Gender Medicine

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Coming up in 2017

April – The Microbiome
June – Emerging Diseases
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Sunday 2nd July - Wednesday 5th July 2017
Glasgow, UK

Speakers and Sessions:

OPENING SESSION (SUNDAY)
Tak Wah Mak (CA), Lewis Cantley (US), Heather Christofk (US)

TUMOUR MICROENVIRONMENT
Jacques Pouysségur (MC), Eileen White (US), Ronald Evans (US), Jurre Kamphorst (UK)

SYSTEMIC METABOLISM
Nissim Hay (US), Michael Pollak (CA), Alex Gould (UK), Paolo Sassone-Corsi (US), Oliver Maddocks (UK)

IMMUNO METABOLISM
Douglas Green (US), Erika Pearce (DE), Jeff Rathmell (US), Russell Jones (CA)

METABOLIC NETWORKS
Christian Metallo (US), Jason Locasale (US), Jens Nielsen (SE), Nathan Lewis (US), Alexei Vazquez (UK)

TUMOUR METABOLISM
Almut Schulze (DE), Matthew Vander Heiden (US), Christian Frezza (UK), Eyal Gottlieb (UK)

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Deadline for registration, payment and abstract submission: Fri 12th May 2017
Make Open Science your New Year’s Resolution

by Freddie Theodoulou, Science Editor

Let’s face it, 2016 brought with it many challenges and uncertainties for science. First came the political events that set the UK on the uneasy path to leaving the EU. Then, while Remainers and Brexiteers alike were reeling from this bombshell, we woke up one morning in November to discover that the US had elected Donald Trump as its next President. Concern has been expressed within the scientific community at his choices of climate-change sceptic and anti-vaxxer advisors. As we go to press, Academic Twitter is expressing further unease at the administration’s temporary move to ban government-funded scientists from sharing scientific information on social media. Although the full implications for science of Brexit and the Trump administration remain to be played out, if new immigration policies dictate the restriction of movement of scientists, a negative impact on the global scientific community seems inevitable.

It’s an emotional response, but the world suddenly feels smaller and more insular. While we may not be in a position to influence immigration legislation, one positive way to make a difference is to support Open Science. The Open Science agenda aims to change the way that science is conducted and encompasses open access, open data, research metrics, citizen science and research integrity. In this spirit, throughout 2017, The Biochemist will be taking a look at citizen science. As discussed in David Pye’s article on page 44, there are several definitions of citizen science, but engagement of the general public in scientific research is the common theme. This isn’t a completely new idea: from the Renaissance to Victorian times, science was a favourite leisure pursuit of the independently wealthy middle classes, with well-heeled ladies and gentlemen collecting fossils, gazing at the solar system, cataloguing plants and observing animal behaviour. A lecture at the Royal Institution was considered a good night out, on a par with the latest play or opera. However, there was more to this than keeping a small section of the population entertained: the endeavours of gentleman scientist Charles Darwin gave birth to arguably the most important and influential theory in biology.

Since the early 20th Century, the practice of science has – rightly, some might assert – become the preserve of professionals, with formal frameworks for training, dissemination, quality control and safety. But in a society that claims to be tired of ‘experts’, are we unwise to exclude the enthusiastic amateur? Modern citizen science is distinguished from its Victorian forerunner in two significant aspects: crowd sourcing and democratisation. It also straddles national boundaries. However, whilst natural history topics such as animal migration are particularly well served by citizen science, it is a moot point whether this model works equally well for molecular bioscience research. Virtual games such as the protein structure solving app, FoldIT have been hugely successful and neatly circumvent the challenges of amateur lab work. Meanwhile, the emerging field of garage biotech continues to create controversy, provoking bioterrorism fears, but has also been hailed as a hotbed of creativity akin to Silicon Valley in the 1970s and eighties. Could the next Darwin be dabbling in a little synthetic biology at the weekend? Amid the hype, there is still much to discuss and debate. Perhaps we should make the pursuit of Open Science our New Year’s Resolution?
As precision medicine becomes more important, is it finally time for increased emphasis on gender medicine?

Gender medicine is the topic of this issue of The Biochemist. In 2014, Francis Collins, Director of the National Institutes of Health (NIH), and Janine Clayton, Director of the Office of Research on Women’s Health (ORWH) at NIH, announced that NIH would begin requiring all preclinical grant proposals to address sex as a biological variable. The ORWH was set up in 1990 with the specific mandate to promote the inclusion of women and minority individuals in all clinical trials going forward. Similar guidelines are imposed by the European Commission and the Canadian Institutes of Health Research.

Despite this mandate, data are rarely evaluated separately for men versus women, thus potentially missing important gender differences. Requests For Applications (RFAs) for sex differences, expert researchers and additional funding to allow these studies to occur may better facilitate sex-specific research rather than requiring all grants to include male and female animals in a challenging financial climate. It is also hoped that the NIH programme directors in the Institutes will evaluate progress reports to make certain that investigators who received funding are actually including males and females in their studies, publishing the results and stating when there are no differences between the sexes. This topic will be discussed at length by Teresa Woodruff and Nicole Woitowich in their article in this issue of the magazine (see p10). The importance of sex differences in basic and translational research will also be addressed in more detail by Deborah Clegg and Aaron Frank (see p6).

The terms, ‘sex’ and ‘gender’ are often confused by investigators. The Institute of Medicine in 2001 set specific definitions for sex and gender in the article, entitled Does Sex Matter?. The term ‘sex’ is the classification of living things, generally as male or female, according to their reproductive organs and functions, and is controlled by chromosomes and sex steroids. ‘Gender’ is determined by one’s self-representation as either male or female, and thus how society relates to the individual. Gender encompasses biology but is also influenced by experience and environment. Thus when comparing men and women, all studies are of ‘gender differences’. In animal studies, however, since we, as humans, are not cognizant of animals self-representing their gender, all studies of males and females are considered ‘sex differences’.

The area of sex differences has become a hot topic in recent years with the increase in the number of studies showing the novel roles that sex hormones play in mediating mechanisms controlling not only reproductive function, but also integrative cardiovascular-renal, endocrine and neurological function on a cellular and/or molecular basis. For just one example, the steroid hormone oestradiol is a transcription factor that binds to oestrogen response elements in RNA to cause synthesis of specific peptides or proteins. Oestradiol can control the synthesis and release of angiotensinogen from the liver to act as a substrate for renin, which is the rate-limiting enzyme in the synthesis of angiotensin II (Ang II) in the renin-angiotensin system (regulates blood pressure and fluid levels in the body). Synthesis of Ang II also requires angiotensin I converting enzyme (ACE) that produces Ang II from angiotensin I. Ang II binds to the angiotensin 1 (AT1) receptor, and is one of the most potent vasoconstrictors that also causes sodium reabsorption by the tubules of the kidney leading to elevations in blood pressure. Oestradiol controls expression of AT1 receptors in vascular, endothelial and renal cells, thus controlling the biological activity of Ang II. Oestradiol also increases the synthesis of ACE2, an enzyme that converts Ang II from angiotensin I. Ang II binds to the angiotensin 1 (AT1) receptor, and is one of the most potent vasoconstrictors that also causes sodium reabsorption by the tubules of the kidney leading to elevations in blood pressure. Oestradiol controls expression of AT1 receptors in vascular, endothelial and renal cells, thus controlling the biological activity of Ang II. Oestradiol also increases the synthesis of ACE2, an enzyme that converts Ang II from angiotensin I. Ang II binds to the angiotensin 1 (AT1) receptor, and is one of the most potent vasoconstrictors that also causes sodium reabsorption by the tubules of the kidney leading to elevations in blood pressure. Oestradiol controls expression of AT1 receptors in vascular, endothelial and renal cells, thus controlling the biological activity of Ang II. Oestradiol also increases the synthesis of ACE2, an enzyme that converts Ang II from angiotensin I. Ang II binds to the angiotensin 1 (AT1) receptor, and is one of the most potent vasoconstrictors that also causes sodium reabsorption by the tubules of the kidney leading to elevations in blood pressure.

