

## LAB MEETING

A discussion on experiments and experimentation: NIH to balance sex in cell and animal studies

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*In 2014, the National Institutes of Health (NIH) proposed a new policy to promote “sex parity” in research. As an extension to the 1993 NIH*

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*Revitalization Act which mandated the inclusion of women and minorities in clinical trials, the new NIH policy will require scientists to include “sex” as a variable in both animal model and in vitro cell line-based research. The end goal is to ensure that NIH funded scientists “balance male and female cells and animals in preclinical studies in all future applications” (Clayton & Collins, 2014, p. 283). Janine Clayton and Francis Collins described this proposed policy in their article: "[NIH to balance sex in cell and animal studies](#)." *Nature*, 509 (2014): 282-283. We asked four interdisciplinary scholars to discuss this proposed policy.*

*~ Curated by Deboleena Roy and Banu Subramaniam*

### **Male-female comparisons are not adequate for addressing sex in cell culture research**

*Stacey A. Ritz, Medical Sciences Division, Northern Ontario School of Medicine, Sudbury, Ontario, Canada*

As a feminist laboratory scientist, my reaction to the NIH’s move (Clayton & Collins, 2014) is decidedly mixed. I emphatically agree that we must meaningfully account for sex in our laboratory work, but I would argue that male-female comparisons are insufficient for developing rigorous understandings of how sex affects health, and will likely serve to perpetuate unhelpful notions of biological determinism and essentialism (Ritz et al., 2014). Moreover, although it may seem straightforward to require that studies include both male and female animals or cells, the realities of laboratory research mean that this is not always possible or useful.

For example, much cell culture research uses transformed cell lines, which are derived from cells that have lost their ability to regulate cell division and have adapted to laboratory growing conditions. ‘Equivalent’ male and female transformed cell lines are not available and would be virtually impossible to produce, and even if such a thing were possible, comparing a ‘male’ to a ‘female’ cell line would be a deeply

flawed approach to addressing sex. Certainly transformed cell lines from a male donor can't be said to 'represent' women, but they shouldn't be understood to 'represent' men either, since a transformed cell line is derived from a single donor, and the methods for producing them mean that they are not 'normal' cells at all. Transformed cell lines must be understood as a *model*, and like all models they have strengths and limitations that must be matched to the purposes of the research; they are extraordinarily useful models in many ways, but 'sex' is not something they model well.

Furthermore, I am increasingly skeptical about the extent to which sex can be adequately represented in *in vitro* systems at all. Although it has become common to say 'every cell has a sex' (Wizeman & Pardue, 2001), it doesn't follow that the totality of what we mean by 'sex' can be understood at the cellular level. Although the sex of the donor of the cells might be identifiable, understanding 'sex' as a trait that individual cells can 'possess' is, I believe, a conceptual slippage from accepting that chromosomal and genetic factors are decisive in *sex determination* into the misapprehension that these *constitute* sex (Richardson, 2013). When a cell is taken out of the body and placed in a dish, it is deprived of the myriad dynamic interactions in the body that are part of what we understand as 'sex'. Thus, any time research is done with cells outside of the body, at best the researcher can claim to be investigating *aspects* of sex, but not sex 'itself' (whatever that may be).

Although I agree that preclinical research should attend to sex/gender issues, mandating inclusion of both male and female cells or animals is not as simple a matter as it may first appear, and raises a host of theoretical and practical issues. Addressing sex is a complex challenge that demands a more nuanced approach than to simply compare males and females.

## **The NIH call to consider sex as a biological variable is conceptually “captured” in the “sex differences” paradigm**

*Daphna Joel, School of Psychological Sciences and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel*

Janine A. Clayton and Francis S. Collins from the National Institute of Health (NIH) have recently argued that sex should be considered as a biological variable in basic research, by including both males and females and examining sex differences in every study (Clayton & Collins, 2014). Clearly, the aim of the NIH is not to study sex differences. The aim is to promote the health of all humans by ensuring that scientific findings are relevant to all. However, the formulation of this call in terms of a search for sex differences does not serve the aim of promoting health for all, but is rather a reflection of a dominant paradigm which assumes that males and females belong to two distinct categories and views sex almost exclusively through the lens of “sex differences.” I discussed elsewhere data that challenge this dimorphic view of sex (Joel, 2011, 2012; Joel & Yankelevitch-Yahav, 2014). Here I want to focus on how the conceptual “capture” of the NIH call in the “sex differences” dogma interferes with achieving the aim of fostering the health of all humans.

