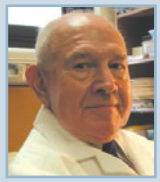
p811 Pest control: The US might ban the EPA from using human tests.

p814 In mitochondria we trust: Scientists say this organelle could control disease.



p816 Blood simple: Aaron Marcus has dedicated his life to platelets research.

Scientists rail against Europe's absence in AIDS research

Europe is squandering scant research funds available for AIDS vaccine research by having them managed by administrators rather than scientists, vaccine researchers charge. In an attempt to gain more control, researchers are lobbying governments for a large, long-term research fund steered by scientists.

Since 2000, Europe has supplied 8% of global funds available for HIV vaccine research, according to a report published in June by international groups including the International AIDS Vaccine Initiative (IAVI) and UNAIDS. The US contributed 81% and the remainder came from other sources, such as the Bill & Melinda Gates Foundation and pharmaceutical companies.

"In terms of HIV vaccine research, Europe is completely absent," says Giuseppe Pantaleo, an immunologist at the University of Lausanne. "Bureaucrats cannot manage complicated scientific programs."

Europe continues to promote fragmented projects, researchers say, while elsewhere, the Global HIV/AIDS Vaccine Enterprise and the US National Institutes of Health (NIH)'s proposed Center for HIV/AIDS Vaccine Immunology are fostering collaborations.

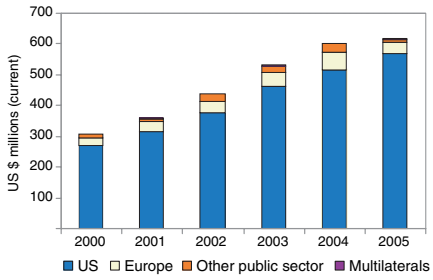
In July, the European Commission invited researchers to apply for a new European network on HIV/AIDS vaccines and microbicides. Officials invited scientists to Brussels and said they would like to fund one pan-European proposal. Octavi Quintana-Trías, director of health at the commission's Directorate General of Research, says the network might have a scientific steering committee, but only in an advisory role.

The announcement hasn't silenced the critics. The €10 million set aside is little more than "seed money," says Peter Liljeström, head of vaccine research at the Swedish Institute for Infectious Disease Control in Stockholm. The NIH's new project, in contrast, could pour up to $315 million over seven years into HIV vaccine research (*Nat. Med.* **11**, 587–588; 2005). What's more, he adds, administrators will once again retain control over the project's direction.

In Europe, 95% of funds for research flows through national channels. The remaining 5% is distributed through the commission's Framework Programmes. Its administrators solicit proposals and, after peer review, fund about 20% of them with grants of up to five years. At present, the commission spends about €25 million per year on AIDS vaccine research carried out by more than 100 research groups and companies.

Although Framework Programmes foster innovation, they are ill equipped to handle long-term, product-oriented vaccine development, says Frans van den Boom, IAVI's European director. A case in point is Eurovacc, a multinational program that from 2000–2005 received €16 million to develop AIDS vaccine candidates.

The program produced four vaccines, but could not get follow-up funding to get them clinically tested. The commission in 2003 instead granted €10 million to the AIDS Vaccine Integrated Project, a research consortium led by Italy's National Health Institute, which aims to develop and test four wholly different vaccines.



Cheap shot: Europe lags far behind the US in funding HIV vaccine research.

"We got five years of funding to develop vaccines. Now that we get to the clinic, the funding stops," says Liljeström, Eurovacc's coordinator. "In my view, that means [the money] has been misspent."

But commission administrators say Eurovacc lost its funding because it couldn't show positive results. "When no results at all are presented or published, proposals have great difficulties competing for new funding," says Quintana-Trías. The commission's long-term commitment to AIDS vaccine research is illustrated by the European & Developing Countries Clinical Trials Partnership (see sidebar), an independent organization it helped launch to boost clinical research into HIV/AIDS, malaria and tuberculosis, Quintana-Trías says.

Eurovacc researchers are meeting with colleagues to discuss a joint proposal for the new pan-European project. But the NIH has already agreed to finance a trial of one Eurovacc product and may fund others. IAVI is also inviting research proposals, to be paid from $10 million set aside by the US Congress to strengthen AIDS vaccine research—not in the US, but in Europe.

Peter Vermij, Amsterdam

Clinical trial scheme off to slow start

The European & Developing Countries Clinical Trials Partnership was intended to make European researchers work together to test promising vaccines and therapies against HIV/AIDS, tuberculosis and malaria. But with the appointment of the partnership's third executive director in as many years, it has yet to fulfill its ambitious premise.

Launched in 2003 by the EU, the partnership was an attempt to build infrastructure for phase 2 and 3 clinical trials in developing countries. With offices in The Hague, Netherlands, and in Cape Town, South Africa, it receives €100 million each year from the European Commission and 15 member states.

But the group's organizational chart resembles the Krebs cycle more than a pyramid, and power struggles between its three management boards and the European Commission marred it from the start. The first executive director was dismissed last September after complaints over the handling of the first set of proposals, and no calls have gone out since. "Basically, nothing has been done," says Giuseppe Pantaleo, an HIV vaccine researcher in Lausanne.

