

[The Human Organism as an Experimental Model](#)

[A review of the Baltimore Case](#)

[The Science of Apartment Hunting](#)

[Announcements insert and more...](#)

[BBS Bulletin Previous Issues](#)

[BBS Calendar](#)

[BBS Bulletin Staff](#)

[BBS Home Page](#)

Volume II, Number 11 - June 1999

Something for Everyone: The Human Organism as an Experimental Model

Dennis A. Ausiello, M.D.

As we reflect on the twentieth century, we find that some of the most exciting accomplishments come from biomedical research, with new knowledge accumulating at astonishing speeds. The reductionist approach to experimental biology has unraveled the most fundamental molecular mechanisms involved in normal cellular processes and in the pathophysiology of disease. Aided by models ranging from amoeba to zebrafish, and armed with the tools and language of cell biology and molecular genetics, biology is rapidly evolving from a descriptive science to the most complex expression of chemistry, physics, and mathematics. The genomic fingerprinting of a large number of organisms, will culminate soon with the complete description of the human genome. What will be the nature of biomedical scientific inquiry in the twenty-first century?

The mission to further the understanding of the human organism has addressed questions far removed from that organism. By necessity, the complexity and uncertainty that the human organism brings to any experimental environment have largely been avoided during the generation of new knowledge concerning biological processes. As we rapidly pass into the era of functional genomics, we are realizing the possibility of understanding and potentially intervening at the subtlest molecular sites of biological activity, as small as a single polymorphism in the

human genome. Thus, we can now approach the human organism as a legitimate, even necessary, experimental model. The ability to stratify phenotypes with genotypes and to correlate complex disease states with the subtle expression of polymorphic differences in normal genes, will rapidly bring scientific inquiry not just from the bench to the bedside, but also from the bedside back to the bench.

One of the extraordinary transitions in fundamental biological research over the last decade has been the seamlessness of the discussions relating the most fundamental discoveries to human disease states. These days, one is just as likely to hear a discussion of the pathophysiology of cancer, diabetes, or obesity during a thesis defense as on ward rounds. Diseases such as familial hypercholesterolemia, nephrogenic diabetes insipidus and cystic fibrosis are among many whose pathology has been directly related to mutations in genes that are involved in fundamental cellular processes such as transmembrane ion and water transport, and receptor-mediated endocytosis. Such discoveries have led to fruitful collaboration and cooperation among physicians and basic scientists who now share a common and attainable goal for improvement of the human condition.

What does this mean for the nature of scientific investigation in the next decade? What changes are required in the educational process to prepare physicians and basic scientists to undertake this research? Teams of experimentalists, including caregivers and scientists irrespective of the nature of their degree, work collectively to define the nature of human disease and to provide new diagnostic or therapeutic interventions. Although no one today would look at cancer as a single disease with a single causation, many other common disorders - such as hypertension, diabetes, and obesity - are still frequently viewed as single diseases, each with a common etiology. This perception rapidly changes as investigative teams stratify phenotypes of these diseases with genotypes, leading to new and selective diagnostic and therapeutic interventions. A hypothetical subset of patients with hypertension who only develop abnormal levels of blood pressure early in the morning might be found to have a

unique set of polymorphisms in angiotensin-converting enzyme genes and other modulatory genes that account for this unique phenotype. A number of surrogate markers will be developed at the biochemical level, which will allow for boutique drug design to target this subset of affected patients. A similar stratification of phenotypes for Type II diabetes might confirm the hypothesis that this is a complex, polygenic disease state with a variety of subtle, but interactive, changes in primary and modulatory genes in the metabolic cascade involved in glucose and lipid homeostasis.

As these research teams evolve, we need to accept the greater complexity and uncertainty which differ significantly from the paradigm of reductionist investigation that has brought us to this point of biomedical knowledge. The use of classical end points in experimental design as fundamental as life or death, or the sacrifice of an organism at particular time periods to look at tissue, organ, or developmental abnormalities will be replaced by the development of surrogate markers. Minimally invasive diagnostic technology, including functional magnetic resonance imaging, new optical techniques, robotics and microelectronics, bring forth an era where device-design for sophisticated physiological monitoring and therapeutic intervention will be as important a component of our future experimental needs, working with human organisms, as was the development of complex tools in cellular and molecular biology in studies of other model organisms over the last several decades.

An important third member of many research teams will be the ever-growing partnership with industry. Industry, of course, has a long history of investment in and collaboration with scientific investigators, both in the basic sciences and in academic health centers. As we look to the next century, these somewhat distant relationships will flourish in a more intimate manner, as the solution of complex problems of human pathophysiology will clearly require the effective integration of investigatory teams from academic health centers, basic science departments, and industry.

