?bid=43695.

The article this news story refers to is S X Wen et al, A plant-based oral vaccine to protect against systemic intoxication by Shiga toxin type. PNAS 103:7082, May 2, 2006. Online at http://www.pnas.org/content/103/18/7082.abstract.

National Network for Immunization Information (NNii). An excellent general resource on immunizations. Articles address individual vaccines, and some of the news stories you may hear about them (see Immunization Issues). http://www.immunizationinfo.org/. From their introduction: "The mission of the National Network for Immunization Information (NNii) is to provide the public, health professionals, policy makers, and the media with up-to-date, scientifically valid information related to immunization to help them understand the issues and to make informed decisions. The National Network for Immunization Information (NNii) is an affiliation of the Infectious Diseases Society of
America, the Pediatric Infectious Diseases Society, the American Academy of Pediatrics, the American Nurses Association, the American Academy of Family Physicians, the National Association of Pediatric Nurse Practitioners, the American College of Obstetricians and Gynecologists and the University of Texas Medical Branch.

Financing Vaccines in the 21st Century: Assuring Access and Availability, a report from the Institute of Medicine, August 2003. This report discusses policy issues regarding vaccines. The economics of vaccine production are complex, and in some cases not very good. What role should the government play in assuring vaccine availability even when "ordinary economics" might seem to argue otherwise? www.iom.edu/Reports/2003/FinancingVaccinesIn21stCenturyAssuringAccessAndAvailability.aspx. As with all IOM reports, you can read it online, or purchase it; a short summary is also available online.

The Jordan Report: Accelerated Development of Vaccines, from the NIAID (National Institute of Allergy and Infectious Diseases). 2007. The purpose of the Jordan Report is "to inform policy-makers, researchers and the public about recent accomplishments and future trends in vaccine research." http://www.niaid.nih.gov/topics/hivaidresearch/vaccines/reports/Pages/default.aspx; the report is listed near the top, under "Vaccines Reports and Articles - General Reports".

A report from the Institute of Medicine (IOM)... K Stratton et al, Immunization safety review: Multiple immunizations and immune dysfunction, February 2002. http://www.nap.edu/catalog.php?record_id=10306. A short summary is that they found no evidence of vaccine-induced problems, but they also note areas where the evidence is insufficient to reach a conclusion and further study is needed.

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**West Nile Virus**

The Contra Costa Mosquito & Vector Control District (CCMVCD) has a short flier, which it distributes to all county residents, about West Nile Virus. It is written, of course, for the general public, and contains a range of useful information -- about the disease, the virus, and prevention measures. They also have a website, with much useful information: http://www.ccmvcd.dst.ca.us. See menu bar at left for items about West Nile Virus.

California West Nile Virus (and dead bird surveillance) web site, from the state Department of Health Services: http://westnile.ca.gov.

Yellow Fever Virus-based West Nile vaccine edges others protecting horses. Microbe 3:11, 1/08. A news story on vaccine development. A similar West Nile vaccine for humans is under development. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at: forms.asm.org/microbe/index.asp?bid=55322.

Some scientists now suggest that the West Nile Virus has "settled in" in North America, and probably peaked. That is, they suggest it is likely to stay, but at the generally low levels now observed. Their view is not entirely accepted at this point. A brief summary, West Nile Virus Settled in, but Perhaps No Longer Expanding in the U.S., is in Microbe (Vol 2, p 167, April 2007); it refers to the primary publication. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at: forms.asm.org/microbe/index.asp?bid=49483.