In addition to the role played by sex steroids, sex chromosomes also play important roles in mediating sex differences. Arnold and colleagues have developed a novel approach to separate the roles of sex steroids and sex chromosomes, entitled the Four Core Chromosome model. In this mouse model, the Sry gene that determines male sex is placed on an autosome rather...
than on the Y chromosome. In this way, it is possible to have XX females and XY females, XY males and XX males. If the animals are then gonadectomized, studies are easily done to separate the sex chromosomal effects from the sex steroid effects that control molecular, cellular and organ functions. For example, these investigators found that the X chromosome is associated with an increase in adiposity. This is one of the areas in which chromosomal effects contribute to sex differences. In this issue of The Biochemist, Eyleen Goh will discuss the treatment of Rett Syndrome, an X chromosome-mediated defect (see p30).

For the most part, the Four Core Chromosomal mouse model has shown that in the majority of cases, the most important factor leading to sex differences in biochemical or physiological systems is the presence or absence of sex steroids. Interestingly, the sex steroids may have different effects based on whether the individual is male or female. For example, oestrogens counteract adipose tissue increases in females, but promote adipose tissue build-up in males. Similarly, androgens cause an increase in adipose tissue in females, but a decrease in males. When ageing and reductions in sex steroid levels are taken into consideration, the changes that occur with regard to molecular, cellular and organ function are equally diverse based on whether the individual is male or female. Thus the area of sex and gender differences in research is rich in new avenues that need to be pursued, especially in this era of precision medicine and in the next with the advent of genomic medicine.

Reproductive biology is one area where the need for sex- and gender-specific research was apparent before the wider agenda of gender medicine was established. This issue of The Biochemist contains reviews on elements of pregnancy such as pre-eclampsia by Eric George (see p22). Pre-eclampsia is new onset hypertension that occurs after the 20th week of gestation and is one of the leading causes of morbidity and mortality of the mother and fetus. Dilys Freeman and Barbara Meyer discuss docosahexaenoic acid (DHA) metabolism and the role DHA supplementation in pregnancy may play in protecting against low birth weight babies (see p26). These studies are very important and timely with the increasing knowledge over the past few years that developmental programming (adverse pregnancy or early life conditions) can predispose (or ‘program’) an individual to cardiovascular and metabolic diseases later in life.

Finally, Georgios Karrarigas and his colleagues in Berlin discuss sex and gender differences in cardiac function and drug response (see p18), and Flavia Francconi and Ilaria Campesi take drug efficacy and kinetics a step further and discuss how the sex or gender of an individual may affect drug responses (see p14). We hope that this collection of articles gives you a useful insight into the depth and breadth of issues within the important and fascinating field of gender medicine.

**References**

Sex and gender matter to biology

Aaron Frank and Deborah Clegg (Cedars-Sinai Medical Center, USA)

Flip through a few TV channels or browse the Internet for a bit and you will be quickly reminded that, in our day and age, everyone is thinking about ‘sex’. Biologists think about sex too – albeit more in the biological sense than the act itself. The problem is they don’t think enough about it. Indeed, though most animals display marked differences in sexual anatomy and reproductive function, sex is regularly overlooked in biomedical research at both the clinical and basic science levels. Over 25 years ago, The National Institutes of Health recognized this as problematic; exclusion of women from large clinical trials blunted their ability to detect sex differences in the safety and efficacy of therapeutic drugs. In 2001, the Institute of Medicine echoed these concerns, calling for expansion of research into sex differences at the biochemical and cellular levels. Despite this, investigators still regularly ignore the sex of cell lines studied in vitro, as well as failing to include both sexes in animal studies. In this article, we briefly discuss the nature of sex differences and highlight their importance to future basic and translational research.

Sex hormones

Many studies of sex differences have focused on how sex hormones directly affect health and metabolism. For instance, when sex is factored into estimates of disease risk, it is well established that premenopausal women are relatively protected from diseases associated with the Metabolic syndrome, such as cardiovascular disease (CVD), compared with similarly aged men. After menopause, however, the prevalence of CVD in women increases to levels comparable to or even greater than similarly aged men. Reproductive-aged women with low oestrogen, as well as women who experience early menopause, are also at increased risk of CVD. These observations led to the generally accepted conclusion that the action of sex hormones and oestrogens in particular, protect against Metabolic syndrome and confer a ‘sex advantage’ to women.

Testosterone has also been investigated with respect to modulating CVD risk, but with conflicting results. Low testosterone levels in middle-aged men are associated with insulin resistance and metabolic syndrome, and also predict cardiovascular events and mortality. However, studies of testosterone therapy in men and women report both beneficial and adverse consequences in terms of CVD events. For example, in the Cardiovascular Risk in Young Finns Study, higher levels of testosterone in younger men (24–45 years old) were associated with lower levels of triglycerides, insulin and systolic blood pressure, as well as higher levels of high-density lipoprotein cholesterol. For women, however, elevations in testosterone, as seen in polycystic ovarian syndrome, are associated with insulin resistance and CVD risk.

Testosterone can be converted to oestrogens by the enzyme aromatase, and the majority of circulating oestrogens in men are derived through ‘aromatization’. Finkelstein et al. found that blocking the aromatization of testosterone to oestrogens actually increased adiposity and reduced sexual function in men. Studies of testosterone therapy in men and women report both beneficial and adverse consequences in terms of CVD events. For example, in the Cardiovascular Risk in Young Finns Study, higher levels of testosterone in younger men (24–45 years old) were associated with lower levels of triglycerides, insulin and systolic blood pressure, as well as higher levels of high-density lipoprotein cholesterol. For women, however, elevations in testosterone, as seen in polycystic ovarian syndrome, are associated with insulin resistance and CVD risk.

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hormones or sex hormone mimetics (for example, oestrogenic compounds in animal feed or cell culture media) could substantially impact research questions that are not expressly designed to detect sex-based effects. Strict characterization and control of the hormonal milieu is, therefore, essential in all experimental designs.

**Sex chromosomes**

While sex hormones are established players in the study of sex-based differences, the contribution of sex chromosomes to gene regulation and disease risk is a less well-studied area of interest. The X and Y sex chromosomes initially evolved from a pair of similarly sized autosomes. Over time, the Y chromosome lost the ability to exchange genetic information with the X chromosome and began to evolve independently. Today, the human Y chromosome contains only 3% of the genes it once shared with the X chromosome. It is present exclusively in men and was once thought to solely govern the expression of male reproductive traits. However, genes conserved on the Y chromosome are also expressed in cells throughout the body and are involved in autosomal gene regulation. For example, single-nucleotide polymorphisms on the Y chromosome are correlated with risk factors associated with CVD, independently of sex hormones. Still, the Y chromosome has mostly been excluded from the larger genome-wide association studies (GWAS) due to the enduring belief that it is a ‘genetic wasteland’.

Women, on the other hand, have two X chromosomes and, therefore, possess two copies of every X-linked gene. To compensate for the fact that men have only one X chromosome, one female X chromosome is randomly ‘inactivated’, allowing for adjustments in the dosage of X-linked genes between the sexes. X-inactivation occurs early in female development, making females more vulnerable than males to genetic or environmental perturbations during embryonic development. Moreover, different different cell types silence X chromosomes in different patterns, providing a mechanism of natural variation at the cellular and tissue levels. Despite this, the X chromosome has also been ‘ignored’ in the analyses of GWAS data, with only 33% of the reported studies from 2010 to 2011 factoring in the X chromosome.