This brave new world of human experimentation at our doorsteps warrants a significant change in our educational programs. We have been remiss in developing, among our physician-scientists, a cadre of clinical investigators who appreciate the enormous wealth of fundamental biologic and genetic information and annotate it in a translational model relevant to the health of the human organism. Training, certainly as early as entrance into medical school, will begin to focus the students¹ thoughts on fundamental science as applied to the complexity of the human organism, as experimental questions are designed and addressed. Equally mindful of the team concept expressed above, more and more members of our graduate educational programs leading to the PhD degree will require, indeed demand, access to training in human biology and in human investigation. Just as the partnerships have developed for experimental studies, partnerships among academic health centers, graduate departments, and industry will develop around educational programs that are specifically designed with the concept that the human organism will be the major experimental model of the future. Significant new obligations will be required of the investigatory teams responsible for these activities, and educators and mentors will need to provide the proper social, ethical, and economic foundation to our experimentation which will make our studies morally as well as experimentally valid.

The results of this new collective approach to human investigation should lead to enormous benefits. We finally reap the rewards of a common molecular language spoken by all scientists, and integrated into the most complex of organisms, the human organism. We are indeed entering the most exciting of all times for biology when scientific achievement will truly be measured by the change in the quality of the human condition.

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[The Human Organism as an Experimental Model](#)

[A review of the Baltimore Case](#)

[The Science of Apartment Hunting](#)

[Announcements insert and more...](#)

[BBS Bulletin Previous Issues](#)

[BBS Calendar](#)

[BBS Bulletin Staff](#)

[BBS Home Page](#)

Upcoming BBS Events

BBS Barbecue

Wednesday, July 14th, 4:30 - 7:00PM-HMS Quad,
Longwood Avenue

Recent Publications by BBS Students

Shannon K.B., (G5), Li R. 1999. The multiple roles of cyk1p in the assembly and function of the actomyosin ring in budding yeast. *Mol Biol Cell*. Feb;10(2):283-96.

Rodriguez, C.R. (G5)*, Takagi, T.,* Cho, E.J. and Buratowski, S. 1999. A *Saccharomyces cerevisiae* RNA 5 [prime]-triphosphatase related to mRNA capping enzyme. *Nucleic Acids Research*. May 15, 27(10):2181-2188. (* denotes co-authorship)

Boxem, M., Srinivasan, D.G. (G3), van den Heuvel, S. 1999. The *Caenorhabditis elegans* gene ncc-1 encodes a cdc2-related kinase required for M phase in meiotic and mitotic cell divisions, but not for S phase. *Development*. 126:2227-2239.

Winter, D. (G5), Lechler, T. (G3), and Li, R. 1999. Activation of the yeast Arp2/3 complex by Bee1p, a WASP family protein. *Curr. Biol*. 9:501-504.

Smith, D.M. (G4) and Tabin, C.J. 1999. Chick Barx2b, a marker for myogenic cells also expressed in branchial arches and neural structures. *Mechanisms of Development*.

80:203-206.

Carmeliet, P., Ng, Y.-S. (G7), Nuyens, D., Theilmeier, G., Brusselmans, K., Cornelissen, I., Ehler, E., Kakker, V.V., Stalmans, I., Mattot, V., Perriard, J.C., Dwerchin, M., Flameng, W., Nagy, A., Lupu, F., Moons, L., Collen, D., D'Amore, P.A., and Shima, D.T. 1999. Impaired myocardial angiogenesis and ischemic cardiomyopathy in mice lacking the vascular endothelial growth factor isoforms VEgf 164 and VEGF 188. *Nature Medicine*. 5:495-502.

Hirschi, K.K., Rohovsky, S.A., Beck, L.H. (G6), Smith, S.R., D'Amore, P.A. 1999. Endothelial cells modulate the proliferation of mural cell precursors via platelet-derived growth factor-BB and heterotypic cell contact. *Circ Res* 84:298-305.

Rohatgi, R. (G3), Ma, L. (G7), Miki, H., Lopez, M., Kirchhausen, T., Takenawa, T., and Kirschner, M.W. 1999. The interaction between N-WASP and the Arp2/3 complex links Cdc42-dependent signals to actin assembly. *Cell* 97:221-231.

Schechter, L.M. (G6), Damrauer, S.M., and Lee, C.A. 1999. Two AraC/XylS family members can independently counteract the effect of repressing sequences upstream of the *hilA* promoter. *Molecular Microbiology* May, 32(3):629-642.

