Thirty Years of Gender-Specific Medicine:

Where We Were, Where We Are Now and Where Should We Go Next?

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The history of scientific research and of medical practice directly reflects the society and culture in which it develops.

Gender-specific medicine evolved from an emphasis on women’s health: the journey was economically and politically motivated and with a few exceptions, not perceived as a scientific imperative.
Modern Scientific Investigation: 1940’s to 1980’s

The Bikini View of Women’s Health
Traditional Biomedical Research Has

- **Made men normative for the entire population.**
  
  (Paradoxically, there has not been a systematic consideration of their unique, gender-specific features.)

- **Was not interested in which characteristics of men and women are hard-wired/*a result of biological sex* and which are the consequences of *environment and experience*.**
1985-1998
Establishing Women’s Health as a National Priority

• **1985:** Task Force on Women’s Health of Public Health Service

• **1986:** NIH urges that more women be included in clinical investigation

• **1990:** GAO says new guidelines are not being implemented

• **1990:** establishment of the Office of Research on Women’s Health: Bernadine Healey chooses Vivian Pinn as its leader.

• **1993:** Congress passes the NIH Revitalization Act gives legislative authority to the ORWH.

• **1993:** FDA reverses 1977 edict excluding women from clinical trials

• **1998:** FDA says it will refuse to file any new drug application that does not include enough women to assess safety and efficacy by sex.
A Personal Journey

- **1990**: AHA requests a book from me about women and heart disease—the result, The Female Heart, wins the AHA Blakeslee Award and captures national attention from cardiologists and the public alike.

- Asked by one of the judges for the Blakeslee award to become a consultant in women’s health to Procter & Gamble.

- I suggested instead a Partnership between Columbia University and Procter and Gamble to open a much wider field of opportunity for both institutions to expand both scientific research and new product development.
Strategy for Winning the Support of the Private Sector: P&G

- **Understand the motives and interests of the target:** P&G is a company interested in the female customer that saw championing women’s health as a significant marketing opportunity.

- **Perseverance is key:** I invested two years of interviews with John Pepper and his chief advisors. The effort culminated in a key question from John: “Do you have the confidence of your university?”

- **Rely on the best data you can find to support your big idea:** I agreed to address 1500 PhD’s at P&G, having developed a book I knew had to be in print to make my case credible: “Gender-Specific Medicine for the Practicing Physician.”

- **Promote exchanges between the players at every opportunity:** I organized a site visit to Columbia by P&G scientists and upper echelon executives, asking investigators from all the departments of the medical school to present gender-specific aspects of what they were studying.

- **Don’t insist on your own view before it is palatable:** The denoument in the dean’s office: a check for $1,000,000 began the program, called in spite of my best efforts, “The Partnership for Women’s Health”. No one was interested in broadening the idea to include a comparison of men and women. That took years to accomplish.
Strategies to Expand and Strengthen the Program

• **Solidify important sources of support and collaboration:** working with the Office of Research For Women’s Health at the NIH with Vivian Pinn: I functioned as one of her key scientists outside the NIH, co-authoring the report “Beyond Hunt Valley: Research on Women’s Health for the 21st Century in 1998.

• **Use international and national travel** to establish centers for GSM in Japan, Korea, Germany, Italy, Israel made GSM a world-wide idea. There is now an International Society for Gender-Specific Medicine with over 700 members.

• **Publish a textbook and found a National Library of Medicine accredited Journal of Gender-Specific Medicine.**

• Change the name of the Partnership for Women’s Health to the Partnership for Gender-Specific Medicine.
What Were/Are the Difficulties and Obstacles?

- **Funding** for a new idea is difficult. There is intense rivalry for turf and money in academia. Private sources of funding are key.

- **Pharmaceutical companies do not want to hear** about the gender-specific advantages of a medication: they repeatedly have asserted that such information eliminates half of potential users!

- Interestingly, there has always been resistance to founding a clinical department **of gender specific internal medicine in clinical settings** because staff physicians feared the loss of their patients. “Women’s Health Centers” continue to be less threatening.
Lessons Learned

• Find the most powerful mentors and allies available: in my case, Myron Weisfeldt and Vivian Pinn were crucially important. Ask for what you want.

• Collect and generate reliable, credible data to support your vision. Use those data to expand and change the view of your colleagues without threatening or antagonizing them.

• The public is a hugely important ally. (It is not your rival and wants your ideas on its behalf to succeed.)

• Think outside the box for funding opportunities: turn every contact into support for your big idea.
Strategies for Young Investigators

- **Decide what’s new** and how you might create your own niche. The best ideas are 10 years ahead of their time.