Peter Lange, outgoing chair of the partnership's Assembly, acknowledges the problems, but says he hopes the organization has left its "turbulent past" behind. With a new director, new procedures and a second call for proposals due within weeks, Lange says the partnership will be "restarted." In June, French researcher Odile Leroy took office as the group's new executive director, but the organizational chart remains complex. "It cannot be changed," says Lange. But, "I hope we now have more clearly established who is responsible for what."—*PV*

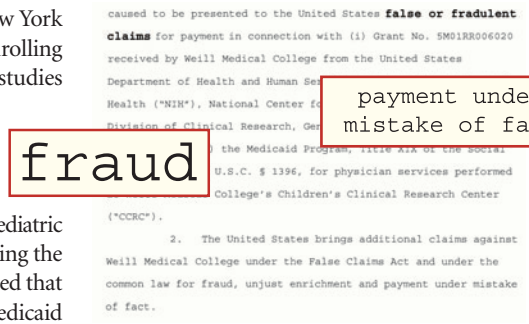
Cornell University scientists face charges of fraud

Researchers at Cornell University in New York are under investigation for allegedly enrolling inappropriate participants in research studies and filing false information on protocols with the US National Institutes of Health (NIH) to maintain government funding for a university research center.

A former researcher at the now-closed pediatric center accused the center's director of using the clinic to treat her adult patients and alleged that clinic staff double-billed the NIH and Medicaid for some patients, among other charges.

In response, the US Department of Justice and the NIH both launched investigations into research activities at the university's Children's Clinical Research Center. After a two-year inquiry, Cornell's Weill Medical College in July agreed to pay the federal government $4.4 million to settle the charges levied by the US Attorney, the Justice Department's litigation arm, in New York City. As part of the settlement, Weill also agreed to cooperate in any subsequent investigations involving research center staff. Cornell did not admit to liability or wrongdoing in the settlement and, in its statement, noted that the case didn't involve "the quality or integrity of the research" and that none of the researchers was the subject of sanctions.

Kyriakie Sarafoglou, then a researcher at the center, first notified the NIH about problems at the center in 2003. Sarafoglou, now an assistant professor at the University of Minnesota, also filed a complaint with the Justice Department. The law allows whistleblowers like Sarafoglou to bring claims on behalf of the government and to share in any financial settlements.



Cornell University has settled a lawsuit charging its researchers with false claims for payment.

In her complaint, Sarafoglou named Weill dean Antonio Gotto, and three administrators and seven physicians at the research center, including former director Maria New, a prominent pediatric endocrinologist. New has since left Cornell and works at the Mount Sinai School of Medicine in New York. Both Cornell and New say her departure was voluntary and New maintains that it was unrelated to the case.

After investigating Sarafoglou's complaint, the US Attorney in July added fraud and other charges, alleging that the center's staff made false statements in grant renewals and annual progress reports and included minimally active or defunct protocols in grant renewal applications. Doctors at the center performed procedures on staff, never enrolled them in protocols and then charged the NIH for the services, according to the charges.

The complaint also says Weill allowed New to "dominate" use of NIH funds for her patients and protocols in violation of NIH guidelines. The NIH, which sponsors about 80 such research sites, limits individual researchers to using no more than 33% of a center's resources.

But when the US Attorney reviewed Weill's database on actual use, it found, for instance, that in 2003 the program director used 80% of inpatient resources and 67% of outpatient resources. "The case is being reviewed by the appropriate authorities and appropriate action will be taken," says NIH spokesperson Don Ralbovsky.

New declined to comment on the case details, citing the possibility of additional legal action. However, she noted that it is not unusual for a single researcher to exceed the guidelines barring them from using more than 33% of a center's resources. But NIH staff say the guidelines are taken "very seriously" and researchers may only exceed them with permission from the agency.

New remains in good standing at the NIH, retaining several grants. In 2003, she was one of eight scientists to be funded through a new Rare Diseases Clinical Research Network. "I have no explanation for this," says Sarafoglou. "It is perplexing."

Tinker Ready, Boston

New York's AIDS 'superstrain' could be two mediocre strains

Months after New York City public health officials announced the discovery of a so-called 'AIDS superbug,' scientists are exploring whether the unusual case is the result of a dual infection, in which a person contracts viral strains from two different people.

Detected in a homosexual man who used methamphetamine, the superbug rapidly progressed to full-blown AIDS and showed resistance to three antiretroviral drugs, features the officials said signaled an "extremely rare" and potentially treacherous strain. Scientists and activists have since criticized the announcement, saying it caused undue alarm before the case was fully understood.

Researchers at New York's Aaron Diamond AIDS Research Center (ADARC) in March reported that the individual had multiple sexual partners in a short period, combined with a dramatic spike in viral load in just two months (*Lancet* 365, 1031–1038; 2005).

But those factors could be the result of a dual infection, says Geoffrey Gottlieb, an infectious disease expert at the University of Washington in Seattle. In a letter to *The Lancet* in June, Gottlieb suggested that the case warranted further investigation to rule out the possibility of dual infection (*Lancet* 365, 1923–1924; 2005). Two other letters in that issue also raised questions about the case.

Dual infections occur in less than 10% of new HIV cases and can result either from 'coinfections,' in which individuals contract separate viral strains before developing immune responses, or 'superinfections,' in which an HIV-positive person gets reinfected years after the first exposure. In both cases, infected individuals rapidly advance to AIDS.

In their response to the letters, ADARC researchers agreed with Gottlieb's suggestion (*Lancet* 365, 1924; 2005). "We cannot rule out the possibility of dual infection," wrote Martin Markowitz, ADARC's clinical director.

There are no commercial tests available to detect dual infections, and the cost of testing could set a research lab back by up to $5,000. Depending on the number of samples available, it could take researchers up to two months to complete the tests. If the New York scientists began testing the superbug after the *Lancet* letters, they might not yet know the results, but "if the researchers delved into [testing] right from February," Gottlieb says, "they'd know the results by now."

The health department and Markowitz remain tight-lipped, declining repeated requests for test details or when results might be expected. For now, Markowitz says, "the epidemiology of this case is being carefully addressed."