**Sex hormones and chromosomes in the transgender population**

Integral to the study of sex in humans is an understanding of how biological ‘sex’ differs from the closely related, but distinct, concept of ‘gender.’ ‘Sex’ comprises biological traits encoded in DNA, such as chromosomes, while ‘gender’ refers to the social behaviours, expectations, and expressions of men and women. While sex informs gender, it does not dictate it. For approximately 700,000 people in the United States, gender does not match biological sex. This estimate of the ‘transgender’ population might actually be low; one account claims a prevalence of over ~1.4 million. Despite this sizable number, the transgender community represents one of the most underserved and understudied populations in healthcare.

Transgender patients may opt for interventions designed to bring their biological sex into congruence with their gender identity. Cross sex hormone therapy (CSHT) and sex re-assignment surgery (SRS) represent two established therapeutic approaches. In CSHT, patients receive exogenous sex hormones in order to induce the appearance of sexual characteristics consistent with their gender identity while suppressing endogenous hormone levels and secondary sex characteristics associated with their biological sex. Within the first 6 months of CSHT,
changes in men transitioning to women (transwomen) include breast growth, decreased testicular volume and decreased spontaneous erections. Women transitioning to men (transmen) experience changes in body fat distribution, muscle mass and hair growth. Critically, since the chromosomal configurations remain unchanged despite CSHT or SRS, studies of transgender populations provide unique opportunities to investigate which metabolic responses are irreversibly sex-differentiated at the sex chromosomal level, which are determined by the prevailing milieu of sex steroids and how chromosomal sex interacts with sex steroids to affect sexually dimorphic biological processes. To this end, we have recently investigated the role of sex hormones and their influence on insulin sensitivity and hepatic steatosis in a population of transwomen with and without testes (Nelson et al., in press, Transgender Health, 2016). Despite receiving similar oestrogen therapies, markers of metabolic health improved in transwomen who elected to have their testes removed compared with transwomen with testes. Furthermore, transwomen with the highest plasma testosterone concentrations also had the highest incidence of hepatic steatosis and insulin resistance (Nelson et al., in press, Transgender Health, 2016). These data suggest that suppression of naturally produced testosterone in transwomen improves insulin sensitivity and reduces hepatic steatosis. These are important considerations not only for future studies of the influence of sex hormones and chromosomes on metabolism, but also possible future transgender care guidelines.

How sex hormones and sex chromosomes impact metabolic phenotypes and disease risk is an area of much-needed research4. Future investigations will require integration of endocrinology with molecular genetics methods to alter hormone action in a cell type-specific manner and manipulate the copy number and expression of X and Y genes to probe the constitutive genetic differences in the complete genome of XX and XY cells, tissues and whole organisms5. In doing so, investigators will gain a deeper understanding of how sex fundamentally influences biology.

**Future directions**

Here, we have discussed the importance of sex and gender in biology research. In order to increase the fidelity of experimental models, clinical and basic researchers must ensure that both sexes are adequately represented in their experimental designs, and that their analyses account for sex-based and, if appropriate, gender-based effects. Sex hormones play a key role in the manifestation of sex differences and must be rigorously characterized and controlled during experimental design. Furthermore, the ability of sex chromosomes to influence metabolic gene regulation needs to be further explored. Statements such as ‘there are no sex differences’ will need to be strongly defended following rigorous characterization of the impact of sex hormones and chromosomal sex.

In conclusion, understanding how sex and gender impact biology is critical for the development of more powerful biological models, and ultimately, to the development of truly personalized medicine.
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References
Policy standpoint: tools to include sex as a variable in biological research

Teresa K. Woodruff and Nicole C. Woitowich (Northwestern University, Feinberg School of Medicine, USA)

The sex of a person, animal, cell or enzyme is the most powerful variable in health and disease. Yet, even after years of advocacy, only recently has the importance of sex as a biological and experimental variable been addressed. Indeed, the majority of biomedical research is conducted with male animals and cells, neglects to report which sexes were studied or fails to mention if any sex-differences were identified. In addition to being an exclusionary practice, this unidimensional approach to biological processes may be a root cause of the concerns regarding rigour and reproducibility of scientific research.

To directly address the lack of reproducibility in science, the US National Institutes of Health (NIH) established a policy requiring federally funded investigators to consider sex as a biological variable in their research design, analyses and reporting. Investigators are asked to thoughtfully evaluate their area of research and identify if, and how, sex may influence their findings and design experiments accordingly. Failing to address this issue can directly impact grant scores, and ultimately funding outcomes. Some may worry that this policy forces investigators to include both sexes in their experimental design with the explicit intent of examining sex differences. To this end, Dr Janine Clayton, Director of the NIH Office for Research on Women’s Health, offered the following clarification, “Considering sex as a biological variable is not the same as looking for sex differences...[the] NIH will not require any specific research design or method for accomplishing this goal.” Furthermore, the NIH recognizes that some areas of research will undoubtedly require the study of a single sex and simply requests the “strong justification” of such instances.

The NIH was not the first major granting agency to include provisions for sex-inclusive science. Notable sex-inclusion policies were established by both the Canadian Institutes of Health Research and the European Commission. In addition, other countries within the European Union have incorporated sex-inclusive policies into their own research funding mechanisms such as the Irish Research Council, or participated in strategic partnerships such as GENDER-NET (http://www.gender-net.eu/) or the League of European Research Universities, which foster the advancement of sex and gender inclusion in research. On the global scale, both the World Health Organization and Global Research Council have position statements encouraging sex- and gender-based research. Thus, the US is not the first but is in the vanguard of biomedical funding organizations considering sex as an important testable and reportable variable of biological science.

One common misconception about the concept of sex-inclusive science, is that it only applies to research involving humans, such as translational or clinical studies. This is not the case, the impact of biological sex can be found on the molecular level. For example, differences in the expression and kinetic profiles of the cytochrome P450 superfamily of metabolic enzymes, can have profound impact on drug metabolism and therefore biological efficacy of the drug in question. Thus, it is essential for biochemists to be aware of the possibility that sex may directly impact their work and have the appropriate tools and resources available to assess sex differences.
To assist investigators and trainees who are interested in conducting sex-based research but may need additional training, guidance or resources, we have established several mechanisms that are open to the community through our website (Figure 1). ‘Sex Inclusion at NU,’ (sexinclusion.northwestern.edu) is an online toolbox that contains educational and training resources that are accessible to scientists, clinicians, trainees and the public. These resources provide detailed information on biological sex versus gender, the influence of sex chromosomes and hormones, sex-based research in model organisms, and statistical considerations for desegregated data analysis and reporting. Also, we host monthly forums which serve as a platform for investigators conducting basic science, clinical or sociological research with an emphasis on sexual dimorphisms and/or sex-inclusive study design. Videos of these forums, as well as the entire programme of the Sex Inclusion in Biomedical Research Workshop & Symposium, which was recently hosted at our institution, are accessible through the Sex Inclusion at NU toolbox, so that those who cannot attend in person still benefit. Contributions to this open site are welcomed from anyone who has information that may be useful to others regarding sex-based research methods or outcomes measured.

In addition, we believe that education about sex- and gender-based research, and its impact on human health, should not begin and end within the scientific community. We engage our local community members through lectures, blogs, newsletters and discussions of sex-specific health topics so that they become active participants in their own healthcare, and advocates for sex-aware science (Figure 1). We also host a ‘Women’s Health Registry,’ for those interested in participating in clinical research. This not only encourages women to participate in research, but also assists investigators in ensuring that both sexes are represented equally in clinical trials.