- **Enlist the public** as well as the biomedical community to popularize your concept.

- **Recruit support** within your own academic environment. Seek out **already established groups** of specialists who might be natural allies.

- **Accept every offer to speak or teach; you never know where it might lead.**
1990-2014: How Far Have We Come and Where are We Now?

- We are more aware of the extent and complexity of the gender specific properties of living organisms.

- We are exploring how the intricate dance between the genome, hormones and the environment creates the phenotype.
The Changing Face of Biomedical Investigation

- Funding sources: NIH reports that proportion of physicians applying for grants declined from 40% in 1969 to 25% by 1998.*

- IN 1949, 100% of studies in the Journal of Clinical Investigation were on humans; by 2009, the number had declined to 29%, largely reflecting a change to rodent models.

A Growing Emphasis on Gender in the Literature*

• There has been a linear increase in the literature incorporating sex and gender differences since 1997.

• With the exception of cardiology, reports of sex differences in research regarding the management of disease were strikingly rare.

Ortelt-Prigione et al. BMC Medicine 2010.8:70
Untying the Gordian Knot:

What major issues need discussion?
Some Important Issues

• Is it *ever* possible to *separate* what is hard-wired into the organism by virtue of biological sex and what is the result of the impact of other factors on the phenotype?

• Given the complexity of how the phenotype is determined, how powerful/useful will the delineation of an individual’s genome be in predicting disease and in choosing therapy?

• *What is the impact of biological sex on gene expression? How does that impact fit into the new discipline of synthetic biology?*
Question 1:
“Sex-specific?”
“Gender-specific?”
(It is impossible to separate the organism from its experience.)
“There is no gene-controlled inheritable trait that cannot be altered by the environment…Humans enter the world as a work-in-progress…Nature/nurture is not an either/or duality but, rather, represents a both/and type of complementarity.”

Parental and Personal Experience Impacts the Genome

• Maternal stress programs the developing fetus and results in premature birth, birth defects and altered neurological development.*

• Early adverse experience is associated with methylation of brain-derived neurotropic factor BNDF, which is vital for brain development and plasticity.**

*Dunn et al. Hormones and Behavior 2011.59:290
**Roth et al. Hormones and Behavior 2011.59:315
How Environmental Factors Impact the Phenotype

- Environmental factors act by
  - mutating promoter and coding regions of genes

- Epigenetic mechanisms include chromatin folding and attachment to the nuclear matrix, packaging of DNA around nucleosomes, covalent modifications of histone tails and DNA methylation. (Dolinoy DC and Jirtle RL. Environ. Mol Mutatgen.49:4.2008)

Question 2: What is the impact of biological sex on gene expression?
The Genetic Gender Gap: The Sexually Dimorphic Gene*

- Thousands of genes showed sexual dimorphism in liver, adipose and muscle; hundreds of genes were sexually dimorphic in brain.

- These differences are highly tissue specific; thousands of genes identified were involved in tissue-specific biological functions and/or pathways relevant to common diseases and showed tissue-specific chromosomal enrichment.

- Only 27 genes showed consistent direction, i.e. all female or all male biased in all tissues.

- A significant portion of sexually dimorphic genes are located on the sex chromosomes, but some are carried on autosomes as well.

“We saw striking and measurable differences in more than half of the genes’ expression pattern between males and females. We didn’t expect that. No one has previously demonstrated this genetic gender gap at such high levels.”

*Yang et al. Genome. 2006

**Thomas Drake, CO investigator
We are only beginning to unravel the genetic basis for the gender-specific differences in normal function and in the experience of disease.

The story is far from complete but as data accumulate it will be apparent that the economy of genes in both health and disease is profoundly impacted by biological sex and experience.

Many of the unanswered questions about the reasons for the differences in risk factors, symptoms and the response to therapy in men and women with disease are beginning to be answered at a more fundamental level than observational studies have been able to provide.
Question 3:
Where do we go from here?
What Are Areas of Special Interest As We Go Forward?

• Focusing a gender-specific lens on men, so that we can better understand their greater vulnerability compared with women.

• Expanding the current science of gender-specific medicine and testing its value in clinical practice.

• Systematically developing a curriculum that incorporates sex-specific differences into all the subspecialties of medicine.
The Next Big Idea

• We know that the sex chromosomes have a universal and significant effect on gene expression.

• What will the role of the sex chromosomes be in the novel and artificially created life forms by the discipline of synthetic biology?

• Synthetic biologists have not considered the impact of the sex chromosomes on their artificially altered DNA.