Yale: Gender Matters (September 17, 2001)
September 21, 2001

The only perspective I can credibly bring to the statement Gender Matters is that of a scientist. I was trained as a biochemist here at Yale in the 1950's. But, labels don't matter very much to biologists any more and, depending on the circumstances, I identify myself variably as biochemist, or molecular biologist, or geneticist. Modern biologists, whether concerned with evolution, heredity, molecular structure, or disease, define their work by the questions they ask. Once a question is shaped, they turn to whatever methods are needed to approach an answer.

If subdiscipline doesn't matter very much in biology these days, does gender? In one sense, it is a simplistic question whose answer is of course 'yes'. Gender, or that sense of the word that is associated with biological sex, is determined by the particular set of chromosomes and genes an individual animal inherits. This matters a great deal to the biology, health, and behavior of the resulting individual, as has been demonstrated by Sally Shawitz in her work here at Yale. Plants, with some exceptions, have taken a different course; a single plant generates both male and female germ cells

(and some animals do the same). Many different kinds of single cell organisms, like bacteria, manage very well without any sex at all although they can, when the opportunity presents itself, incorporate and use genes from another cell ...a fact that was established here at Yale by Lederberg and Tatum half a century ago.

Others, like fungi / Seyla's mushrooms - also 2 sexes -

However, the relation of gender to sex is not ~~my~~ topic today's. The registration booklet introduces our agenda by asking how gender ~~Rather, I thought it pertinent to ask whether the gender of biologists~~ affects the subjects we study. ~~affects their research.~~ I will try to address this question by telling you ~~two~~ a story - perhaps a second if there is time ~~stories, one in some detail and one more briefly.~~ ~~These stories, in different ways, lead to similar conclusions. First, that~~ The story says gender **can** matter when a biologist determines what question to ask. ~~And second~~ But it also illustrates, that gender ~~can not~~ is unlikely to play a role in experimental or observational ~~programs if the~~ designed to answer the question if it research is to be successful...that is, if it is to advance knowledge and understanding of biology.

original Seyla's remarks

Registration booklet new kinds of questions not new kinds of answers.

The ~~first~~ second story has to do with breast cancer. Anecdotal historical information pointed to the possibility that breast cancer could run in families...not that all or even most breast cancer appeared to be familial, but rather, some subset of the disease. A

collection of family trees showing several afflicted and other unafflicted individuals cannot, in most cases tell us if the trait is the result of genetic inheritance or of common environmental factors or of both. Nor can experiments with model mammals like mice answer the question for humans.

Many knowledgeable physicians and scientists were skeptical that genetics played any role in the tendency toward breast cancer. The only way to obtain definitive data was to identify the candidate gene or genes and demonstrate the dependence of familial breast cancer on the presence of that gene in a mutated form.

Until this year, this was a very difficult task; the determination of the human genome makes it somewhat simpler, but still not simple. The problem was that knowing the complex outcome of a gene's action....what biologists call the phenotype, in this case, breast cancer, does not necessarily say anything about the function, characteristics, or DNA sequence of the gene. No real clues exist, except perhaps serendipitously, about where to look among the 3

billion DNA base pairs and tens of thousands of genes in the human genome.

The person who started off the productive hunt for genes associated with breast cancer was Mary Claire King, now professor of biology at the University of Washington. King's undergraduate education was in mathematics and in 1965 she went to Berkeley where she decided to do her Ph.D. in biostatistics. Berkeley was, in those years, a focal point for student unrest over the war in Viet Nam. King's reaction to the closure of the campus was to pursue a personal, socially responsible agenda. She took leave and worked for a while with Ralph Nader. When she returned to graduate school she used her mathematical skills to study human evolutionary biology, and demonstrated that the chimp and human genomes are 99% identical.

Her first research job was at a UCSF Cancer Center, where people were just beginning to recognize that genes and their mutant forms were highly relevant to cancer quite apart from the question of inheritance. That is, in our body cells, the perfectly normal genes

we inherit from our parents can acquire mutations that contribute to a process whereby a normal cell becomes a tumor cell. King decided to investigate whether genes were responsible for at least some cases of breast cancer.

A couple of basic facts may be helpful. Natural selection works to build a genome containing genes that provide important functions for the basic shape and life of an organism or to allow appropriate responses to frequently encountered, changing environmental conditions. Contrary to the biologists' short hand that has been confusingly adopted by the public media, there are no genes "**for**" genetic diseases such as Tay Sachs, or Sickle Disease or cancer. Each gene is "**for**" some normal function. But genes come in different versions that reflect alterations, or omissions from, in their DNA sequence that we call mutations. The versions of a particular gene are called its **alleles.** Genetic diseases are associated with the presence of faulty alleles. People inherit genomes with a set of particular alleles, most of which work normally and some of which do not and may be associated with a predilection for a particular disease. This is the fundamental concept in the approach King took.

First, she searched the geneologies of some 1500 families from the population at large including their medical histories (M-C. King and L. Cavalli Sforza). This analysis convinced her that only one copy of the allele causing breast cancer, if it existed, was necessary to bring on the disease. Then, she had to search blindly in the DNA from cells of the breast-cancer prone families to see if they shared unusual alleles for any gene, alleles that did not turn up in families without histories of breast cancer. When she started in 1974, it was impossible to start by looking at genes one-by-one. Rather, she looked for large segments of DNA with unique structures and even that was a huge job of data collection and analysis. She limited the search to the DNA from families with a history of breast cancer in which the cancers appeared before the age of 45; occurred in both breasts; and included those few families with afflicted males. In all she analyzed 23 multigenerational families and 329 people, with 146 cases of breast cancer. It took 17 years.