Congratulations are in order!

Kristen Kwan (G3) and Charlie Murtaugh (G5) were recently engaged. Jay Harper (G6) and Melanie Stock were recently engaged. Margie Oettinger and Kevin Struhl were blessed with the birth of Isaac Oettinger Struhl, born on March 27, 1999 at 7 lbs 8 oz.

BBS Awards

The BBS Awards Committee solicits your nominations for: BBS Service Award, BBS Award for Teaching, BBS Award for Mentoring. Here is a chance to let your favorite BBS

workers- faculty, students and staff- know that you appreciate their efforts that go far beyond the call of duty. Do you know someone who does a lot of behind the scenes work for BBS? What about all those people who plan the retreat so you can just show up and enjoy it? Was there a teacher that inspired your interest in a certain field? Someone who forced you to think about a problem in a different way? Is your advisor the best around, helpful in providing training and feedback? Maybe there's a faculty member other than your advisor that you go to for support and guidance? Here is a chance for us to recognize outstanding members of our graduate program. To submit a nomination go to the BBS home page: <http://www.hms.harvard.edu/dms/bbs/> and follow the link to the BBS Awards.

The following information has been collected from the ranks of BBS students & faculty.

Be sure to have your news announced in upcoming issues! (email cgibilisco@hms.harvard.edu)

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[The Human Organism as an Experimental Model](#)

[A review of the Baltimore Case](#)

[The Science of Apartment Hunting](#)

[Announcements insert and more...](#)

[BBS Bulletin Previous Issues](#)

[BBS Calendar](#)

[BBS Bulletin Staff](#)

[BBS Home Page](#)

The Science of Apartment Hunting by Roy Auty(G1)

Apparently, scientific journals suffer a downturn in submissions during summer months. I used to think this reflected a myriad of trips, conferences and workshops. However, these are not the only drains on a scientist's time and resources during the summer. May to September represents peak moving season for graduate students. In their quest for the perfect property, many graduate students move a number of times. To help avoid expensive mistakes, members of the BBS program created a guide for incoming students. Prices and comments from a survey of current students have been adapted and reprinted below:

Brookline - Brookline Village is an attractive neighborhood with a mixture of apartments and pretty homes. The walk to Longwood takes 15 - 20 minutes while the bus or T halves that. There is a supermarket 10 minutes walk away along Harvard Street towards Coolidge Corner, another popular neighborhood. Coolidge Corner boasts a number of restaurants, boutiques, a³classic² cinema and (at least) three identical pharmacies. Downtown Boston is 20 minutes by T and Harvard Square is 20 minutes by bus (#66) and 40 minutes by T. Prices in both neighborhoods are high with 1 bedroom apartments fetching \$950 - \$1100, 2 bedrooms for \$1450, 3 bedrooms for \$1400 - \$1700, 4 bedrooms for \$1800 - \$2200.

Brighton/Allston - Across the river from Cambridge near Boston College, it is renowned for a high concentration of students (in fact the overall population density is greater than that of Manhattan). The medical area is 30 minutes by foot or T. The #65 and #66 take about 20 minutes. Rent is considerably cheaper and parking is possible. Prices are modest¹ -- 1 bedroom apartments go for \$800 - \$950, 2 bedrooms for \$800 - \$1300, 3 and 4 bedrooms for \$1300 up.

Longwood/Brigham Circle/Fenway - Despite high rent, the convenience of these close-by areas cannot be matched except by dormitories. Downtown Boston is close by T and the Museum of Fine Arts provides a high cultural rating. This will be somewhat diluted closer to Kenmore Square, a favorite haunt of (drunk) Boston University students. Prices are \$700 - \$1200 for a Studio, \$1000 - \$1200 for a 1 bedroom, \$1200 - \$1400 for 2 bedrooms.

Jamaica Plain (affectionately known as J.P. by its loyal residents) - Although getting there is hard, once there you may not want to leave, according to the idyllic descriptions by some residents. After experiencing the delights of the Arnold Arboretum and Jamaica Pond, the 20 - 30 minute walk to Longwood seems a small price to pay. The rent is also a small price to pay, starting at \$700 for Studio and 1 bedrooms, \$1000 - \$1200 for 2 bedrooms, \$1100 - \$1600 for 3 bedrooms.