If the case turns out not to be the result of a dangerous new strain, it will weaken the accompanying public health warnings about safe sex and drug use, says Richard Jefferys, basic science and vaccine project director of the nonprofit Treatment Action Group. "If there are issues around dual infection," he says, "I hope that they quickly reveal the work that they've done and explain exactly what is going on."

Paroma Basu, Madison

US Senate votes to ban pesticide tests on humans

The US Congress is considering whether to temporarily ban the Environmental Protection Agency (EPA) from using human tests to determine whether a pesticide should be marketed.

Lawmakers on Capitol Hill will soon decide whether to place a one-year moratorium on the conduct and use of studies that expose participants to pesticides. In most cases, trials are conducted by companies seeking to have their pesticides approved by the agency for marketing.

On 29 June, the Republican-controlled US Senate voted 60 to 37 to enact such a moratorium, in an amendment to the spending bill that funds the EPA. The amendment would prohibit the agency, beginning on 1 October, from conducting human exposure tests or using data from tests conducted by third parties in its pesticide risk assessments. An identical amendment was passed by the House in May.

"The moral and ethical issues surrounding these pesticide experiments are overwhelming," California Democratic Senator Barbara Boxer, who introduced the amendment, said after the vote. "The EPA should never have been considering them to begin with."

Companies became interested in human testing seemingly in a bid to circumvent a 1996 law that made it more difficult to use animal tests to meet agency standards for protecting vulnerable populations such as children from pesticide residues. The EPA now considers human testing data on a case-by-case basis, rejecting only experiments deemed scientifically unsound or 'fundamentally unethical' by EPA staff.

The EPA also last year announced that, along with the industry-backed American Chemistry Council, it would sponsor a study that would pay mainly low-income families in return for allowing the observation of their young children's exposure to in-home pesticides. EPA Administrator Stephen Johnson cancelled the study in April after Boxer threatened to hold up his nomination in the Senate.

Supporters of the amendment say the EPA's policy has been putting children at risk, but critics say that the amendment puts potentially important data out of regulators' reach. "Foreclosing on data that could determine the usefulness, the applicability and the toxicity of pesticides is an extremely bad idea," says Henry Miller, a research fellow at the conservative Hoover Institution.

The pesticide industry, represented by the Washington lobbying group CropLife America, adds that it is "troubled by the blatant manipulation of the facts" by Democratic senators. "Sound science and public health protections have affirmed the safety and ethics of human data studies," the group said in its statement.

CropLife also cited a 2004 report by the US National Academy of Sciences as supporting its position. That nuanced report called for an expert board of scientists and bioethicists outside the EPA to assess controversial third-party studies. The EPA has thus far rejected that recommendation in favor of in-house review. A recently leaked document of a proposed EPA rule also does not include establishing an outside board. A final version of the rule is due for publication in 2006.

Tom Williams/Roll Call Photos

Senator Barbara Boxer has proposed a one-year moratorium on using human tests for pesticides.

Lynn Goldman, a physician who led the EPA's pesticides division from 1993–1998, says a moratorium is prudent. "A year's delay in considering these studies while the EPA puts in place some rules of the road is very reasonable," says Goldman, now a professor at the Johns Hopkins University School of Public Health.

Despite its healthy margin of support in the Senate, the Boxer amendment's passage into law is not a given. A competing amendment, sponsored by Republican Senator Conrad Burns, also passed the Senate by a vote of 57 to 40. That version would allow the EPA to use third-party human tests in licensing decisions, within careful constraints. Unlike the Boxer amendment, it does not prohibit the EPA from conducting its own tests. A joint House-Senate committee is expected this summer to determine which version prevails.

Meredith Wadman, Washington D.C.

➤**http://books.nap.edu/catalog/10927.html**

Budget spats put European Research Council in jeopardy

The European Commission on 18 July announced the first scientific council for the European Research Council (ERC) but researchers are increasingly concerned that the agency may not materialize if EU leaders cannot reach an agreement over the budget.

Discussions about the ERC as an agency to fund basic research began in 2002. The ERC was initially seen as functioning independently, but over time it became clear that its funds would best be channeled through the commission. In April, the commission unveiled its Seventh Framework Programme (FP7), which doubled research spending up to €73 billion by 2013, a move widely seen as Europe's attempt to catch up to the US.

The commission, which had initially opposed plans for an ERC, also set aside $13.5 billion to fund the ERC. But disagreements about the overall budget of the FP7 doomed that plan's prospects from the beginning. In early June, Luxembourg, which held the EU presidency until 30 June, proposed a 40% cut in the FP7 budget. The following week, a two-day budget meeting in Brussels collapsed, leaving the both the FP7 and the ERC in limbo.

Achilleas Mitsos, head of the commission's Directorate General of Research, says nothing has yet been finalized. "We have created a lot of expectations among the scientific community and don't want to disappoint them," he told *Nature Medicine*. But Octavi Quintana-Trías, head of health at the Directorate, says that if substantial cuts are imposed, the commission may limit the research topics covered by the ERC, advertise projects once every two or three years instead of every year, or only fund projects that encompass at least three countries in order to minimize expenses.

John Marks, director of science and strategy at the European Science Foundation, says all three possibilities are "undesirable." Restricting research topics "creates the possibilities for political influencing of the choice of topics," he notes. Instead, he says, it might be better to limit grants to scientists who have, for example, completed between two and six years of postdoctoral training.

The Initiative for Science in Europe, established in 2002 and representing more than 50 European research organizations that support the ERC, on 30 June sent an appeal to the commission's top authorities. "[The ERC budget] should quickly become of the order of the budget of the larger national research councils, otherwise its impact would not be felt," it said. "The member states must realize that they cannot be penny-wise and pound-foolish."