Achieving this aim depends on including males and females in every study, as requested in the call,<sup>1</sup> and looking for **interactions** between ‘sex’ and other independent variables. It is not achieved by searching for the main effect of ‘sex’, that is, for sex differences. This is because if the effects of an independent variable, for example ‘Treatment A’, do not interact with ‘sex,’ then even if there are sex differences (for example, if females are on average more resilient than males in *all* treatment conditions), this has no relevance for the study’s question regarding the effectiveness of Treatment A. Obviously, finding such a sex difference, provided that the effect size is large, may form the basis for a new study with a new aim, namely, unraveling the mechanisms that make females more resilient than males in this model.

Understanding this has direct implications for one of the major objections to including both males and females in every study—the belief

that this necessarily entails doubling the number of animals. But doubling the number of animals would be needed only if the category of Sex interacts with other variables. If such interactions are not found, the number of subjects in a study that includes both sexes will be the same as in a single-sex study.

The challenge we face is how to support the NIH call as it has the potential for improving the health of all humans, while making sure it is not abused to reinforce the “men from Mars, women from Venus” dogma. I believe this challenge can be met by supporting the justified request to include both females and males in every study while at the same time objecting to the practice of listing sex differences. This objection should be accompanied by developing new methods of analysis that are not based on comparing differences between means and on treating variability as noise, but that rather focus on individual differences.

### ***Considering sex in experiments vs. producing sex differences***

*Anelis Kaiser, Social Psychology and Social Neuroscience, Department of Psychology, University of Bern, Switzerland*

It is indeed very important to include both females and males (as well as any other modes of sex expression) into biomedical and psychological studies in order to ensure that we consider all variation that concerns sex/gender.

Thus, the NIH is doing the right thing in aiming to “balance sex” (Clayton and Collins, 2014, p. 282) in cell and animal studies. Many scientists are critical about this and claim that the estrous cycle in animal studies will introduce variability and thus the sample sizes (n) required will have to be larger in order to obtain significant effects, making experiments more complex and expensive. Since only very few studies, particularly in preclinical research, focus primarily on potential “sex differences” but rather on other independent variables (usually drugs), the required sample size (n) actually does not have to be much larger just because we include individuals from the two common sexes/genders.

So far so good.

The problem arises when "considering sex" (Clayton and Collins, 2014, p. 282) compulsory means the operationalization of two fundamentally distinctive sexes/genders, forcing all researchers to categorize humans into one of two groups and report the results (see also Rippon, Jordan-Young, Kaiser, & Fine, 2014). This is precisely what you do when you treat women and men as independent variables. When looking and reporting about "sex differences" without any concise *a priori* hypothesis, you are obliged to categorize these groups as if they were essential categories—which they are not—rather than recognizing that they belong to a hormonal, behavioral and even genetic continuum.<sup>2</sup>

By unproblematically embracing a binary sex/gender, the researchers reduce human variation into just two categories, blurring the singularity of individuals by reducing complex biological, behavioral, cognitive and identity related processes into a binary mode of female/male differences. Further the NIH protocol paper by Clayton and Collins (2014) unfortunately does not always use the term "sex," "gender," "female/male" appropriately (Kaiser, 2012). They also seamlessly move between evidence from animal research and human studies as if it was unquestionable to compare these entities for one and the same purpose. These are precisely the points that feminists who have studied sex/gender have long raised. The NIH protocol ignores thirty years of scholarship in feminist science studies.

The absence of a feminist voice in these debates is striking. Since the 1980's, feminist and sex/gender research within and outside biomedicine has worked to analyze the naturalized "evidence" of a fixed, invariant and discrete conceptualization of sex/gender in biology. In turn, gender studies and feminist scholars have pointed to, among others, the many assumptions and inaccuracies within the processes of creating knowledge through biomedicine, including the overemphasis of sex/gender differences as compared to sex/gender similarities in body and behavior, the confusion of sex/gender dimorphism with sex/gender difference, the certitude of a dichotomous and permanent sex/gender

identity, the inconclusiveness of results, the methodological uncertainties, the contextual influences during experimentation and the bias towards a perceived abundance of sex/gender differences within scientific publications.