Then, in 1990, King and six coauthors published an electrifying paper in Science Magazine (Hall, JM et al.). They

identified a region of the long arm of chromosome 17 that occurred in more than 30 different forms in the afflicted families but ~~not~~ in a single, typical form or those without cancer. individuals who suffered late-onset breast cancer. Somewhere in this region, they argued, lay the gene whose alleles played a role in causing breast cancer and, as it turned out, ovarian cancer as well.

Did King's gender play a role ~~in this work~~ her choice of research? As far as anyone knows, breast cancer was not a factor in her own family. Yet listening to her, it is plain that at least part of her motivation was to address a disease of enormous concern to women. It was more complex than that. Recently, King was asked why she had persisted for so long when many others didn't even believe that a gene/alleles associated with breast cancer existed. "I have (also) learned that it is really important to follow your ideas even if everybody thinks they are nonsense. There is objective proof out there. One of the great things about doing science is that you are looking for objective reality. It is unlike a lot of other fields of endeavor in that way" (Kelly S. Mccardle. 2001. in Portraits of Great American Scientists. L. M. Lederman, ed. Prometheus Books, Amherst, New York).

Very quickly, other groups of scientists raced with King to identify the actual gene in question. First to publish was an international group lead by Mark Skolnick at Myriad Genetics, Inc., (and including scientists from the University of Utah, the NIH, and McGill U. in Canada). A few years later, other biologists implicated a second gene in other groups of families with breast cancer. And evidence is mounting that even in cases of sporadic breast cancer, that is with no inherited predilection, random mutations in these same genes contribute to the origins of the tumors. A large number of people now populate this field which is producing very interesting basic biological knowledge as well as information about cancer. One reason for the burgeoning of this research is that substantial research funds are now available for grants.

The increase in support for breast cancer research was not an accident. A year after Mary-Claire King's paper was published, the National Breast Cancer Coalition was formed. This effective umbrella lobbying organization now represents more than 500 different organizations and several million patients and their families and medical personnel. Its goal is to eradicate breast cancer by the

promotion of increased funds for research into cause, treatment, and cure of the disease as well as training of scientists. Since its founding, the Coalition has seen a more than 600% increase in funding (now greater than $700 million a year). This includes obtaining an unusual commitment by the Department of Defense for a multimillion dollar research effort. Notably, the Coalition promotes public education on the biomedical research, the inclusion of patients on committees determining access to research funding, and maintains watchdog activities to assure that the federal money is spent on research and not on bureaucratic projects (Science Mag. News Stories). (Knowledgable about research)

The second story concerns the search for a genetic predisposition or predilection for male homosexuality in at least some subpopulation of contemporary male homosexuals in the US. The study was undertaken by Dean Hamer, a brilliant biologist with a substantial record of outstanding research in other, what I might characterize as main-stream areas of molecular genetics. The search for possible genes followed much the same path as the breast cancer work. Hamer assumed that only a small subset of male

homosexuality might be inherited, just as only a small subset of breast cancers have inherited genetic origins.

Verification of the homosexual phenotype was challenging and had to depend on inherently problematic psychological methods. Once phenotype was determined or at least estimated, the goal was the same as with breast cancer...only the identification of particular allele(s) that was specifically associated with homosexuality would allow any firm choice between environmental and genetic effects.

Unlike the breast cancer situation, the initial period of this research turned up a serendipitous clue. The multigenerational family trees Hamer collected indicated that the genetic trait, if it existed, was delivered to men from their mothers. Two brothers, for example might be gay and have gay male cousins born to their mother's sisters and gay maternal uncles. Their fathers and paternal relatives were not gay. This is exactly the inheritance pattern for diseases known to be related to genes on the X chromosome. So, the gene search could be limited to the DNA on the X chromosome, and

the rest of the genome, which King had to include in her work, could be ignored. Hamer and his colleagues found that the particular DNA characteristics on one region of the X-chromosome showed a statistically significant correlation with homosexual orientation. This region comprised 4 million base pairs and several hundred genes.

After the results were published in 1993 (Hamer et al, 1993), this story pretty much ended. Others who tried to reproduce the work obtained variable or negative results. Observations like these are very sensitive to the details of family characteristics, data collection, and analysis. Definition of the phenotype, depending as it does on self-description, is uncertain. Moreover, the number of families available for analysis was small compared to the large number of families with recurring breast cancer.

Very likely, the massive media attention that engendered homophobic public reaction was also discouraging, especially as Hamer works at the NIH, a federal institution that was leary about continued funding. The work was put aside. Within the last year,

No one else pursued it either

however, Hamer's lab has picked it up again. The data from the Human Genome Project makes it feasible to take a targeted approach to relating the DNA changes to particular genes.

Hamer chose an interesting question to ask, but also a politically sensitive one. His own homosexuality certainly influenced the choice of question. Although he has never been secretive about his sexual preference to friends, family, and colleagues, he rightly declined to respond to media questions about his homosexuality. Like King, his personal outlook may have influenced his choice of research projects, but the resulting data ~~must~~ has to be evaluated and interpreted on their merits.

The influence of personal concerns are also apparent with scientists who choose to investigate diseases that afflict members of their families, like cancer and juvenile diabetes. But once the problem is chosen, success depends on putting aside personal aspirations and wishes and replacing them with scientific reality and rigor.

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