It is important for the ERC to be launched, adds Ernst-Ludwig Winnacker, former president of the European Heads of Research Councils—even if only with reduced funds.

Xavier Bosch, Barcelona

Race-based heart drug might stall search for better markers

The landmark approval of BiDil, a drug touted to treat heart failure specifically in blacks, has raised questions about the role of race-specific drugs in medical practice. Hearing early reports that the drug is already being prescribed to people outside the prescription guidelines, experts are calling for a biological marker that can better predict who will respond to the drug.

The US Food and Drug Administration (FDA) in June approved BiDil after studies showed that it improves mortality after heart failure by 43% among blacks; the drug was found to be ineffective in whites (*N. Engl. J. Med.* **351**, 2049–2057; 2004). It is not yet clear why the drug should be more effective in blacks, but one theory holds that BiDil compensates for a nitric oxide deficiency common in this population.

"Being black increases the likelihood of having that physiology, but it's no guarantee," says Jonathan Sackner-Bernstein, a member of the FDA advisory panel that recommended BiDil's approval. "Other people also respond nicely."

Geneticists and ethicists contend that race is a poor indicator of the underlying genetic or biochemical differences among different populations and could be a proxy for social factors (*Nat. Med.* **10**, 1266; 2004).

Sandy Huffaker/KRT

Color blind: The heart drug BiDil is prescribed specifically for blacks, but others are already clamoring for it.

Manuel Worcel, chief medical officer of Massachusetts-based NitroMed, Bidil's manufacturer, says the company is actively looking for genetic, biochemical or physiological markers that can predict who will respond to BiDil. "I believe this will expand the patient population," he says. Once the company identifies reliable markers, NitroMed aims to design a clinical trial that uses the biomarkers, rather than ethnicity, to select participants. Other researchers are meanwhile analyzing genetic data from a subset of participants in the original trial.

The FDA's prescription guidelines for BiDil are relatively broad, specifying the drug can be used for individuals with heart failure who identify themselves as black. But others are already asking their doctors about the drug—and some doctors are complying. "I would prescribe to non-African Americans who are already on standard therapy and not doing well," says Flora Sam, a cardiologist who led a segment of the BiDil trial at the Boston Medical Center. She says she has no financial arrangements with the company.

The drug's label allows for the broadest possible patient base, notes Sackner-Bernstein. "I don't think the product insert gives NitroMed major incentives to do further studies," he says. NitroMed set BiDil's price at $1.80 per pill, adding up to almost $10 per day, nearly double the cost of other heart-failure treatments.

BiDil is made up of two generic drugs, isosorbide dinitrate and hydralazine, an older blood pressure medication that has been associated with lupus, an autoimmune disorder three times more common among black women than white. Researchers conducting the BiDil trial did not routinely test for lupus, but report one case of the disorder among 518 trial participants. NitroMed officials say BiDil's hydralazine component is too small to be of concern, but more lupus cases may arise as the drug is used more frequently and for longer durations, says Sackner-Bernstein.

Emily Singer, Boston

Cholesterol drugs cut cancer risk, studies suggest

Drugs used to lower cholesterol levels may have unexpected benefits: some statins may also reduce the risk of breast and other cancers, according to evidence from six large epidemiological studies.

Statins cut the risk of breast, pancreatic, prostate and lung cancer by about 50%, scientists reported at cancer meetings in April and May. The studies together looked at more than 500,000 individuals.

Introduced in the 1980s to lower the level of LDL, or 'bad,' cholesterol, statins are the best-selling drugs in the US, with more than 11 million consumers spending more than $12.5 billion each year. But the cancer prevention aspect has come somewhat as a surprise.

"When the drugs were developed, there was some evidence that high doses caused liver cancer in rodents, so studies were done to determine whether they were carcinogenic," says Jim Dimitroulakos, senior scientist at the Centre for Cancer Therapeutics at the Ottawa Hospital Research Institute.

Instead, most evidence seems to indicate that the drugs reduce cancer risk. The most recent results build on previous epidemiological studies and show that people taking statins can cut their risk of pancreatic cancer by 59%, prostate cancer by 50% and colorectal cancer by 49% (*N. Engl. J. Med.* 352, 2182–2192; 2005). Some studies show that in comparison with other classes of cholesterol-lowering drugs, such as fibrins and bile acid–binding resins, statins may be superior in lowering cancer risk (*Arch. Int. Med.* 160, 2363–2368; 2000).

Evidence of statins' preventive power is mounting particularly with breast cancer. In a study of 2,000 women in Seattle, those taking statins for five years on average had a 30% lower risk of breast cancer (*Cancer* 100, 2308–2316; 2004). Lead investigator Denise Boudreau is conducting a prospective study of 84,000 women to examine the link between statins and cancers of the breast, prostate and reproductive organs over 14 years; results are expected in 2006. Data from analysis of statin use among 150,000 women in the Women's Health Initiative are expected later this year.

Statins' effect on cancer risk is plausible because the drugs inhibit many molecules necessary for crucial functions such as membrane integrity, cell signaling, protein synthesis and cell cycle progression, says Boudreau. For instance, cerivastatin has been shown to inhibit signaling pathways associated with metastasis in a breast cancer cell line and lovastatin inhibits mammary tumor formation and metastasis in mice (*Carcinogenesis* 22, 1139–1148; 2001; *Breast Cancer Res. Treat.* 50, 83–93; 1998). In cancer cells, statins have been shown to arrest growth, prevent invasion of distant sites, sensitize cells to the damaging effects of radiation and trigger cell death. Statins' effect might also be linked to cholesterol production in hormone-sensitive cancers, some researchers suggest.