Although the NIH claims that it “plans to address the issue of sex and gender inclusion across biomedical research multi-dimensionally — through program oversight, review and policy, as well as through collaboration with stakeholders including publishers“ (Clayton & Collins, 2014, p. 282), I really wonder why feminist science studies and feminist scholars of sex/gender, especially scientists, are absent as co-players in this multidimensional approach, at a time when cooperation is urgent and necessary.

### **Is the new NIH policy good for women?**

*Sarah S. Richardson, History of Science and Committee on the Studies of Women, Gender, and Sexuality, Harvard University*

When the new NIH policy was first announced in May, comedian Stephen Colbert featured the news next to an image of a lab rat “co-ed” wearing lipstick and mascara (The Colbert Report, 2014). But a female rat—not to mention a cell line—is not an embodied woman living in a richly textured social world. Rodents have sex differences, but they are different than human sex differences. For example, female rats bear large litters, males play no role in rearing, and males and females cannot be caged together in the lab (Ritz et al., 2014).

In humans, sex is a composite of many biological systems—chromosomes, genes, gonads, genitals and hormones—and it is deeply entangled with culture. Sex difference research is complex and requires great care to do well (Schiebinger, Klinge, Sánchez de Madariaga, Schraudner, & Stefanick, 2011-2013). A *Journal of the American Medical Association* study reanalyzing 432 published, peer reviewed claims of genetic sex differences found only 14% of them to be adequately documented, nominally statistically significant, and internally valid

(Patsopoulos, Tatsioni, & Ioannidis, 2007). Outside of the reproductive system, most sex differences are overlapping, small and highly variable (Joel, 2012; Springer, Mager Stellman, & Jordan-Young, 2012). Sex interacts with age, weight, and sociocultural variables. When clinical research suggests that sex is plausibly relevant to health outcomes, we should investigate the contribution of biological aspects of sex and the cultural factors that may drive female-male differences in health. But requiring all scientists to look for sex differences in their basic research will produce a proliferation of sex difference findings that are hard to interpret and in many cases will be meaningless.

The reality is that differences in health outcomes between women are much starker than those between male and female-derived cells in the Petri dish. In the US, for example, the breast cancer death rate is 60% higher for black women than for white women (“Black Women’s Health Imperative,” n.d.), and a Louisiana woman has a 27% likelihood of having a Cesarean section compared to just 12.5% in Utah (Osterman & Martin, 2014). Globally, a woman living in Japan has an average life expectancy of 84.5 compared to 58 in Liberia (Central Intelligence Agency, 2014). Demanding more non-hypothesis-driven sex difference research in basic laboratory materials is not a wise use of resources in the face of these overwhelming women’s health challenges.

As I argue in *Sex Itself*, “sex-based biology,” the philosophy and movement underlying the new NIH policy, represents an elite vision of women’s health that is disconnected from feminist science studies frameworks (Richardson, 2013). In its essentialist focus on sex, the new NIH policy diverges strongly from feminist interactional analyses of gender, sex, and the body. It also neglects feminist intersectional understandings of the subjects of women’s health activism that would include not just XX and XY bodies (or cells) but diversely sexed and gendered individuals inflected by race, ethnicity, sexuality, disability, class and age.

The mantra to study sex in every cell leaps over the conceptual sophistication of sex-gender analysis. It displaces the core values that

motivated a women's health movement in the first place: addressing urgent issues of health inequity in the real lives of women and sexual minorities. From this perspective, the policy, if implemented, is a travesty. Yet it is also an opportunity for reinvigorated debate, to which I hope feminist science studies scholars will avidly attend, about the methods and aims of the women's health movement in our present moment.

## Notes

<sup>1</sup> Including males and females in every study is a critical component of the NIH call because it ensures that more of a species' variability is included compared to a situation in which only one sex is used. This is true regardless of whether males and females belong to two distinct categories or not.

<sup>2</sup> See <http://www.nature.com/news/sex-redefined-1.16943>.

