

Sex in Biomedical Research: A Case Study of Organ-on-a-Chip As Undone Science

A Research Paper submitted to the
Department of Engineering and Society
Presented to the Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science, School of Engineering

By

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Spring, 2022

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Sex/gender bias in biomedical research contributes to decreased health outcomes for women (Plevkova et al., 2021). Women and non-human female models have been historically excluded from biomedical research (Plevkova et al., 2021). Male-only cells, tissue cultures, and animal models are seen as the convention in studies, even those that focus on predominantly female conditions (Blanchard et al., 1995; Plevkova et al., 2021). In 1977, the FDA set guidelines explicitly excluding premenopausal women from clinical trials (Liu & Mager, 2016). This was reversed by the Revitalization Act of 1993, when the NIH mandated the inclusion of women in clinical research for the first time (Liu & Mager, 2016). Yet, medical research that uses in vivo animal models and in vitro models continues to exclude females (Heidari et al., 2016). A review of biomedical research conducted in 2012 found that 80% of animal model studies that reported sex used solely male animals and 71% of cell studies that reported sex used solely male cells (Yoon et al., 2014). Without valid justification, the results from majority or all-male studies are extrapolated to include females. This underrepresentation prevents researchers from understanding how a drug or treatment will affect female physiology, which can lead to worse outcomes and higher rates of adverse effects for female populations (Heidari et al., 2016, Plevkova et al., 2021).

This thesis will use the undone science framework to examine how counterpublics influence women's health research. Organ-on-chip technology will be presented as an example that illustrates the struggles and successes of counterpublics to include women in the expansion of a new biomedical research area. Gender and sex in biomedical sciences is a topic that has been studied in a variety of ways by many STS scholars, women scientists, and feminist advocates. Undone science is a theoretical integration of science and technology studies and social

movement studies popularized by David Hess (Frickel et al., 2010; Hess, 2016). Undone science describes areas of research that have been recognized by civil society as needing more research but are underfunded, incomplete, or ignored. This framework rests on the assumption that there is a systematic tendency for scientific research to reflect cultural assumptions and interests of elite groups. Despite elite interests dominating, the framework emphasizes that there also exists a space for research that supports social movement perspectives due to division among elites, differences in social movement organizations, diverse funding sources, and autonomy in the scientific field (Frickel et al., 2010).

Advocacy Groups Drive Policy Change

With increased pressure from feminist advocacy groups and more female representation in STEM fields, there has been change in policy over the past three decades that mandates inclusion and encourages research on women's health through federal funding. In 1990, the Society for Women's Health Research (SWHR) was founded by Dr. Florence Haseltine, who worked at the NIH, to advocate for the inclusion of women and minorities in clinical trials at both the NIH and the Food and Drug Administration (FDA). This goal was ultimately achieved with the reversal of the 1977 FDA guidelines that excluded premenopausal women from clinical studies and the introduction of the NIH's Revitalization Act of 1993, which mandated inclusion of women and minorities in clinical trials. Additionally, the NIH established the Office of Research on Women's Health (ORWH) in 1990 and the FDA established the Office of Women's Health (OWH) in 1994. The primary goals of ORWH and OWH are increasing scientific inquiry in women's health areas, providing direction on policy that relates to women's health, and promoting inclusion of women in clinical studies.

The SWHR has continued to work towards closing gaps in women's health by promoting research on biological sex differences and influencing policy. Research shows that sex is an important variable in drug efficacy/dosing and in numerous diseases and conditions. Many sex differences in cellular responses can be traced to direct or indirect effects of hormones associated with reproductive organs (Medicine et al., 2001). However, hormones do not solely account for differing responses to drugs in males and females (Medicine et al., 1994). Other contributing factors include physiological sex differences like body weight, length, surface area, total body water, and extracellular/intracellular water (Medicine et al., 2001). Pharmacokinetic and pharmacodynamic sex differences like drug absorption, distribution, metabolism, and elimination are also contributing factors (Medicine et al., 2001). These factors emphasize the importance of inclusion of women in clinical trials. Instead of assuming the results from trials performed on men will directly translate to women, additional testing should be performed in order to optimize drug efficacy/dosing for women.