If further studies confirm these results, the public health implications are significant. But randomized placebo-controlled studies must first clarify the exact nature of the effect, says Boudreau. "We also need to understand more about the risks associated with long-term use of statins."

Vicki Brower, New York

Small boost proposed for NIH budget

The US Senate appropriations committee in July approved a $1.05 billion increase to the 2006 budget of the National Institutes of Health (NIH). The raise, which is $905 million more than the amount proposed by President Bush, would bring the total NIH budget to $29.4 billion, 3.7% more than the 2005 budget.

Research advocacy groups applaud the increase but are concerned the bill won't pass. The US House of Representatives in June approved a budget increase of 0.5%, similar to the President's request. Congress will need to reconcile the two bills later this year.

The House health subcommittee also proposed a bill that would strengthen the NIH director's ability to move money among the various research institutes. The bill aims to address concerns that the NIH's diffuse structure leads to redundant research at different institutes. The bill also includes a possible 5% cap on NIH's annual budget between 2007 and 2009, which has drawn concern from research lobbyists.

Meanwhile, the NIH's National Institute of Allergy and Infectious Diseases in July announced that its new Center for HIV/AIDS Vaccine Immunology, a consortium to develop and test AIDS vaccines (*Nat. Med.* **11**, 587–588; 2005), would be led by Barton Haynes of Duke University. The virtual center is slated to receive $15 million in its first year, and up to $300 million over the following six years.

Over objections, journal publishes bioterror paper

Overruling objections from government health officials, the *Proceedings of the National Academy of Sciences* published a paper in its 12 July issue detailing how terrorists could poison the US milk supply.

In an accompanying editorial, Bruce Alberts, president of the US National Academy of Sciences, advocated publishing analysis of potential terror threats—provided the analysis uses information that is already in the public domain—because such reports drive prevention efforts.

The US Department of Health and Human Services had requested that the research, originally scheduled for publication in May, not be released, saying the paper could act as a roadmap for terrorists. After extensive review and discussions with government representatives, the academy decided that the information in the paper was already available online and published it without major changes. The research highlighted vulnerabilities in the US dairy system and estimated that more than 500,000 people could be poisoned, half of those lethally, if a milk truck were to be laced with 10 grams of botulinum toxin.

Alberts suggested the paper be used as a case study for the newly formed National Science Advisory Board for Biosecurity (*Nat. Med.* 10, 319; 2004), which was created to set guidelines for research that has potential negative uses.

Deadly parasites share genetic core

Scientists have unlocked the genetic secrets of three parasites that kill millions in the world's poorest countries. Researchers say the newly sequenced genomes will be crucial in developing vaccines for the deadly infections.

CDC

The parasite *Trypanosoma brucei* causes African sleeping sickness and infects 300,000–500,000 people a year in Africa. Chagas disease, spread through the infected feces of an insect—sometimes called the 'kissing bug' (pictured right) for its habit of biting near a person's mouth—is caused by *T. cruzi*. The disease, which kills 50,000 people per year and infects an estimated 18 million in Latin America, can lead to heart failure. *Leishmania major* is the culprit behind leishmaniasis, characterized by disfiguring skin lesions, and affects as many as 300 million people in 88 countries. A large portion of the genome sequencing was conducted in Africa and South America, regions hit hardest by these diseases.

Although the three parasites cause different diseases, they share surprisingly similar genes. Scientists say this common genetic core could provide targets for new drugs to fight all three infections (*Science* **309**, 404–442; 2005). A comparative analysis of the genomes sheds light on how they infect people and trigger disease, and why they are carried by different insects. For example, *T. cruzi* has a novel set of 1,300 genes that may allow the parasite to evade the human immune system.

WHO's AIDS drug goal unlikely to be met

Access to AIDS drugs in the world's poorest countries is far short of the World Health Organization (WHO)'s goal to treat 3 million people by 2005, according to a report released in June.

Since June 2004, the number of people on antiretroviral therapy has doubled to 1 million worldwide and tripled in sub-Saharan Africa and Asia, the two regions hit hardest by HIV/AIDS. Despite this progress, the report estimates that only 11% of those in sub-Saharan Africa and 14% of those in Asia have access to AIDS drugs. In India, which has more than 5 million cases of HIV/AIDS, the drugs are available to fewer than 10% of those who need them.

The WHO says a shortage of trained health workers, insufficient technical support and lack of reliable funds from donor countries are making it difficult to meet the '3 by 5' goal set in 2003. Donors have so far delivered only $9 billion of the $27 billion they committed to HIV/AIDS treatment and prevention efforts over the next three years.

Follow-up studies debunk early medical research

Nearly one-third of prominent medical studies fail to hold up to further research, according to a report released in July.

The study analyzed 45 of the most commonly cited research articles published in 20 journals between 1990 and 2003, including all clinical research in the Journal of the *American Medical Association, The New England Journal of Medicine* and *Lancet*. Researchers found that subsequent research contradicted seven of the studies and tempered the conclusions of seven others. The follow-up studies were usually larger or better designed, the authors note.

For example, studies refuted earlier claims that vitamin E prevents heart attacks, that vitamin A cuts breast cancer risk or that nitric oxide improves survival in people with respiratory failure. The researchers reported that nonrandomized trials were most likely to be altered by further research. In their analysis, the researchers found that 5 of 6 nonrandomized trials, compared with 9 of 39 randomized trials, fell into this category.

News briefs written by Emily Singer

Deity of disease

A small group of scientists argues that one organelle is the silent cause of the body's decline into disease. Charlotte Schubert surveys the realm of 'mitochondriacs'.

"I'm a believer," says Richard Weindruch. Soft spoken though he is, Weindruch has spent years upholding the object of his faith, convinced that it holds the key to aging and mortality.

He's not the only one.

