**Agenda Item: Opening Keynote Address - Dr. Bernadine Healy**

Women carry most of the burden of chronic disease, they take most of the medications, they visit doctors more, and they have more surgeries than do men. An anecdote: shortly after I left NIH, I was the fourth speaker at a large cardiovascular conference. The first speaker was presenting his clinical trial of a particular drug in cardiomyopathy. In the darkness of the room, he started to say, "we would have gotten this trial done a lot faster if we didn't have to include women," and he started moaning about the fact that there just were not enough women participants so, as a result, his trial was delayed. When I got up to speak, I was delighted to hear that there was a little bit of pain going on out there, because it meant that inclusion of women in clinical trials was really taking hold.

The reality is: women are different. It is not a particularly outlandish statement but, in fact, that notion challenged the common orthodoxy—the orthodoxy of sameness and the orthodoxy of the mean, which has dominated much of the thinking in medical science. In the world of physiological research, the more uniform your animal model could be, in gender and breed, the better the model was because there were fewer variables. This view often impaired our attitude toward clinical research in those days—we tended to want to reduce the human to that 60 kilogram white male, 35 years of age, and make that the normative standard—and have everything extrapolated from that tidy, neat mean, "the average American male."

Challenging the concept of sameness usually got to the core of basic science and clinical work. Around the time the women's health effort was fully underway, it was deemed "just too difficult" to do a lot of testing in humans and it was considered better and easier to work with animals. In only a decade, so much of that orthodoxy has changed, in both basic science and clinical science.

Regarding genomics and diversity, we hear that 99.9 percent of the human genome is exactly the same among all humans. Although only 0.1 percent of the human genome is different, that difference is enormous and it determines health and illness and how we are unique. Diversity has to be a key element of our thinking with regard to medicine. Pharmacogenomics is currently concentrating on tailored treatments, with the realization that no one particular therapy is appropriate for all illnesses or for all population groups. Tailored therapy is based on a more thorough understanding of that 0.1 percent difference and of personal biochemistry. In many ways, that is a logical extension of the fallacy of sameness, which led to the exclusion of women from clinical research and from hypotheses in the basic laboratory.

Recognition of diversity has gone beyond the obvious difference of a man and a woman to include recognition of age. Both ends of the age spectrum have been left out of biomedical research. Certainly it is more difficult to conduct research and there are bigger ethical issues in a study on a pharmaco-psychodynamic agent in a 3-year-old who appears to have depression. It is much more difficult to conduct research in octogenarians or centenarians. It may be more difficult and more expensive, but it is necessary. Those ideas are part of the spectrum of focusing on women's research.

Another trend in science—a focus on the human—has taken enormous momentum during the past decade, in large part because of the human genome mapping. Neither the Drosophila genome nor the mouse genome commanded the excitement of the mapping of the human genome. It is the human genome that captured attention and interest, and has led to a much greater focus on human-related research. An essay in the *Lancet*, written by Dr. Rabson, stated succinctly, "When you are expounding on human disease, please, at the least, consider data from the human." When we think about clinical trials, we must recognize that this is the highest form of science that is based on a platform of basic science, and that it must be grounded solidly in recognizing the diversity of its models and in understanding human differences. We will see a resurgence of anatomy and physiology, and integrative medicine will become mainstream.

Clinical trials are one of the highest forms of science within the field of medicine, and they must be conducted with exquisite care, must be heavily invested in, and must receive the kind of attention we have finally seen occurring during the past decade. Records kept and published by the NIH Office of Research on Women's Health show the gratifying number of grants and studies being conducted in the human organism.

Much of the evolution of our thinking about women's health has been part of a major social trend, viewed in terms of three phases of women's suffrage: the first occurred about 150 years ago, the second occurred about 50 years ago, and the third occurred about 20 years ago. Some of us in this room were privileged to be part of two of those movements. Women's health is a movement; when I was at the NIH, people recognized that having a woman director of the NIH was part of that movement.

This "movement" has three phases. One of the most heroic and extraordinary eras was that of women's suffrage. These were the women heroes who were viewed as utter heretics, the so-called revolutionaries in petticoats, who were doing all sorts of dastardly deeds to demand the right to vote. It took two generations, about 70 years, and finally the suffrage movement got the momentum to really make a difference. It opened a small door in the big scheme of things because there had been little support for these changes even among women. These women were often seen as being on the fringe and were often treated that way by other women; there was also not much male support. Even getting the right to vote was granted to women by a one-vote majority in 1919.