Diseases/conditions known to have important sex differences include autoimmune diseases, cancer, heart disease, depression, diabetes, obesity, and infectious diseases (*What Is Women's Health Research?* | Office of Research on Women's Health, n.d.). For example, cardiac disease presents differently in men and women (Gao et al., 2019). Despite its incidence being lower in women, the mortality rate is significantly higher compared to that in men (Gao et al., 2019). This is because in women, cardiovascular disease is commonly under-diagnosed, treatment strategies are not as aggressive, and due to the underrepresentation of women in clinical trials, the FDA-approved drugs are less effective for women (Maas & Appelman, 2010). Due to these substantial differences in drug efficacy and disease presentation, sex should be an important variable to consider in biomedical research (Medicine et al., 2001). Not only should

women and female models be included in studies, but researchers should perform sex-based analysis in order to identify sex differences. In 2016, with support from the SWHR, the NIH implemented a policy called Sex as a Biological Variable (SABV). This policy recommends researchers carefully consider the role sex may play when designing studies and requires researchers to provide justification for single-sex studies (*NOT-OD-15-102: Consideration of Sex as a Biological Variable in NIH-Funded Research*, n.d.).

In 2019, a study was done to evaluate how the Sex as a Biological Variable policy has changed the proportion of female models used in biomedical research (Woitowich et al., 2020). The study highlighted the sex used in studies across multiple disciplines in 2009 compared to 2019. The results showed significant progress towards inclusion: both sex studies increased from 28% to 49%, male-only studies decreased from 33% to 27%, and unspecified sex studies decreased from 16% to 6% (Woitowich et al., 2020). However, 27% of both sex studies did not provide a description of the sample size by sex, and the percentage of both sex studies that performed sex-based analyses decreased from 50% to 42% (Woitowich et al., 2020). With no description of the sample size by sex, it is plausible that female representation in both sex studies is lacking. The decrease in sex-based analyses is particularly concerning as a major part of the motivation behind the Sex as a Biological Variable policy was to increase knowledge about sex differences. Overall, the Sex as a Biological Variable policy motivated progress by increasing the amount of females included in studies, but much science still remains undone since sex-based analysis is deficient.

Additionally, many single-sex studies still did not provide justification for being single-sex or the justification that was provided is not scientifically backed. The justification for male-only studies included prior knowledge of sex-differences, the potential for increased

experimental variability, experimental conditions which limited the use of both sexes, and difficulties in animal husbandry (Woitowich et al., 2020). The idea that there is a potential for increased experimental variability with inclusion of women has been proved incorrect and is a flawed research practice (*Inclusion of Females Does Not Increase Variability in Rodent Research Studies - ScienceDirect*, n.d.). Experimental conditions which limited the use of both sexes could denote high cost and increased time. Using all males in biomedical research has historically been accepted based on the justification that it is more convenient and cost-effective (Blanchard et al., 1995). There is some validity in this point, since the inclusion of females would essentially require all experiments to be replicated with females, which could increase experimental time and cost. However, in many cases the sample size does not need to be increased— half of the males can simply be replaced by females— which would prevent increases in time and cost. Even if sacrifices in time and cost are necessary, these losses are outweighed by the enormous potential to gain knowledge in women’s health. The SABV recommendation echoes this sentiment by encouraging researchers to include both sexes despite any constraints. Further studies need to be done to evaluate how the SABV policy has affected inclusion in biomedical research.

The Struggle of Female Scientists

Female researchers are more likely than their male counterparts to include female samples and to perform sex-based analyses (Nielsen et al., 2017; Sugimoto et al., 2019). Studies that report sex and perform sex-based analyses are associated with being published in lower impact journals (Murrar et al., 2021; Sugimoto et al., 2019). Women are less likely to be published in high-impact journals, and articles published in high-impact journals are cited less when the primary or senior author is a woman as opposed to a man (Chatterjee & Werner, 2021).

In academia, the impact of scholarly work is extremely important for career advancement. Therefore, the association between women authors and low impact acts as a barrier to women becoming primary/senior authors, achieving tenure, acquiring funding for research, and being promoted to leadership positions (Chatterjee & Werner, 2021). This issue is expected to become exaggerated in the midst of the COVID-19 pandemic. Women may face barriers to academic productivity as schools and businesses shift to operating from home and women scientists carry a larger share of household and family-care responsibilities compared to their male counterparts (Woitowich et al., 2021). If women submit fewer abstracts to journals, the percentage of articles authored by women and the percentage of both sex studies are likely to decrease. This would prevent progress towards equality in biomedical sciences. The combination of promoting the professional advancement of women in scientific research and the inclusion of female participants in studies is essential to increase knowledge about women's health.