Cambridge - For those requiring the full Harvard experience (or who cannot bear to leave MIT behind), Cambridge may provide the perfect place. An eclectic place, it combines seats of higher learning, heavy industry and low income housing with a smattering of Starbucks and overpriced futon shops. The red line of the T and the M2 shuttle provide quick (<30 minutes) access to downtown Boston and Longwood. Prices vary by neighborhood, and availability is the biggest problem.

Dormitories - At both Cambridge and Longwood, these are great for first year students (and beyond) if available. Rooms in Cambridge are traditionally in short supply, with higher probability of getting a nice room if the expensive meal plan is purchased. This raises the price of a nice room from \$480 to \$620. Very basic rooms start at \$330. The commute to Longwood is a 15 minute walk and 30 minute M2 ride. Rooms in Vanderbilt run from \$500 - \$575 with a 15 second walk to the nearest exit and a 30 second walk to Longwood. Vanderbilt rooms are generally regarded as very nice, although the hotel-like atmosphere feels clinical after a while. This may help the majority of residents (medics) feel at home. As of June 1999, accommodation may be hard to get as an extra 140 students from the School of Public Health will be vying for the same rooms. The biggest advantage, and major drawback, is high density living with lots of exciting students. A good cheap source of listings is posted at www.townonline.com. Other online resources include the rental section of www.boston.com, www.bostonapartments.com, and rent.net. Happy Hunting!

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[The Human Organism as an Experimental Model](#)

[A review of the Baltimore Case](#)

[The Science of Apartment Hunting](#)

[Announcements insert and more...](#)

[BBS Bulletin Previous Issues](#)

[BBS Calendar](#)

[BBS Bulletin Staff](#)

[BBS Home Page](#)

A Review of The Baltimore Case **by Robin Lucas (G5)**

Kevles, Daniel J. *The Baltimore Case: A Trial of Politics, Science, and Character*. New York: W.W. Norton & Company, Inc., 1999.

As one of the most infamous government investigations in recent U.S. history, it marked the fall of a powerful Goliath in the face of an apparently insurmountable stack of evidence and an ever-expanding list of transgressions. A tale of deceit, corruption, and abuse of power leaked freely from investigators to front pages of newspapers and magazines, ruining friendships, reputations, and careers. To many, it was a witch hunt led by a zealous bully determined to prove wrong-doing no matter what the cost.

No, this is not about Ken Starr's investigation of the Clinton/Lewinsky scandal. This case is far worse, says historian of science Daniel Kevles, because here, no one had done anything wrong. In his book, *The Baltimore Case: A Trial of Politics, Science, and Character*, Kevles tells "the story of how a great injustice was perpetrated in the name of scientific integrity and the public trust (12)." In the preface, he admits initially believing that Thereza Imanishi-Kari was guilty of committing fraud while conducting research at MIT and that her collaborator, Nobel Prize recipient David Baltimore, was "foolhardy in defending her so vigorously (10)." After interviewing most of the individuals involved in the case and carefully examining the evidence, however, he "became persuaded that Imanishi-Kari was innocent of the charges against her (12)."

The book begins with brief descriptions of Imanishi-Kari and her post-doc, Margot O'Toole. Kevles writes that Imanishi-Kari, born to Japanese immigrant tenant farmers in Brazil, "fought to get an education" instead of devoting her life "to marriage and family" as her parents expected (24). Although she married and has a daughter, Imanishi-Kari "knew all about the conflicts women scientists face (54). " Kevles quotes one of Thereza's colleagues at MIT who noted "ironically, instead of sympathizing with you as a woman because of what she's given up, [Imanishi-Kari] expects you to sacrifice for your career as well (55)."

"**O**'Toole seems...to have wanted a life in science," writes Kevles, "but not the seven-day-a-week life exemplified by Imanishi-Kari (55)." This, along with O'Toole's inability to repeat an experiment performed by other members of Imanishi-Kari's lab and published in *Cell* in April 1986 led Imanishi-Kari to wonder "whether O'Toole had the necessary tenacity and devotion" for science and made O'Toole increasingly unhappy and frustrated (55). Kevles demonstrates that O'Toole never bore unhappiness quietly, pointing to problems during her previous postdoctoral work in Donald Mosier's lab at Fox Chase Cancer Research Center in Philadelphia (Mosier eventually asked her to leave), run-ins with administrators, and her involvement as a very active witness in a police brutality case soon after arriving in Boston. Mosier tells Kevles that O'Toole "had an instinct for polarizing laboratory members over minor issues" and was intense, political, ready to leap on an issue (22).