Fellow devotee Doug Wallace has gathered a reputation for his tendency to expound on his faith to anyone who will listen. And Italian Claudio Franceschi's ideas have led him through the towns of Italy and the hills of Sardinia in search of those who have lived past 100 years of age.

The object of all this devotion is tiny—microscopic, in fact. Thousands of copies of it, each pulsing with energy, are crammed into every cell in the human body.

Weindruch, Wallace and a growing number of others are 'mitochondriacs'—a term playfully coined by Weindruch—who believe that these tiny organelles might wield control over the body's decline into ailments as diverse as cancer, diabetes and Alzheimer disease.

The biggest risk factor for most of these diseases is age, so understanding how the body ages might unlock the disease process. Mitochondriacs, led in large part by Wallace, have argued that the key to aging is the decline of and damage to mitochondria over time.

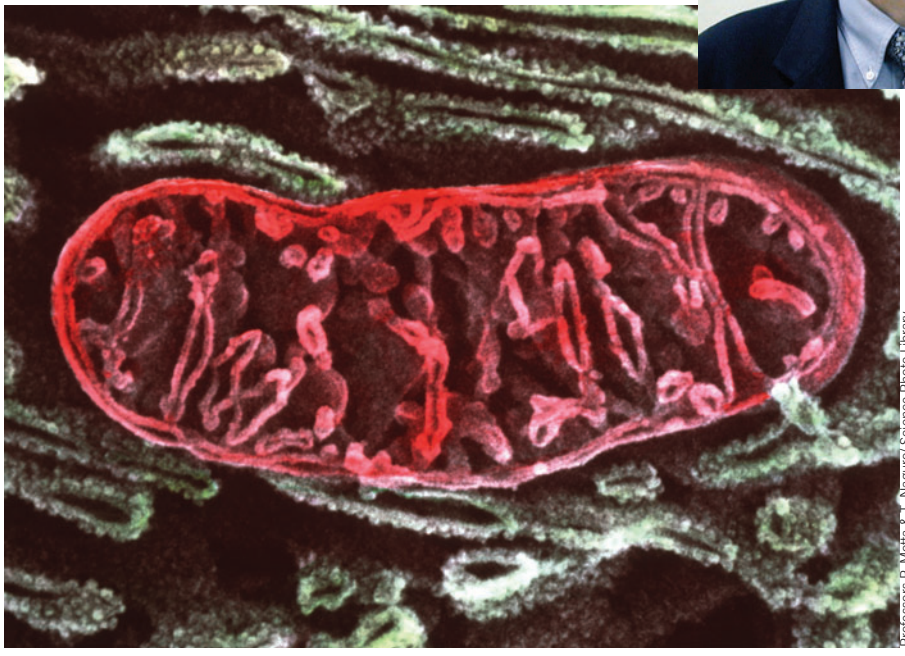
Not surprisingly, they have encountered some resistance.

"[Wallace] is not a nutcase because in a sense he is probably right," says Mark Cookson, a neuroscientist at the US National Institutes of Health, and perhaps the most generous of Wallace's critics. "I don't think there are many people who would go around saying there is no way mitochondria could contribute to these diseases," Cookson says. "But is he overstating what he is saying? That is a subtle point."

Skeptics like Cookson have thus far maintained a distance from the mitochondriacs, saying the data are murky and often contradictory. But in recent months, solid research from various labs showing that mice age rapidly when their mitochondria are damaged and that protecting mitochondria can extend lifespan has resuscitated the topic.

"It's been one of those fields where it came off the boiler and now it's looking more interesting again," says Cookson.

Courtesy: UC Irvine



Professors P. Motta & T. Naguro/ Science Photo Library

Powerhouse peril: Mitochondria are the source of the body's energy. Doug Wallace (right) says biologists underestimate the organelles' role in causing age-related diseases.

Radical theories

Everything in the world, if you ask Wallace, boils down to structure and energy, but biomedical researchers have so far overlooked the importance of energy. In the body, mitochondria are the generators, pumping out millions of ATP molecules. Like most energy production schemes, this too results in hazardous waste: free radicals.

During energy production, electrons in the mitochondria's inner membrane flow down the electron transport chain. But this ordered process can misfire, diverting electrons off course—and directly onto oxygen molecules. The result is reactive oxygen species, which act like molecular lightning, frying almost every molecule they touch.

A popular theory in aging research, first proposed in 1956 by Denham Harman, holds that damage to cellular components by free radicals drives the aging process. Some researchers, including Wallace, who is a professor at the University of California in Irvine, say reactive oxygen species also drive damage to mitochondria, which prompts them to spew out more free radicals in a vicious cycle[1].

The end result is activation of another key mitochondrial function—cell death, or apoptosis. Dead and dying cells in turn propel the body's decline.

Wallace's ideas emerged after he began studying individuals with hereditary mitochondrial disorders in the 1980s. Those individuals often also had symptoms of diabetes and heart disease, and illness took hold gradually, as it does during normal aging.

Wallace's analyses showed that the severity of such diseases correlates with two factors: the proportion of mutant mitochondria in each cell—and age. "I was convinced that mitochondrial DNA damage was the aging clock," he says.

In line with that notion, numerous groups have found that damage to mitochondrial DNA, lipids and proteins ramps up during normal aging. More recently, researchers have reported that mitochondrial damage is also accelerated in many chronic diseases[1,2]. But some of those studies are disputed.

Last year, for instance, Wallace's group reported that that those with Alzheimer disease accumulate a particularly high level of mutations in regions of their mitochondrial DNA[3]. But Douglass Turnbull, a neurology researcher at the University of Newcastle upon Tyne, says he has examined those same regions and found no evidence of damage[4].