After that, it was not until World War II that women were "discovered" as a necessary group of workers. My own medical school did not decide to admit women until the end of World War II. The war had not ended yet and no one was sure how long it was going to go on. None of the male medical students were enrolled and the school was not producing any doctors, so Harvard broke its "commandment" not to have women in their medical school, largely in order to fill their classes because of the World War II depletion. That was also a time when women could not be physicians in the military because they could not hold commissions. It was a strange time in my lifetime, and I think of those years with great awe.

Women's Lib, which exploded onto the social scene in the 1960s and early 1970s, was an extraordinary movement—a movement to which everyone in this room must pay homage. It was a challenging time that brought great strides in another area for women: money and brains.

Women began to enter into the realm of higher education, although there were 1 million fewer women than men in college at that time. When I was in college in the 1960s, it was common for women to attend college for 2 years to be "finished"; getting a degree was not considered important. This was an extraordinary and exciting time in many ways, in part because the attitude toward women and education was changing. (There were quotas for women going into medical school; when I applied to Harvard, I had to be interviewed by a psychiatrist to find out why I was so "kooky" as to want to attend medical school.)

The real movement during that time was a movement for education and for economic control, both of which are critical to any societal change. Control of the purse strings is key, whether developing a village in Africa or working on women's health. If you do not have money to support these endeavors, everything else you do goes nowhere. Secondly, societal change is fueled when there is a mass of talent and brains—a movement of people who are educated and connected.

The Women's Lib movement penetrated our communities thoroughly, much more vastly than did the Suffragette Movement, but women in each of these early suffrage movements gave up a lot. The mantra of the suffragettes was, "act just like a man: take on their vices, take on their views, you've got to fit in." Although Women's Lib focused more on "we are women," there was the sense of, for instance, taking up smoking—and now we see lung cancer in women at rates never before seen—or male sexual patterns of behavior, which have not been beneficial to women.

The third and perhaps healthiest phase of women's suffrage is Women's Health, which is now at least 15 years old as a movement. In the two previous suffrage movements, women believed that had to "be like men" to accomplish what they needed to get done. However, in the Women's Health movement, women were able to be women; we were able to say, "we are not the same as men and we do not want to be the same. We are going to give up our cigarettes; we do not need to mimic male behaviors. Men are not the normative standards for our mental or physical health." We recognized that women could be different than men without giving up any of the rights we had gained so carefully over more than a century.

The Women's Health Initiative and the impetus of the NIH Office of Research on Women's Health gave significant support to the notion that money must support these kinds of grants and offices like the ORWH that Vivian Pinn has been heading so well. You also have to put women in leadership positions. You have to have women's perspective and women's eyes, and it is not surprising that women have been a critical part of the third phase of women's suffrage—women in Congress, women in journalism, women on the street corners and in homes, and the next generation of educated women who are reflected here.

At the time of its inception, the Women's Health Initiative was called the mother of all clinical trials, which I thought was a delicious title for it! It was the biggest trial at that time and that was a major reason why it was treated initially by some as too big and too expensive. (I have never figured out "too expensive"—$700 million over 14 years is not too expensive.) In terms of its size, the "too big" concern reflected a bias at the time that clinical trials should be small—the tyranny that you could only do good work on a small scale. Large clinical trials were

a relatively new phenomenon. You must decide the best modality to answer the scientific question at hand, and in order to accomplish the goals set for the WHI, a study of that magnitude was necessary.

From the very beginning of the WHI, we knew it was not only about women versus men; it was about bringing women of all backgrounds, including the groups that had been traditionally marginalized, into the mainstream of scientific research and specifically into this large study. At that time, there were no trials at the NIH that had ever focused on how to recruit Centers that would reflect the diversity of America. Hypotheses that estrogen is good for women – some thought it unethical to do a trial about this.

The WHI has been criticized for not being ethical because it deprived women of hormone replacement therapy and estrogen; the reigning hypothesis was that estrogen was good for women. There is a certain humility about WHI results to date, because what we believe with such certainty now might change at any time in the near future as further results are uncovered.

We have learned three basic lessons from the history of women's health to date and from the WHI in particular: think about money, think about institutionalizing studies, and think about the importance of critical mass.