As we enter the era of personalized medicine, the need for sex-based science is not just a statement of policy – it is a scientific imperative. The

**Figure 1.** Tools to enable sex-inclusive scientific research. To increase the awareness and implementation of sex-based research, we focus on three main categories: Education, Research Support and Outreach. The ‘Sex Inclusion at NU’ toolbox (sexinclusion.northwestern.edu) houses the majority of resources listed above and is available to the public.
implementation of sex-inclusive policies is only the first step towards improved health and well-being for both men and women. Going forward, education and outreach regarding sex-inclusive science must continue to be a priority. And we predict that a generation of new discoveries will emerge that were inspired by the opportunity to explore an uncharted new dimension of scientific space – that of the XX and XY enzyme, cell, animal and ultimately us.

Join the conversation:
www.womenshealth.northwestern.edu/blog.

References
One drug does not fit all: impact of sex and gender on pharmacological response

Flavia Franconi (Assessorato alle Politiche della Persone di Basilicata Region, Potenza, Italy and Università degli Studi di Sassari, Italy) and Ilaria Campesi (Università degli Studi di Sassari, Italy)

It is important to remember that gender health and illness should not to be conflated with women’s health and illness. Turshen reports that numerous studies with ‘gender’ in the title use the word gender as a synonym for ‘women’ and as a result, men’s gender-specific needs are missed. In addition, in reporting demographic characteristics of the study participants, some clinical trialists use the term ‘gender’ and some ‘sex’ to indicate men and women and this may create confusion. It can be difficult to separate the two concepts, because there are continuous and constant interactions and relationships between sex and gender. In other words, sex and gender work together. However, little attention is paid to the fact that gender is a sex modifier. It is relevant to have in mind that both sex and gender affect health and illness.

Testing bias

From animal studies to clinical trials, drugs are often tested only on males, even in studies of diseases that disproportionately affect more women. Currently, sex has also been neglected in cell-based studies, the majority of which do not indicate the sex of cells and do not consider the donor history (lifestyle, socio-economic status, etc). Fascinatingly, at least in primary cultures, recent results suggest that cells retain a memory of the sex and environment of the donor from which they derive.

Access to healthcare

Gender and sex influence access to care including single treatments and individual use of the healthcare system. For example, women receive less total joint arthroplasty than men, despite the fact that they have more osteoarthritis. Women also receive less treatment for end-stage kidney disease and young women with heart problems such as acute coronary syndrome have a lower access to care versus men with the same syndrome. In fact, women receive less fibrinolytic therapy, and women with ST-segment elevation myocardial infarctions (heart attacks) receive less reperfusion therapy, and women with non-ST-segment elevation myocardial infarctions or unstable angina receive less non-primary percutaneous coronary intervention than men with the same conditions. In this context, it is important to recall that healthcare access is strongly influenced by racial and ethnic aspects. For instance, people of African-
American and Hispanic origin receive poorer quality of care than people of Caucasian origin\textsuperscript{10}, suggesting that ethnic and racial aspects and sex and gender may interact.

**Pharmacokinetics and pharmacodynamics**

Women consume more drugs than men, but they are enrolled in far fewer clinical trials. The results from such studies are often applied and recommended for women without any critique and justification. Thus, it is not surprising that adverse drug events (injury resulting from administration of a medication, including errors in administration) are significantly more frequent and severe in women than in men\textsuperscript{10}.

Indeed, over the last few years it has emerged that the way in which the body processes a drug (pharmacokinetics) is different in women and men (Table 1). Gastric pH is more acidic in men than in women, whereas gastric and enteric mobility and intestinal blood flow are higher in men than in women and that may influence absorption after oral administration of drugs. The different body dimensions and composition (on average, men are taller and heavier and have more muscular tissue and water than women, whereas women have a higher amount of fat tissue) affect the distribution volume of medications in the body\textsuperscript{5,10}. Differences are also evident in renal function, which influences the excretion of medications. For example, female kidneys tend to clear a drug at a slower rate than male ones. But the most relevant differences are described in the metabolism of drugs\textsuperscript{5,10} (Table 1). The role of epigenetic factors in the regulation of drug metabolism and transport suggests that drug metabolism is influenced by sex and gender\textsuperscript{12}. Notably, sex hormones can modulate all pharmacokinetic parameters (Table 1). This is particularly relevant in women because premenopausal women are exposed to monthly hormonal fluctuations, pregnancy and puerperium. Furthermore, menopause and use of contraceptives or synthetic hormone replacement therapies may alter pharmacokinetics. Despite the differences, sex-specific dosage recommendations are still lacking with some exceptions (see the case of Zolpidem). Several years after its introduction onto the market, the US Food and Drug Administration (FDA) recommends that the initial dose of the sedative Zolpidem for women should be half the dose recommended for men, due to risks of next-morning impairment after use. The FDA now requires lower recommended doses for certain drugs containing Zolpidem (ambien, ambien cr, edluar and zolpimist)\textsuperscript{13}.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sex difference</th>
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<tbody>
<tr>
<td>Body weight</td>
<td>Male &gt; Female</td>
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<td>Total water</td>
<td>Male &gt; Female</td>
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<td>Fat content</td>
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<td>Muscle mass</td>
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<td>Gastric pH</td>
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<td>Gastrointestinal motility</td>
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<td>Renal function</td>
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<td>CYP1A2</td>
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<tr>
<td>CYP2D6</td>
<td>Male &gt; Female</td>
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<tr>
<td>CYP3A4 (liver)</td>
<td>Male &lt; Female</td>
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<tr>
<td>P-glycoprotein</td>
<td>Male &gt; Female</td>
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The influence of sex and gender on pharmacodynamics is more difficult to evaluate due to testing bias. However, in recent years, the number of studies demonstrating the effect of sex and gender at the molecular level has increased, at least in part due to initiatives by grant-giving and policy bodies (see 5–10–12 and quoted literature). For example, sex and gender impacts on the endothelin system, which is involved in controlling blood pressure. Endothelin antagonists have been found to have a superior benefit in women versus men in the treatment of pulmonary hypertension5.

As already mentioned, women have a higher rate of adverse drug effects than men and these tend to be more severe. Indeed, risk factors for having an adverse drug event, such as taking more than one drug, aging and depression, are more frequent in women than in men. To be a woman appears to be a potential risk factor for thiazolidinedione-induced bone fracture, iatrogenic systemic lupus erythematosus and iatrogenic long QT syndrome5-10. Several drugs (anti-arrhythmic, anti-infective drugs, antipsychotics, gastro-kinetic stimulants, antihistaminic and opioid pain killers) may prolong the QT interval, leading to increased risk of cardiac problems. In addition, high levels of potassium or sodium in the body induced by antihypertensive agents, nausea, vomiting and haematological toxicity induced by anticancer drugs, bleeding induced by anticoagulants and salicylates, antipsychotic drug-induced weight gain, and metabolic syndrome are more frequent and severe in women than in men5. Thus, adverse drug effects represent a source of greater health concern in women than in men producing a significant increase in female individual, social and economic costs.

Are women worse than men at taking drugs?

Adherence to therapy is needed for therapeutic efficacy. However, only approximately 50% of patients with chronic diseases take their medications as prescribed and a poor adherence elevates morbidity, mortality and costs. In particular, adherence is lower in individuals with lower socio-economic status and those taking multiple drugs. On average, women have lower economic status and take more drugs than men so it is not surprising that some studies report that women are less adherent than men. However, these are not unambiguous results10. The negative evaluation of a drug is another factor that decreases adherence. Women tend to evaluate drugs in a more negative way than men and this could be linked to the adverse drug effects that are more frequent and severe in women than in men5. Finally, more women than men are elderly and this may decrease the adherence to drugs prescribed for cognitive disorders10. It is evident that the lack of adherence to therapy is a growing issue. Therefore, it is important to increase the awareness of sex and gender effect on drug adherence.