"The literature is very confusing," says Turnbull. "To an extent we are both wrong because we haven't [got] enough numbers."

Root of all illness

Even in labs that don't study mitochondria, scientists investigating diabetes and neurodegenerative disorders such as Alzheimer and Parkinson diseases are finding unexpected evidence of the organelle's importance.

Gerald Shulman, an expert on type 2 diabetes at Yale University, has found that mitochondrial ATP production wanes about 40% with age. Aging is also associated with an increase in fat accumulation in muscle and with insulin resistance, key events in diabetes[5]. Similar events occur even in the lean, healthy offspring of diabetics.

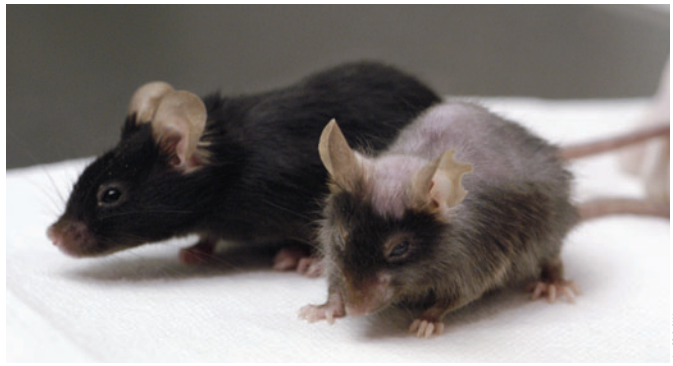
Other hints of the role of mitochondria —that a protein that regulates mitochondrial growth is central to diabetes, for instance—have also emerged.

In neurodegenerative disorders, recent data add to a line of curious findings. For instance, one study suggests that *PINK1*, a gene underlying Parkinson disease, localizes to mitochondria and has a protective function. Other researchers report that amyloid-β, a protein central to Alzheimer disease, is found in mitochondria, where it might suppress formation of free radicals.

Cancer and atherosclerosis researchers might also join the ranks of the mitochondriacs. For instance, several cancers are associated with an abundance of mitochondrial DNA mutations, and aberrant metabolic processes affecting mitochondria are a hallmark of tumors.

In his studies, Franceschi, an immunologist at the University of Bologna, has noticed that many centenarians are free of the conditions most often linked to mitochondrial damage—such as diabetes. He is investigating whether centenarians with a mitochondrial variant that confers longevity are protected against free radical damage. He has also helped enlist researchers worldwide for large-scale projects on mitochondrial DNA, health and lifespan.

Like most other mitochondriacs, Franceschi is paying close attention to how other aspects of aging might be integrated with the organelle. For instance, caloric restriction can extend lifespan in animals, reduces insulin resistance and, according to studies by Weindruch and others, also lessens free radical damage.



Jeff Miller

Dying young: Mice with defects in key mitochondrial enzyme age rapidly and have gray hair and weak bones (right) compared with normal mice (left).

Age-old questions

The fundamental question in the field is the classic chicken-or-egg conundrum: does mitochondrial damage drive disease or does the disease cause the damage?

Over the past few months, two research groups have published studies that attempt to resolve that question[6,7]. Both groups created mice with defects in a mitochondrial DNA polymerase that lead to mutations in mitochondrial DNA.

In each case, the results were dramatic: the mice appeared to age rapidly, showing symptoms of old age at between six and nine months, young adulthood in mouse terms. These mice died young, at less than half the age of their wild-type counterparts, with afflictions ranging from weak bones to gray hair.

The second study, by a group that included Weindruch at the University of Wisconsin in Madison, found that in addition to the aging phenotype, the mice also had high levels of apoptosis. The researchers found no evidence of free radical damage in the animals, but Wallace maintains that the results are consistent with the theory that reactive oxygen species can drive mitochondrial DNA damage and, ultimately, cell death.

He and his colleagues have some evidence to support this theory. When the researchers created mice with mitochondria that overexpress catalase, an enzyme that sucks up free radicals, those mice lived about 20% longer and were protected from heart disease[8].

These new studies are beginning to impress some skeptics. Referring to Wallace's catalase study, "that was good," says Raj Sohal, an aging expert at the University of Southern California. Still, he has reservations about the theory overall. For instance, he says, nobody has been able to connect an increase in oxidative stress with mitochondrial DNA mutations.

If the free radical hypothesis is true, any agent that gets rid of the radicals ought to extend life and stave off illness. But antioxidants such as vitamin E and C, touted to counter free radicals, have not dramatically extended lifespan or protected from disease in clinical trials, puncturing the free radical theory of aging.

The key is to design drugs that can mop up more free radicals, says Simon Melov of the Buck Institute of Age Research in California. Researchers are developing small molecules that mimic the effects of powerful antioxidants such as superoxide dismutase and catalase.

The compounds have already been shown to extend lifespan in invertebrates and counteract certain diseases in small animals, but have not yet been tested in clinical trials. Proteome Systems, based in Sydney, Australia, is planning to develop drugs for individuals with Friedreich ataxia, a rare inherited mitochondrial disorder associated with high levels of free radical damage.

If the trials pan out, and combined with basic data linking mitochondria to age-related disease, the organelle's importance in disease and aging is likely to attract many more believers, says Weindruch: "The numbers are much higher now."

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Aaron Marcus

It's fair to say that Aaron Marcus has science in his blood. After more than 50 years of studying platelets, he shows no signs of slowing down.

The Veterans Affairs Medical Center on New York's East Side looms over a vast stretch of high-rises built to ease a housing crunch after World War II. Families began moving in during the summer of 1947, and by the time the complexes filled, they boasted the largest concentration of US veterans.