But Kevles does not imply that O'Toole was entirely responsible for the conflict between herself and Imanishi-Kari. Henry Wortis describes Imanishi-Kari as a "tough customer" who "could be harsh and mercurial (48)." Kevles chronicles incidents in which Imanishi-Kari was openly hostile, screaming, attacking, and berating O'Toole for not getting enough accomplished. O'Toole was not the only one who didn't get along with Imanishi-Kari. Another lab member told Kevles that "it was as bad as it got between Thereza and Charlie [Maplethorpe]," a graduate student in Imanishi-Kari's lab (60). "By all accounts," says Kevles, "Maplethorpe hated Imanishi-Kari.

O'Toole's scientific dispute with Imanishi-Kari over the effectiveness of a particular reagent and certain overstatements and misstatements in the Cell paper moved from the lab on to NIH's "fraud-busters" Walter Stewart and Ned Feder via Charles Maplethorpe, and finally reached Representative John Dingell. Along the way, O'Toole altered and expanded her charges against Imanishi-Kari, ultimately accusing her of falsifying and fabricating data. Kevles provides detailed accounts of conversations, arguments, and conclusions during all investigations as remembered by different participants. He explains scientific principles involved in the case and the Weaver et al. Cell paper, providing figures from the paper and copies of primary data taken directly from laboratory notebooks to demonstrate points of contention.

Kevles expresses strong opinions about how the case was handled by Stewart and Feder, Dingell, NIH's Office of Scientific Integrity (OSI), and the Office of Research Integrity (ORI). On May 5th at a seminar sponsored by the Genetics Training Grant, Kevles summarized those opinions to students and faculty at Harvard Medical School declaring that this decade-long investigation "involved the hounding of a defenseless individual, namely Imanishi-Kari." In his book, he adds that she was "gravely disadvantaged in the contest by her weakness in English, by her lack of resources, and by Margot O'Toole's overpowering articulation of events (388)." He states that Imanishi-Kari was "denied due process" and insists that she "had not had a fair trial. She had been convicted in the court of public opinion and nowhere else (11)."

Kevles's book vilifies many investigators in the case, quoting descriptions of Dingell's staff as "thugs," "bullies," and "junkyard dogs" who "leaked material to journalists" and were "totally unethical (232)." Kevles points out that while Dingell had over 150 people on his staff, Imanishi-Kari couldn't pay her over \$1 million legal fees and her attorneys worked pro bono. Early in the investigation, however, her attorneys could do little to help her since OSI denied Imanishi-Kari access to evidence and refused to

reveal the evolving charges against her. "OSI," says Kevles," acted as investigator, prosecutor, judge, and jury."

Meanwhile, David Baltimore, Imanishi-Kari's collaborator on the Cell paper, publicly defended her, eliciting censure by many, including Jim Watson, Mark Ptashne, and Walter Gilbert. Kevles never uncovered any cause for bad will between the Harvard critics and David Baltimore to explain their condemnation of his behavior. The controversy led Baltimore to resign from the presidency of Rockefeller University. The investigation also took its toll on Imanishi-Kari. "On April 11, 1990," Kevles writes, " the NIH canceled one of Imanishi-Kari's research grants...without explanation other than an allusion to incriminating evidence that the OSI was finding (223)." He continues, "Imanish-Kari says that the accusations against her felt like a constant weight bearing down on the back of her head (315)." After the OSI and ORI found her guilty of fraud, she was suspended from her position as an assistant professor at Tufts in 1994.

Imanishi-Kari was eventually given access to the evidence against her and her lawyers could finally defend her before a panel set up by the Departmental Appeals Board. Kevles meticulously reports the testimony and evidence presented during that hearing as well as the decision released by the Appeals Board on June 21, 1996. He feels that his belief in Imanishi-Kari's innocence was " reinforced...by the outcome of the case....Thereza Imanishi-Kari was officially exonerated on all the counts that had been brought against her (12)." Tufts immediately reinstated her to the faculty and has since granted her tenure. Despite the damage to her career and reputation, Kevles says that Imanishi-Kari "did not [intend]...to sue the government for damages... explaining that no amount of money could repay her for what she had suffered...She preferred to get on with her life (388)." David Baltimore is also getting on with his life as president of the California Institute of Technology.

The Baltimore Case delivers answers about a high-profile case that has haunted the scientific community for a decade. But in the end, I was left with many more questions. What are the rights and responsibilities of scientists in reporting their data? How much freedom of

interpretation should we allow ourselves? When is it okay to omit certain data from a publication? When does an error in a publication merit a letter of correction? How should disagreements between scientists be resolved? How do we balance the rights of the whistleblower with the rights of the accused? Should scientists be held accountable for their judgements by the government that funds them?

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