Lifestyles influence drug response

Women are more vulnerable to the toxic effects of alcohol and cigarette smoking14. It is also important to remember that alcohol and nicotine have a different metabolic pathway in the two sexes14. It is known that alcohol and smoking may modify the activity of prescribed medications interfering with the metabolism of drugs. For example, alcohol modifies all pharmacokinetic parameters and lowers the safety profile of drugs15, whereas tobacco smoking induces the metabolism of some drugs. Considering the number of people who smoke and consume alcohol, clinical studies are needed in order to determine the effect of alcohol and nicotine on pharmacological responses in the different sexes. Dietary habits also diverge between the sexes and this difference could play a role in food–drug interactions. It must also be noted that lifestyle is strongly influenced by racial/ethnic group and socio-economic status.

There are still many gaps in our knowledge regarding sex influences in therapy, stressing the urgent need for a clear definition of experimental conditions and the inclusion of both sexes in preclinical and clinical studies. In fact, a more precise sex- and gender-based approach is necessary to have more evidence-based therapy in men and in women. ■
and vascular smooth muscle cells), monocytes and EPCs.

Focuses primarily on the identification of gender-specific humoral and cellular markers in the cardiovascular field, with particular reference to sex-gender differences in macroautophagy and role of the redox state in rat tissues with particular reference to sex-gender differences in humoral and cellular markers in the cardiovascular field, focus.

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References


Glossary

Acute coronary syndrome: A set of symptoms caused by the decrease of blood flow in the coronary arteries which no longer work properly
Antiarhythmic: A drug used to control an abnormal cardiac rhythm
Gastro-kinetic stimulants: Drugs used to stimulate gastrointestinal motility
Iatrogenic long QT syndrome: elevation of QT (a segment on an electrocardiogram) caused by medications
Long QT syndrome: A congenital cardiac disorder characterized by a prolongation of the QT interval on electrocardiograms
Iatrogenic systemic lupus erythematosus: An autoimmune disease in which the body attacks healthy tissues (skin, bones, kidney, brain and others). Iatrogenic lupus is due to the assumption of some drugs (as example isoniazid and hydralazine)
Metabolic syndrome: A condition in which there are at least three of these medical features: abdominal obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and/or low high-density lipoprotein levels. Metabolic syndrome is a risk factor for cardiovascular disease and type 2 diabetes
Percutaneous coronary intervention: A non-surgical procedure of coronary angioplasty that allows to treat stenosis of the coronary artery using a balloon catheter to dilate the artery
Osteoarthritis: A condition that affects joints that results from breakdown of joint cartilage and underlying bone
Puerperium: The period between the delivery of the placenta and the return of the uterus to its normal size
Reperfusion therapy: Treatment (surgical or pharmacological) able to restore blood flow of blocked arteries, especially following a heart attack
ST-segment elevation: The ST segment on an electrocardiogram has a high and abnormal value in comparison with the baseline
Thiazolidinedione: A class of drug for diabetes mellitus type 2 treatment
Unstable angina: Chest pain that occurs apparently without a cause (during sleep or even at rest) and worsens over time. An attack of unstable angina may lead to a heart attack, and therefore needs immediate medical treatment
Role of biological sex in cardiovascular disease: the case of hypertension and related target organ damage

Individual characteristics, such as age, biological sex, race, fat mass and genetic factors, have a major impact on physiological and pathological processes. Consequently, individuals can respond differently to the development and manifestation of disease, treatment, outcome and the recovery process. In fact, there are major differences in the function of the biological system of men and women, who do not differ only on the basis of their reproductive system. Sex chromosomes and sex hormones, together with other factors, interact in a complex manner, thereby leading to sex-specific protective or maladaptive mechanisms. In this context, studying the role and effects of biological sex is crucial for the identification of novel therapeutic targets, whose therapeutic exploitation will promote a personalized and improved treatment and care according to individual needs. The vast influence of biological sex is recognized in many diseases. Here, we focus on hypertension, due to its high prevalence and importance, since it is the primary risk factor for premature death and disability worldwide.

Recent data report a prevalence of hypertension of around 30–45% in the general population of high-income countries and between 20–40% in low-income countries. In fact, around the globe, 31.1% of the adult population (1.39 billion people) had hypertension in 2010.

Hypertension is a complex disease influenced by characteristics of the individual, such as age, sex and sex hormones, race, body mass index (BMI), adipokines, genetic factors, and by environmental factors, lifestyle and dietary habits, such as salt intake (Figure 1). The prevalence of hypertension is higher in men than women at younger ages, but following menopause, blood pressure in women increases steeply, thereby affecting more women than men in elderly individuals. Consequently, the prevalence of hypertension is lower in women than men until 45 years of age, but it is much higher in women than men over 65 years of age. Furthermore, women are at greater risk of developing resistance to antihypertensive treatment than men.

Patients with hypertension and lack of blood pressure control have a high probability of developing target organ damage, such as cardiac hypertrophy; vascular alterations, including arterial stiffness; and renal damage. The development of these cardiovascular
complications also differs significantly between men and women (Figure 2). Therefore, it is important to study and understand the sex-specific mechanisms involved in the development of cardiovascular diseases.

**Influence of body fat**

Interestingly, higher BMI is associated with an increased risk of hypertension development over time\(^1\); however, one sex may be more vulnerable than the other. Data from the Framingham study revealed that overweight and obese women had a higher risk of developing hypertension compared with overweight and obese men\(^6\).

In addition, women may have higher levels of body fat (adipose tissue) compared with men and greater risk of developing metabolic syndrome\(^6\). Adipokines, such as leptin – a metabolic regulator and feedback signal of body fat to regulate appetite – and adiponectin – an anti-inflammatory hormone – are cytokines released by the adipose tissue. These hormones have gained attention due to their capacity to influence the inflammatory system with pro- and anti-inflammatory actions. Adipokine levels can be impaired in obesity and metabolic syndrome, thereby contributing to cardiovascular complications, including insulin resistance, diabetes, atherosclerosis and hypertension\(^8\). Some evidence has shown that women can present with higher levels of adipokines and, interestingly, these adipokines may be associated with vascular and renal damage\(^8\), arterial stiffness\(^8\) and lack of blood pressure control\(^10\).

**Sex differences in cardiac hypertrophy**

Cardiac hypertrophy is the response of the heart to injury and overload and is a major risk factor for heart failure and sudden death. In the development of pressure overload-induced hypertrophy, distinct molecular processes are regulated between men and women. In particular, maladaptive remodelling occurs more frequently in men than women, which is associated with greater activation of pro-fibrotic and inflammatory mediators\(^11\).

Sex hormones, especially 17β-oestradiol (E2), play an important role in the development of cardiac hypertrophy and sex-specific responses. In particular, reduced E2 levels associated with menopause are expected to be a contributing factor to the higher vulnerability of post-menopausal women to develop hypertension. Along this line, in female animals, E2 confers protective effects on the heart under pathological conditions\(^12\). However, the genetic composition of the model studied may lead to divergent effects\(^11\). On the
other hand, in males, E2 leads to impaired contractile function of cardiomyocytes\(^\text{14}\). Further animal studies have demonstrated major sex differences in the development of hypertension-induced cardiac hypertrophy, where males develop greater cardiac hypertrophy and dysfunction than females\(^\text{1}\).

**Sex differences in arterial stiffness**

Arterial stiffness is characterized by reduced capability of an artery to expand and contract in response to pressure changes. This process is intimately associated with hypertension and has emerged as an important predictor of adverse cardiovascular events and mortality. Arterial stiffness is mainly determined by age, sex and blood pressure. Importantly, markers of arterial stiffness may differ between men and women. Studies have demonstrated a higher prevalence of aortic stiffness in older women than men\(^\text{15}\).

Sex hormones contribute to sex differences in vascular biology and to tissue and cellular differences resulting in sex-specific responses to various stimuli. In particular, E2 directly affects arterial wall remodelling by increasing elastin production and decreasing collagen deposition in human arteries. Along this line, the post-menopausal period is associated with increases in arterial stiffness and administration of hormonal therapy ameliorates arterial stiffness in post-menopausal women\(^\text{15}\).