Over the past two decades, women have received increased funding from the NIH. The percentage of research grants awarded to women has increased from 24% in 2000 to 35% in 2020 (*NIH Data Book - Data by Gender*, n.d.). The percentage of R01-equivalent grants awarded to women increased from 22% to 32% (*NIH Data Book - Data by Gender*, n.d.). The difference in average size of research grant funds between men and women has decreased from \$60,631 in 1998 (constant dollars, 1998) to \$40,671 in 2018 (constant dollars, 1998) (*NIH Data Book - Data by Gender*, n.d.). Although this gap has shrunk, the average funds men are awarded is still significantly higher than that of their female counterparts. The fraction of women among PIs also has increased over recent years, but remains unequal. The percentage of female PIs of NIH research grants increased from 34% in 2016 to 37% in 2020 (*NIH Data Book - Data by Gender*,

n.d.). Strategies need to be developed and implemented to promote more equality among biomedical researchers.

Battle Over Funding

In addition to the NIH, many private organizations and wealthy individuals also fund research projects. These groups often fill in the gaps of unknown science by funding areas of research that have public awareness, but have not received a large amount of funding from the government. Organizations in particular are commonly formed to help a particular cause. They function not only to provide funds to researchers, but also to raise awareness about the condition to the public, as well as to advocate at the governmental level to increase funding in their area.

For example, endometriosis, a painful and chronic condition wherein the lining uterus grows outside the uterus, remains widely underfunded and under researched (As-Sanie et al., 2019). This may be due to a number of factors including: clinical gender bias, inequities in the treatment of pain based on gender, and social stigma surrounding endometriosis symptoms like infertility, menstruation irregularities, and bowel issues (*BMJ Open*, n.d.; Liaudat et al., n.d.). Due to the lack of knowledge and innovation around this problem space, the diagnosis and treatment options for endometriosis are limited (As-Sanie et al., 2019). Although in the past many women did not seek medical care for endometriosis due to social stigma or lack of education, it is now known to affect 10% of women, therefore awareness about the condition is growing among the public (Shafir et al., 2018). In 2014, a non-profit organization called the Endometriosis Foundation of America (EndoFound) was founded to address the gap in research on endometriosis (*About Us*, 2020). This organization currently is offering grants up to \$25,000 to scientists who want to focus on learning more about endometriosis (*Research Grants -*

Endometriosis Foundation of America | Research | Weill Cornell Medicine, n.d.). In 2019, EndoFund helped form the Congressional Endometriosis Caucus to support increased federal funding towards endometriosis research. In March 2022, EndoFound finally was successful in helping HR 2471, the FY22 Consolidated Appropriations Act, pass in the Senate (*Endometriosis Research Funding Bill Passed in Congress*, 2022). The HR 2471 is a piece of legislation that increases the federal funding to the National Institute of Child Health and Human Development (NICHD) by \$92 million (*Endometriosis Research Funding Bill Passed in Congress*, 2022). Therefore, the NICHD now has the ability to increase federal funding towards endometriosis. This demonstrates how public awareness and non-profit organizations can impact federal funding and help to decrease health disparities.

Training of Healthcare Professionals Is Key

Fueled by public concern that medical students were not receiving adequate training on women's health, in 1993 Congress called for the Office of Research on Women's Health at the National Institutes of Health (NIH), the Health Resources and Services Administration (HRSA), and the Public Health Service Office on Women's Health to evaluate the extent to which women's health is addressed in medical school curricula (Henrich et al., 2008). From 1994-1995, the Association of American Medical Colleges (AAMC) conducted a survey to gather this data. The results showed that there was a wide variation in women's health curricula across the 95 schools that were captured in the survey (Silverton, 1999). The survey found that almost all medical schools taught about sexual and reproductive function, medical interviewing and examination skills, and diagnostic tests specific to women (Silverton, 1999). However, few schools taught sex/gender-specific information on leading causes of death and disability in women or on chronic medical disorders that disproportionately affect women (Silverton, 1999). Furthermore, only

14% of schools had a women's health curriculum, 28% offered a clinical rotation in women's health distinct from an OB/GYN clerkship, and 10% had an office/program whose purpose was to incorporate women's health into the curriculum (Silverton, 1999). This study showed that there was a need for a more uniform incorporation of women's health into the curriculum.

