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Putting gender on the agenda

Biomedical research continues to use many more male subjects than females in both animal studies and human clinical trials. The unintended effect is to short-change women's health care.

Differences in the physiology of males and females, and in their response to disease, have been recognized for decades in many species — not least *Homo sapiens*. The literature on these differences now encompasses everything from variations in gene expression between male and female mice, to a higher susceptibility to adverse drug reactions in women compared with men. Moreover, hormones made by the ovaries are known to influence symptoms in human diseases ranging from multiple sclerosis to epilepsy.

And yet, despite the obvious relevance of these sex differences to experimental outcomes, three articles in this issue (see pages 688–690) document that male research subjects continue to dominate biomedical studies. Some 5.5 male animal models are used for every female in neuroscience, for example. And apart from a few large, all-female projects, such as the Women's Health Study on how aspirin and vitamin E affect cardiovascular disease and cancer, women subjects remain seriously under-represented in clinical cohorts. This is despite reforms undertaken in the 1990s, when sex discrimination in human trials was first widely recognized as a problem.

Admittedly, there can be legitimate reasons to skew the ratios. For instance, researchers may use male models to minimize the variability due to the oestrous cycle, or because males allow them to study the Y chromosome as well as the X. And in studies of conditions such as heart disease, from which female mice are thought to be somewhat protected by their hormones, scientists may choose to concentrate on male mice to maximize the outcome under study.

However justifiable these imbalances may be on a case-by-case basis, their cumulative effect is pernicious: medicine as it is currently applied to women is less evidence-based than that being applied to men.

The research community can take a number of steps to address this problem. Journals can insist that authors document the sex of animals in published papers — the Nature journals are at present considering whether to require the inclusion of such information. Funding agencies should demand that researchers justify sex inequities in grant proposals and, other factors being equal, should favour studies that are more equitable.

Funding agencies and researchers alike should also start thinking seriously about how to deal with the most fundamental sex difference: pregnancy. Pregnant women get ill, and sick women get pregnant. They need therapies, too, even though they are carrying a highly vulnerable fetus and their bodies are undergoing massive changes in hormonal balance, immune function and much else besides. Entering pregnant women in clinical trials is problematic in the extreme, for a host of ethical reasons. But ignoring the problem is not an answer either — the result is that physicians will prescribe drugs whose effects during pregnancy are poorly known. One possible solution is systematic retrospective data collection from women who have had no choice but to take an unproven drug while they were pregnant.

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More generally, drug regulators should ensure that physicians and the public alike are aware of sex-based differences in drug reactions and dosages. And medical-school accrediting bodies should impress on their member institutions the importance of training twenty-first-century physicians in how disease symptoms and drug responses can differ by sex. Finally, speeding more women into the senior ranks of science, which they still struggle to reach (see page 832), could well have a salutary effect in creating an environment in which all such efforts can thrive.

These may be the first steps in the direction of truly personalized medicine — what, after all, is more personal than sex. But they are urgently necessary ones. ■

Unknown quantities

It is in researchers' interests to help funding agencies quantify the economic benefits of their work.

When research agencies are pressed by politicians to quantify the economic value of scientific research, it is only natural that they reach for whatever numbers they can find and then repeat them as well-established fact. Natural, but wrong. The reality is that few of those numbers — typically, assertions that each unit of research investment will yield a certain amount of additional economic activity — rest on a secure basis (see page 682).

Economists can say with some certainty that basic scientific research plays a substantial role in fostering innovation — by which they mean new technologies, services and business methods. They also have good evidence that innovation is essential for strong economic growth, especially when society faces constraints on key inputs such as labour, capital and materials.

Beyond that, they can't predict which disciplines of scientific research will lead to future innovation — that would require a time machine. Nor, thus far, can they trace how additional research investment will influence a society's ability to innovate.

The problem is that innovation is not a simple, linear system in which basic research begets technology, and technology begets innovation — although that has always been the easiest model for policy-makers to envisage. Innovation is a complex, highly nonlinear ecosystem, full of interdependencies and feedback loops that aren't