**Sex differences in renal dysfunction**

Chronic kidney disease (CKD), defined by reduced estimated glomerular function rate and/or albuminuria levels, caused by hypertension. CKD is a worldwide health problem associated with high rates of morbidity and mortality. Compared with pre-menopausal women, CKD can be more severe in post-menopausal women or age-matched men, with higher progression rate and mortality risk. In most experimental models of CKD, males progress more rapidly than females.

Influence of sex hormones, sex differences in kidney anatomy, lifestyle, diet, lipid metabolism and blood pressure have been suggested to contribute to the sex-specific aspects of CKD, where females appear to be less vulnerable than males. In fact, sex hormones play an important role in biological mechanisms associated with variability in CKD prevalence and differences in CKD development between men and women\(^\text{16}\).

**Importance of studying the role of biological sex**

In order to perform research, it is necessary to define who will be studied. The goal of such research is to make generalizations beyond the given individuals studied to others with similar characteristics and conditions. To make such generalizations, the assumption is made that the responses of the individuals studied will be representative of the overall population considered. However, given that mechanisms of disease differ between men and women, how should this be addressed?

Here, we discuss two main ways. First, the individuals included in the research can be studied combining men and women together in the same group. However, some factors should be taken into account. When studying two or more groups with different subjects, the differences that could bias the results should be equally distributed between the groups. Therefore, there should be similar numbers of males and females in the group studied to avoid
over- or under-representation of one or the other, which could lead to false positive or false negative data. Second, men and women could be studied separately to try to understand any given effects involved within each sex (Figure 3).

Several experimental and clinical studies have demonstrated the importance of understanding the role of sex and the underlying mechanisms in many diseases, highlighting that sex differences represent important biological phenomena that need further investigation. Considering medical practice, what would the application of this knowledge be? The number of deaths related to cardiovascular diseases in many cases differs significantly between men and women, thereby demonstrating the need for sex-specific research aimed at unravelling the complex interactions of sex and cardiovascular (patho)physiology, along with other factors. Consequently, a better understanding of the role of sex, not only in the cardiovascular field, but rather overall, may facilitate the identification of targets that respond to specific therapies, ultimately contributing to a more personalized medical care. Therefore, the elucidation of sex-specific disease mechanisms and therapeutic targets may contribute to the development of more efficient treatments for men and women.

References
The disease of theories: unravelling the mechanisms of pre-eclampsia

Eric M. George (University of Mississippi Medical Center, USA)

Perhaps no disease of pregnancy has been more thoroughly studied than pre-eclampsia (PE), and yet despite all of our efforts we are only beginning to understand the molecular mechanisms which underpin the disease. Many people are surprised by the frequency of PE in the population, as it is believed to occur in approximately one pregnancy out of 20 in the United States, with similar rates throughout the developed world. In severe cases the disorder can progress to eclampsia, which is characterized by maternal seizures and can lead to death. PE can only be treated by ending the pregnancy, often by inducing labour prior to term, making PE a leading cause of premature birth and all of the associated health complications which accompany it. All in all, PE is one of the leading causes of maternal and fetal morbidity and mortality. It is now also becoming apparent that PE disposes both the mother and the baby to increased risk of cardiovascular disease throughout life, meaning that we still don’t fully understand the long-term implications of the disease.
**Historical perspective**

PE is one of the oldest documented obstetrical disorders, arguably being mentioned in a wide variety of texts coming down to us from antiquity in a variety of cultures. These early scientists recognized a common constellation of symptoms which have been used as the basis of diagnosis until very recent times: hypertension, protein in the urine (proteinuria) and oedema, (swelling due to fluid retention, especially in the extremities). In recent years, we have recognized that PE is a spectrum disorder, and that while new-onset hypertension is almost always present, sometimes proteinuria and oedema are not. However, if new-onset hypertension is associated with cerebrovascular and visual disturbances or organ damage, among other symptoms, a diagnosis of pre-eclampsia is indicated.

While the existence of the disorder has long been appreciated, it is only in the last 40 odd years that we have begun to understand the underlying problem, and in the process understand a fundamental process of pregnancy. To briefly summarize a large volume of research, it was found that during healthy pregnancy, cells (invasive cytotrophoblasts) from the placenta (and by extension from the developing fetus) invade the arteries of the uterus (termed spiral arteries). These blood vessels are normally small diameter, low-flow vessels. The invading cells displace the endothelial lining of the vessels, as well as part of the smooth muscle around them and increase the size of the vessels to increase the amount of blood that can flow to the placenta and nourish the fetus. The most common finding in PE is that these cells are unable to invade the maternal vessels. As a result, the placenta doesn’t receive enough blood and is deprived of oxygen. In the short term this is termed hypoxia, and the long-term deprivation of oxygen to a tissue is termed ischaemia. It is now commonly recognized that placental ischaemia is the central causative factor of PE.

**The big question: what causes pre-eclampsia?**

Although it is generally (though not universally) accepted that placental abnormalities are the central cause of the maternal symptoms, there is no commonly accepted initiating cause of the disorder and it remains one of the great unsolved questions in obstetrics. Tellingly, though pre-eclampsia normally resolves after delivery of the baby and placenta, several case reports found that if portions of the placenta remained undelivered, the disease remained. This led to the hypothesis that hypoxia was causing the placenta to secrete factors which caused the maternal symptoms of the disorder. While there is much debate, it is believed that the underlying cause could be partially through immune mechanisms.

While the placental (and fetal) cells get half of their genetic information from the mother, they...
also get half from the father. As such, the mother’s body has to tolerate an entirely new organ (the placenta), these invasive cells and the developing fetus which the immune system could recognize as being foreign. Could it be then, that the invasive cells which normally remodel the maternal blood vessels are being recognized by the immune system as foreign invaders? The epidemiology suggests that this may be the case, specifically prior exposure to paternal antigens. For women who have normal first pregnancies, their risk of developing PE in second pregnancies is lower if the subsequent pregnancy is from the same father. This suggests a build-up in immune tolerance to the father’s antigens. There are also studies suggesting that prolonged exposure to paternal antigens lessens the risk of pre-eclampsia generally. While there is still a significant amount of work to do in this area, it is likely that immune intolerance between the mother and father could be a significant contributing factor to the development of the disease.

From placental dysfunction to maternal hypertension

The question remains, how does placental ischaemia lead to all of the symptoms seen in the mother? The first clue came from studies which found elevated production of a protein called soluble Fms-Like Tyrosine Kinase-1 (sFlt-1). sFlt-1 as it turned out, was a splice variant of a receptor for the cytokine Vascular Endothelial Growth Factor (VEGF). VEGF-A (one of a complex family of signalling proteins) is often associated with growth of new blood vessels in response to increased oxygen demand due to prolonged hypoxia or ischaemia. Many don’t recognize that it is also important for maintenance of vascular endothelial health in arteries. The full length Flt-1 protein recognizes VEGF and has signalling activity in the cell. However, this spliced variant was secreted from the cell and bound VEGF, preventing VEGF activating its receptors as normal. As a consequence, the maternal vasculature, in particular the renal arteries, constricts; causing an increase in vascular resistance and a reduction in renal perfusion. This latter constriction would then lead to reduced sodium excretion and increased blood pressure. Besides supporting studies looking at the effect of sFlt-1 excess in animals, we have strong supporting evidence for the effects of VEGF loss in cancer patients who receive antibodies to VEGF for their treatment. These antibodies bind and sequester VEGF similarly to sFlt-1, and tellingly, these patients often present with hypertension and proteinuria, suspiciously like pre-eclampsia patients.