In 1996, federal funding was allocated to develop a comprehensive medical curriculum for academic medical centers across the US (Henrich et al., 2008). In 2000, the Association of Professors of Gynecology and Obstetrics (APGO) and the Women's Healthcare Education Office (WHEO) released two guidance documents on incorporating women's health into the medical school curriculum: *Women's Health Care Competencies for Medical Students: Taking Steps to Include Sex and Gender Differences in the Curriculum* and *Women's health care competencies for medical students* (APGO Women's Healthcare Education Office., 2000; APGO Women's Healthcare Education Office, 2000). The same year, the National Centers of Excellence in Women's Health Program (CoE) created an overarching model for academic health centers that incorporated recommendations on women's health research, teaching, clinical care, public education and outreach, and career advancement for women (Gwinner et al., 2000).

A decade later, in 2004, a study was conducted to reevaluate what women's health and gender-specific information was incorporated into the medical school curriculum (Henrich & Viscoli, 2006). Using data gathered by the AAMC, this study found that only half of the schools taught at least 11 of the 18 recommended women's health topics and less than 30% of schools included any gender-specific information in their curricula (Henrich & Viscoli, 2006). Only nine of the 95 schools surveyed met criteria for an interdisciplinary women's health course/clerkship (Henrich & Viscoli, 2006). The study found that having a designated women's health program was positively associated with inclusion of women's health and gender-specific information

(Henrich & Viscoli, 2006). Despite the APGO defining competencies and providing guidance on how to incorporate these into the curriculum, the implementation across medical schools was deficient. This shows that along with tools, more oversight is needed in order to drive change.

In 2005, in collaboration with the organizations listed on the 1993 congressional directive, the American Women's Medical Association (AWMA), an organization dedicated to the advancement of women in medicine, surveyed medical students from all 125 allopathic schools on what women's health/gender-specific information students felt was incorporated into the curriculum (Henrich et al., 2008). This added a new perspective to the AAMC's data that surveyed school administrators in the previous studies mentioned. The results of the study showed that there was only brief to moderate coverage of most women's health/gender-specific topics in the curriculum (Henrich et al., 2008). The category that received the least coverage was the influence of sex and gender differences in common medical conditions (Henrich et al., 2008). This is concerning since it has been proven that sex and gender have an influence on many medical conditions, yet most medical students are not made aware of this research. Other categories that received low ratings include gender identification, sexuality, interpersonal violence, and certain reproductive topics (Henrich & Viscoli, 2006). AJOG and other organizations with influence over the curriculum of medical schools should place an emphasis on incorporating these low-coverage topics. Additionally, medical school administrators should hire and retain faculty that are knowledgeable about these subject areas so that students can be adequately taught these topics.

The 2015 National Healthcare Quality and Disparities Report (QDR), a study performed under the National Quality Strategy (NQS) established by the Affordable Care Act, found that women were less likely than men to report good patient-provider communication and having

medical needs addressed (Moore et al., 2018). The QDR also showed that 83% of health disparities between men and women remained constant between 2000 and 2013 (Moore et al., 2018). The areas that require the most attention in women's health were identified to be cardiovascular disease, behavioral health, and access to care (Moore et al., 2018). Although there has been focus on improving medical education in women's health areas since 1995, gaps still remain between women and men in terms of clinical care and health outcomes. It is extremely important to continue to study the ways in which care and outcomes differ between men and women so training of healthcare professionals can be enhanced accordingly. It will take time, advocacy, and continued changes in training for these health disparities to be reduced.

Case Study: Organ-on-a-chip

An emerging technology, organ-on-a-chip, presents enormous opportunities to advance women's health, yet much of this science remains undone. Barriers in the form of funding, stigma, limited experts in the field, and lack of attention have hindered this research. Yet, a dedicated scientist, Dr. Teresa Woodruff, has overcome these barriers and pioneered the way for other researchers to utilize organ-on-a-chip technology to study women's health.

Traditionally, it is difficult to model female physiology like hormone levels within the context of an in vitro system (Nawroth et al., 2018). Recent innovations in organ-on-a-chip technology and microfluidic devices have made it possible to model complex and specific microenvironments. The development of organ-on-a-chip technology has the potential to be a more predictive model of normal physiology and drug testing as compared to animal models or 2D in vitro models (Low et al., 2021). One study showed that 80% of drugs tested with animal models fail clinical trials due to the lack of reproducibility in humans (Low et al., 2021).