Aaron Marcus arrived here in 1958 to run the hospital's fledgling hematology-oncology division. Along with a faculty appointment at Cornell University, this center has served as his sole professional base.

Others might have traded on their success to move up, but Marcus insists there is nothing he would change. Among Marcus' many mottos: "As long as you're getting results, you can work in a trash can."

The drab, dimly lit hospital draws periodic predictions that it will be closed due to funding cutbacks, and the corridors of glazed brick and powder-blue paint give it the atmosphere of an old bus terminal.

"I still remember that creepy lab up on the thirteenth floor—it was creepy then, too," says Charles Serhan, who trained with Marcus as a fellow in the early 1980s. "[Marcus] was very clever about that, though, because all that glitters is not gold," says Serhan, director of The Center for Experimental Therapeutics at Brigham and Women's Hospital in Boston. "What seems to be like isolation gave him a sanctuary to create his Japanese garden of science."

As an 18-year-old pharmacist's mate in the US Navy in 1944, Marcus cared every day for 20 patients—casualties of the Pacific Island invasions of World War II—at an abandoned desert base near Palm Springs. He later pursued a career in clinical research, but remaining close to veterans has been an important factor in his lengthy tenure at the center.

"My family, especially my grandmother, always ridiculed me," says Marcus, who moves his jaw up and down, as if chewing a roll, in between sentences. "She thought, coming from Russia, that working for the government was the lowest form of work you could do. But I didn't mind it as long as each year was an improvement over the last."

Although his surroundings have remained inert, Marcus has managed to keep his work fluid. He is noted for classifying the molecular composition of platelets and for describing their role in the formation of blood clots (*J. Clin. Invest.* **41**, 2198–2212; 1962). While studying the antithrombotic effect of aspirin in the 1970s, he discovered that platelets communicate with red and white blood cells to synthesize inflammatory agents and other metabolic products. Regulating these interactions, Marcus says, can block the formation of clots on atherosclerotic plaques in the blood vessels, a key antecedent of heart attack and stroke.

The US National Heart, Lung and Blood Institute recognized Marcus' results in 2004, awarding him a 10-year, $2.8 million Method to Extend Research in Time grant to pursue a new regimen to augment traditional aspirin therapy as the next generation of antithrombotic agents. "You have to have what I call a 'macrocosmic view,'" Marcus says. "If you get a result with an experiment, whether in a test tube or in a patient, the first question I ask myself is, 'how will this look three to five years from now?'"

Marcus' associates describe him as a purist—a meticulous investigator who never allows his zest for science to be diluted by entrepreneurial demands. "Aaron doesn't have a big lab—almost all of his work, he does with his own hands," says Robert Schwartz, a deputy editor at the *New England Journal of Medicine* who met Marcus in 1954 when they were both training at Montefiore Medical Center. "He's not like those investigators with $50 million grants and fellows whose last names he doesn't even know."

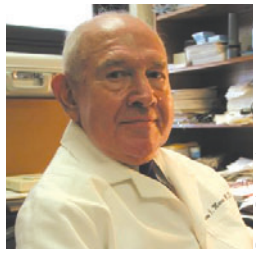
Drawing a modest paycheck and scant support quickly taught Marcus the value of grants. He received his first US National Institutes of Health (NIH) award in 1954 and, with the exception of a period in the 1960s, has enjoyed 50 years of virtually uninterrupted funding from the agency. His current grant has been renewed for 26 years, and according to Marcus—though officials say it's impossible to verify—he is the longest-running beneficiary of NIH support.

The rigors of fluctuating funds have taught Marcus about ingenuity. When a request to buy expensive gas chromatography equipment was rejected in the 1960s, Marcus procured the hulking machine one part at a time, debited his supply budget and assembled the unit from scratch. "We've done that over and over again," he says. "That's how I've survived."

Now widely accepted, Marcus' early description of transcellular metabolism was initially rejected for publication by a top-ranked journal. Not wishing to squander time on another peer review, Marcus settled for a lower journal and moved on.

"Marcus has always been able to find a way to sidestep the obstacles and stay focused," says Ralph Nachman, Cornell's chairman of medicine, who has worked with Marcus for more than 40 years. "He's a bit of a throwback to the old investigator, working on his own, and he sticks with it in spite of all the hullabaloo."

"Any morning I get up and I have nothing more to say—that's when I won't go to work anymore."



Bruce Diamond

There were, to be sure, projects that didn't pan out. After years of work in the late 1970s, Marcus believed he was on the verge of isolating the receptor for serotonin. But an insurmountable snag in his methodology forced him to admit defeat. "I made the resolution then that I would only work in areas where one experiment would lead to another," he says.

Marcus also has devoted considerable energy to nurturing protégés, trying to act as the proper mentor he says he never had. He speaks fervently about recruiting and training young doctors to do translational research.

Marcus's current project is a recombinant form of the protein CD39, which he says controls blood fluidity (*J. Clin. Invest.* **99**, 1351–1360; 1997). The protein, injected to supplement the body's supply, has been shown to inhibit clot formation in small animals, Marcus says, and could treat heart attack and stroke. He plans to test it in a baboon model of stroke before launching human trials.

The project consumes the bulk of his 16-hour workdays, but Marcus keeps taking on more work. He says he hopes to raise seed money to develop a center of excellence in vascular biology, at the Veterans Affairs hospital or at Cornell, that would assemble cardiologists, neurologists and vascular biologists to conduct research through interdisciplinary collaboration.

Marcus turns 80 in November, but becomes visibly irritated at any suggestion of tapering his workload. He says he is frequently asked when he plans to retire. "I always tell them the same thing," he says. "Any morning I get up and I have nothing more to say—that's when I won't go to work anymore."

Bruce Diamond, New York