This wasn’t the only mechanism that emerged, however. It became clear over time that women that had PE were exhibiting signs of increased inflammation. Interestingly, the earliest theories about the disorder focused on a belief that toxins were eliciting the maternal response, and for this reason pre-eclampsia was originally described as ‘toxaemia of pregnancy.’ Studies from both human patient populations and animal models of the disorder have repeatedly suggested that there is an increased activation of the maternal inflammatory response during PE. This takes the form of complement activation, inflammatory cell recruitment and activation, and production of inflammatory mediators known as inflammatory cytokines. Chief among these are the protein Tumour Necrosis Factor-α (TNF-α) and Interlukin-6 (IL-6). Animal models of pregnancy have reproducibly shown that infusion of inflammatory cytokines like TNF-α during pregnancy cause a hypertensive response which mimics that seen in PE, though they do not fully explain the range of symptoms. It has also become more and more apparent that inflammation can play a major role in cardiovascular disease and
hypertension by acting directly on the vasculature and altering its function. It is now commonly accepted that the maternal symptoms of pre-eclampsia are at least partially dependent on excess production of inflammatory factors, though their origin and exact composition are still an active area of research.

Where do we go from here?

Despite the intense body of research targeting pre-eclampsia in recent years, we are still far from understanding the disorder, and little in the way of new treatments have been forthcoming. The single biggest question is the nature of the (possibly immune-mediated?) underlying cause. This question has remained elusive, as suitable spontaneous animal models of pre-eclampsia have been unavailable, and studying human pregnancy in the earliest stages is difficult to impossible. Likewise, though we understand the importance of pathogenic proteins like sFlt-1 and inflammatory factors, we still don’t fully understand the molecular mechanisms which regulate these molecules, or ways that we could try to target them with drugs to help pre-eclampsia patients. And, while several potential therapies (PDE5 inhibitors, various anti-inflammatories, statins, etc.) have been suggested by animal research, a great deal of research remains to be done on their safety and efficacy during pregnancy and in both experimental models of pre-eclampsia and in the patient population. For all of our efforts, pre-eclampsia remains one of the great obstetrical complications without adequate treatment options. However, the inroads that we have made into understanding the disorder give us hope that new innovations are forthcoming in the near future. Regardless, a great deal of work remains before us if we’re to fully understand and treat this complex disorder.

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Recommended Reading

Brain food for babies

How does a mother supply a key building block of the brain required for neurodevelopment to her fetus in pregnancy? The critical requirement of docosahexaenoic acid (DHA) for fetal brain development, and the poor efficiency of its synthesis in humans, is a tricky metabolic problem to be overcome in pregnant women. Supplying this unique fatty acid to the fetus requires exquisite specificity and timing, processes that can unravel in disease conditions such as pre-eclampsia.

Long chain polyunsaturated fatty acids (LC PUFA), particularly docosahexaenoic acid (DHA, 22:6 n-3), have been shown in population and intervention studies to be extremely important for neurodevelopment, learning and cognitive function. DHA comprises a high proportion of brain fatty acids, mainly found incorporated in brain membranes, and has particular structural properties that enhance membrane fluidity. DHA has been shown to promote neurone survival and is required for neurone connectivity in the brain. In cases of DHA deficiency, another LC PUFA, omega-6 docosapentaenoic acid (n-6 DPA, 22:5n-6), appears to substitute for DHA in brain membranes. DHA is a LC PUFA of the n-3 series synthesized from an n-3 fatty acid precursor molecule obtained from the diet. The enzymes that synthesize the n-3 LC PUFA are shared with the n-6 series LC PUFA derived from an n-6 precursor in the diet. Given that human dietary n-6 precursor intake is up to eight-fold higher than dietary n-3 precursor intake, this means that the n-6 pathway predominates and in humans the synthesis of n-3 LC PUFA is rather slow. The production of DHA is however higher in women than in men.

Metabolic adaptations in pregnancy

The first brain cells are formed by day 15 of gestation; at 22 days the primitive brain is developing and the first nerves with their extending fibres are observable. By 28 days of gestation, closure of the neural tube (the precursor to the central nervous system) occurs and the head of the embryo grows fastest over the earliest gestational weeks. Thus it is evident that a ready supply of DHA will be required by the embryo very early in gestation. Tracer experiments show transfer of DHA via the placenta resulting in fetal plasma that is enriched in DHA when compared with their mother. These data show that the placenta is capable of selectively transferring DHA from maternal plasma to fetal plasma and a number of transport processes with selectivity for DHA have been described.

The physiological adaptation to pregnancy involves large increases in maternal plasma triglycerides: triglycerides are the storage form of fatty acids. We and others have shown that from the end of the first trimester until term there is a steady increase in maternal red blood cell and plasma DHA content of about 26%, which falls below trimester one concentrations after delivery. This maternal mobilization may provide sufficient DHA for the rapid growth phase of the fetus. It has not yet been determined where this DHA comes from. Potential sources include maternal dietary intake, release from maternal adipose tissue and membrane stores or increased maternal liver synthesis, but there are no data that confirm whether one or more of these sources are important.

Studying the earliest changes in pregnancy

As mentioned above, some of the key events in neurodevelopment occur very early in the first trimester. The studies just described have only looked at time points that are conveniently sampled, i.e. end of the first trimester and beyond. Most women book for antenatal care between 9 and 13 weeks of gestation and it is very difficult to sample at earlier time points in a free-living population. Indeed, during the very earliest week of pregnancy many women are not aware that they are pregnant. We know from our longitudinal studies that red blood cell DHA content is already 19% higher at the end of the first trimester than it is after delivery, suggesting that DHA mobilization may be occurring prior to this time point. In order to study these earliest changes we turned to a population of women undergoing assisted conception where accurately timed samples could be taken immediately before, and in the weeks after, conception. Women undergoing frozen embryo transfer, but who also retained their natural menstrual cycle were recruited so that we could avoid the potential metabolic interference of the high concentrations of reproductive hormones used for artificially reconstructing menstrual cycles in those women who have none.
In this population we observed that maternal plasma DHA concentrations started to rise at day 18 of pregnancy with the greatest rate of increase between day 18 and day 29, exactly the time of the earliest neurodevelopmental events including neural tube closure. Furthermore, we observed that DHA concentrations were higher in twin compared with singleton pregnancies. As we had measured a full fatty acid profile in the samples we could also see that omega-6 DPA (the ‘back-up’ brain fatty acid) was also much higher in the women with twin pregnancies. It is impossible to directly measure tissue activities of the enzymes involved in LC PUFA synthesis in pregnant women; however, product precursor ratios are often used to infer particular enzyme activities in the pathway. Using this substitute measure for Δ6-desaturase (a key enzyme in the DHA synthetic pathway), a strong correlation between Δ6-desaturase activity and the rate of change of DHA concentration at day 29 of pregnancy was observed, suggesting that maternal DHA synthesis may indeed be switched on in early gestation. It was also seen that plasma levels of the precursor of the n-6 pathway decreased markedly over the first 45 days of pregnancy, which would reduce the competition between the parallel n-6 and n-3 series pathways and allow the n-3 pathway to proceed at a greater rate.

Pre-eclampsia – when pregnancy lipid metabolism goes awry

Pre-eclampsia is a disease of pregnancy that only occurs naturally in humans and higher apes, although animal models for the disorder have been created. While the number of maternal deaths resulting from pre-eclampsia are in decline, at least in the developed world, the disease still results in many prematurely delivered infants. The primary defect in pre-eclampsia is located at the placenta with inadequate or compromised formation of the blood supply to the placenta. The defective placental function is associated with a maternal response of widespread endothelial dysfunction which results in the clinical features of water retention, protein in the urine and hypertension. The only real cure for the disease is to deliver the placenta and child, hence the high rates of prematurity. Pre-eclampsia is a rather mysterious disease and the disease pathways are not well understood (see feature by Eric George on p22).