Organ-on-a-chip technology also may be used for personalized medicine in the future because cells taken from a patient can be used to test drug effectiveness and proper dosage for that individual (Ashammakhi & Elzagheid, 2018). This has provided a great opportunity for the expansion of women's health to in vitro research because of the increased ability to control the physiology of the system, making it easier to induce female-specific conditions. Researchers also have the ability to model multiple organs on one chip, demonstrating how organs and organ systems work together. In the context of women's health, this is a groundbreaking tool because it can finally help researchers learn about the impact of the female endocrine system on other systems.

The use of female cells and female-specific conditions in organs-on-chips should be encouraged for all tissue/disease models, as it could help increase knowledge about sex differences in many conditions. The 2016 NIH policy that encourages researchers to consider sex a biological variable in their studies applies to this emerging field of research. There have been studies that have used this to close gaps in recent years, but this innovation is still under-used for women's health applications (Nawroth et al., 2018). The most widely funded organs-on-chips focus on non-sex-specific organs and minimally consider the impacts of female-specific physiology on these systems (Wu et al., 2020).

In addition to the potential organs-on-chips have to induce female-specific conditions, this technology also has great potential to close gaps in knowledge in conditions solely or predominantly affecting women. For example, modeling the placenta and fetal membrane is currently very difficult because of the lack of human subjects and limited reproducibility in animal models (Richardson et al., 2020). Organ-on-a-chip technology could be used to better mimic the placental and fetal membrane tissues. This would help researchers learn more about

fetal-maternal communication and factors that influence preterm labor (Richardson et al., 2020). It would also provide a safe and more accurate model to test new therapeutics (Richardson et al., 2020). However, this research has not yet been pursued. One of the main barriers to this research is the lack of funding.

In 2017, the NIH awarded \$15 million to support the development of organs-on-chips as part of the Tissue Chip for Disease Modeling and Efficacy Testing program (*NIH Awards \$15 Million to Support Development of 3-D Human Tissue Models*, 2017). One of the collaborators of the project is the NIH Office of Research on Women's Health. However, only one out of thirteen of the projects that received funding focused on a condition relevant to women's health, and only two out of thirteen of these projects included a woman as one of the primary investigators (*NIH Awards \$15 Million to Support Development of 3-D Human Tissue Models*, 2017). The most heavily funded and thus most technically advanced organs-on-chips include the lung, liver, intestine, heart, and kidney (Wu et al., 2020). None of these organs have yet been altered to show the influence of female-specific conditions. Researchers who focus on conditions that solely or disproportionately affect women often struggle to gain funding, the knowledge may become stigmatized, and the researchers may lose credibility (Frickel et al., 2010).

The sole NIH-funded project relating to women's health is led by Teresa Woodruff, Ph.D., a Professor of Obstetrics and Gynecology at Northwestern University. The Woodruff lab's primary focus is on female reproductive health. The ultimate goal of this particular project is to develop and validate an organ-on-a-chip technology that integrates the five major organs of the female reproductive tract: the vagina, uterus, fallopian tubes, cervix, and ovary (*Grants | Woodruff Lab*, n.d.)). The team has made progress by modeling 3D reproductive tissues that respond to sex hormones. However, this is an active project so their work is yet to be published.

Dr. Woodruff hopes her research will help develop individualized treatments and investigate how females metabolize drugs differently from males. This would make an enormous impact on translational medicine and drug development as a whole— improving the efficacy of treatments for women.

Conclusion

It has been established that underrepresentation of women and female models in biomedical research has contributed to a wide knowledge gap, or undone science, that results in worse health outcomes for women. There is a need for organizations and individuals to work together to push for change in order to close this gap. At the organizational level, advocacy groups like ORWH, OWH, and SHWR can challenge the status quo in the NIH and FDA and encourage changes in policy and funding distribution. At the agency level, the NIH and FDA have a responsibility to oversee inclusion and identify any barriers to inclusion. Additionally, the NIH can directly promote research on women’s health topics by allocating a higher proportion of funding towards this area. At the institutional level, medical schools, nursing schools, pharmacy schools, etc. can incorporate women’s health/gender-specific information into the curriculum. At the individual level, researchers can design their studies to incorporate female models and perform sex-based analyses. Although progress may not be seen immediately, these steps can be taken to “do” the science that has long been undone and improve women’s health.

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