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## Bios

**Daphna Joel** received her Ph.D. in psychology in Tel-Aviv University in 1998, and joined the faculty of TAU, after receiving the Alon fellowship for young Israeli scientists. Joel is presently the head of the Psycho-biology graduate program and the Chair of the PhD Committee at the School of Psychological Sciences and a member of the Sagol School of Neuroscience. Joel studies the neural mechanisms of normal and abnormal behavior, using mainly animal models of psychopathology. More recently she has expanded her work to research questions related to brain, sex and gender, including the complex interplay between sex and environment in the development of psychopathology.

**Anelis Kaiser**, Ph.D., a co-founder of the international research network, NeuroGenderings, is a Marie Heim-Vögtlin Fellow at the University of Bern, Switzerland, where she is working on the classification and registration of sex/gender in fMRI human science. Kaiser has examined sex/gender in the brain as it relates to exploring the existence of paradigmatic, methodological, and statistical defaults that interfere with assessing the presence or absence of sex/gender differences. She received her Ph.D. in psychology from University of Basel, Switzerland.

**Sarah S. Richardson** is John L. Loeb Associate Professor of the Social Sciences at Harvard University. She is jointly appointed in the Department of the History of Science and the Committee on Degrees in Studies of Women, Gender, and Sexuality. A historian and philosopher of science, Richardson's research focuses on race and gender in the biosciences and on the social dimensions of scientific knowledge. She is the author of *Sex Itself: The Search for Male and Female in the Human Genome* (Chicago, 2013) and co-editor of *Revisiting Race in a Genomic Age* (Rutgers, 2008) and *Postgenomics* (Duke, 2015).

**Stacey Ritz** is an Associate Professor in the Medical Sciences Division at the Northern Ontario School of Medicine. Her background in laboratory sciences focused on experimental studies on allergy, immunology, and air pollution. Since 2009, Ritz has led the Biology Working Group of the CIHR Team in Gender, Environment, & Health, exploring how biomedical laboratory scientists can address sex/gender issues in their work.

**Deboleena Roy** is Associate Professor of Women's, Gender, and Sexuality Studies and Neuroscience and Behavioral Biology at Emory University. She received her PhD in reproductive neuroendocrinology and molecular biology from the Institute of Medical Science at the University of Toronto. She is currently Associate Faculty in the Neuroscience Program, Graduate Division of Biological and Biomedical Sciences and Senior Faculty Fellow at the Center for Ethics at Emory University. Her fields of

interest include feminist theory, feminist science and technology studies, neuroscience, molecular biology, postcolonial theory, and reproductive justice movements. Her research and scholarship attempt to create a shift from feminist critiques of science to the development of feminist practices that contribute to scientific inquiry in the lab. She has published articles in *Signs: Journal of Women in Culture and Society*; *Hypatia: A Journal of Feminist Philosophy*; *Neuroethics*; *Australian Feminist Studies*; *Rhizomes: Cultural Studies of Emerging Knowledge*; *Endocrinology*; *Neuroendocrinology*, and the *Journal of Biological Chemistry*. She has also contributed to several anthologies including *Handbook for Feminist Research: Theory and Praxis* (2011); *Neurofeminism: Issues at the Intersection of Feminist Theory and Cognitive Science* (2012); *Gendered Neurocultures: Feminist and Queer Perspectives on Current Brain Discourses* (2014); and *Mattering: Feminism, Science, and Materialities* (2016).

**Banu Subramaniam** is Professor of Women, Gender, Sexuality Studies at the University of Massachusetts, Amherst. Trained as a plant evolutionary biologist, she seeks to engage the feminist studies of science in the practices of experimental biology. She is author of *Ghost Stories for Darwin: The Science of Variation and the Politics of Diversity* (University of Illinois Press 2014), and coeditor of *Feminist Science Studies: A New Generation* (Routledge, 2001) and *Making Threats: Biofears and Environmental Anxieties* (Rowman and Littlefield, 2005). Spanning the humanities, social, and natural sciences, she works at the intersections of biology, women's studies, ethnic studies and postcolonial studies. Her current work focuses on the xenophobia and nativism that haunt invasive plant species, and the relationship of science and religious nationalism in India.