The ability to understand pre-eclampsia is not helped by the variety of presentations of the disease (early or late presentation, mild or severe disease) and the variety of risk factors (first pregnancy, maternal obesity, etc.). The maternal metabolic adaptation to pregnancy also goes awry in pre-eclampsia and, amongst other changes, there are exaggerated increases in plasma triglycerides.

We were interested to find out how disturbed triglyceride metabolism in pre-eclampsia might affect DHA metabolism and found that, in pre-eclampsia, the third trimester maternal DHA levels were 40% lower than normal pregnancy levels and fetal plasma levels only a little better at 35% lower than normal. In maternal adipose tissue in women delivered by Caesarean section, we found that expression of enzymes involved in the synthesis of LC PUFA in pre-eclampsia was less than half of that in control tissues, suggesting that maternal LC PUFA synthesis may be inhibited in pre-eclampsia. LC PUFA synthesis is also inhibited in non-alcoholic fatty liver disease where high amounts of fat are deposited in the liver. We wondered whether the same thing might be happening in pregnant women

![Diagram highlighting the main sources of DHA and the transport pathway of DHA from mother to fetus. PE = pre-eclampsia; VLDL = very low density lipoprotein.](image-url)
with pre-eclampsia. In the absence of being able to sample maternal liver, we looked at the key organ involved in the transfer of DHA to the fetus, the placenta itself. A detailed comparison of all the fats in healthy and pre-eclampsia placenta demonstrated that placenta from women with pre-eclampsia did indeed have significantly higher levels of stored fat\(^9\).

**Parallels with type 2 diabetes**

The characteristics of poor fat handling we observed in pre-eclampsia, or at least that subset of pre-eclampsia with maternal obesity as a risk factor, made us think of the parallels with type 2 diabetes. Our current understanding of the disease process in type 2 diabetes involves the failure of subcutaneous adipose tissue cells to expand and hence safely store excessive fatty acids as lipid droplets resulting in fat accumulation in tissues such as the liver. Therefore we looked more closely at adipose tissue in pre-eclampsia and found that there was a higher proportion of smaller adipose cells in women with pre-eclampsia compared with healthy women suggesting a reduced ability of these cells to expand and store fat\(^10\). Functional studies of adipose tissue cells in the laboratory also confirmed that pre-eclampsia adipose tissue released more fatty acids than that from healthy pregnant women. Thus it is possible that a similar disease process to that observed in type 2 diabetes is occurring in obese women who develop pre-eclampsia in pregnancy.

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Gas Chromatogram of extracted erythrocyte fatty acids showing the main peaks. Docosahexaenoic acid (DHA) is the last peak (at 18.5 minutes) of the chromatogram.
Where next?

We are only a part way down the road of understanding how DHA is mobilized in pregnancy by the mother, transferred to her baby and how this might be disrupted in pre-eclampsia. Further interrogation of our database on the detailed fat composition of placenta will tell us about LC PUFA levels and composition in healthy and pre-eclampsia placenta. We are currently undertaking studies to look specifically at particles secreted by the liver that carry fats in maternal plasma (very low density lipoprotein) both in very early and later gestation in order to get a window into the fat composition of the maternal liver. Very little is understood about how DHA is preferentially transported across the placenta and in what form. What we do know is that DHA is an extremely important nutrient for the fetus and that transport processes in pregnancy appear to be exquisitely geared towards the early maternal mobilization of DHA. As the fetus can only acquire this important building block for the synthesis and development of brain tissue from the mother and our data demonstrate that the mother mobilizes DHA just prior to neural tube closure, this suggests that DHA supplementation (commonly taken as fish oil capsules) around the time of conception and in early pregnancy has the potential to be as important as folate supplementation over the same time period.

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References
Rett syndrome: a sex-biased neurodevelopmental disorder

Eyleen Goh (Duke-NUS Medical School, Singapore)

Decades of research on neurodevelopmental disorders have focused on genetics. Although there has been significant progress, the aetiology of many neurodevelopmental disorders still remains unknown. Deciphering genetic sequences of the whole genome can identify disease-causing mutations in individuals. However, the same genetic sequences do not necessarily result in similar gene expression profiles, or the consequential biochemical profiles in every cell and in all individuals. In particular, studies have shown that differential biochemical profiles in males and females, possibly play a role in neurodevelopmental disorders being biased towards a different gender. Interestingly, autism spectrum disorder (ASD) is biased towards boys although it is not an X-linked disorder, whereas Rett syndrome, an ASD-related disorder where the disease-causing gene is located on the X-chromosome, is found almost exclusively in girls.

Gender bias in autism

Data released by the Centers for Disease Control and Prevention (CDC) in 2014 on the prevalence of autism in the United States indicated that 1 in 42 boys and 1 in 189 girls suffer from ASD. This is consistent with sex ratios for ASD cases worldwide. Why is there such a huge discrepancy in the occurrence rate of ASD between boys and girls? Are there intrinsic behavioural differences between boys and girls that might affect disease diagnosis? Or is it simply due to biological differences between boys and girls? Both intrinsic behaviours and biological differences could underlie the apparent gender bias in autism, but these are not the only contributing factors.

Diagnostic test skewed towards the intrinsic behaviours of boys

Intrinsic behaviour can affect disease assessments and diagnosis. Questionnaires and tests for autism are biased towards identifying behavioural traits that deviate from ‘normal’. A clinical diagnostic instrument for assessing autism in children and adults, the Autism Diagnostic Interview-Revised (ADI-R), focuses on behaviours in the quality of social interaction, communication and language as well as repetitive, restricted and stereotyped interests and behaviour. In general, prepubescent girls show more social communication and interaction compared with boys, and boys are more active and show more anxiety and aggressive behaviour than girls. These intrinsic traits in boys indicate that the existing diagnostic tests will preferentially detect a higher percentage of boys that seem more ‘abnormal’ compared with girls.

Genetic differences – more is better?

Genetic difference is a well-accepted scientific explanation for the gender bias in the occurrence of autism. Boys have only one copy of the X-chromosome, while girls have two. So, girls have a ‘backup’ copy that can dilute or compensate for any mistakes that might occur on one specific copy. X-inactivation occurs to make sure only gene products from one X-chromosome are made in females, so that their levels are comparable to gene products made in males. As X-inactivation is a random process, it is unlikely that the genes on one particular X-chromosome will be inactivated in every single cell. This means a disease-causing mutation in
an X-chromosome located gene will likely cause more homogeneously severe symptoms in boys than girls.

Interestingly, girls diagnosed with ASD or other neurodevelopmental disorders have 1–3 times more severe genetic alterations (or mutational burden) than boys with the same disorder. It seems that the genetic advantage of girls having two X-chromosomes is the ability to tolerate more devastating genetic alterations. However, ASD is not an X-linked disorder despite evidence showing that some ASD-associated genes are located on the X-chromosome. Thus, X-inactivation is not able to explain the hundreds of other ASD susceptible genes that are not located on the X-chromosome. In fact, studies have shown that several genes that are expressed more in males than in females are also found enriched in autistic brains. This illustrates the complexity in deciphering the genetic underpinnings of autistic traits.

**Gender bias in Rett syndrome**

Rett syndrome is one neurodevelopmental disorder with a better-known aetiology. The Rett disease-causing gene, methyl-CpG binding protein 2 (MECP2) is located on the X-chromosome. Rett syndrome used to be classified under ASD, due to its autism-like clinical features. However, Rett syndrome has since been removed from the ASD category in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), largely due to its known molecular aetiology and the presence of Rett-specific clinical features that are distinct from ASD.

Rett syndrome affects 1 in 10,000 girls and is rarely seen in boys. This is because boys with mutations in MECP2 rarely survive till birth. Mutations in MECP2 typically occur during spermatogenesis, and such mutations are usually on the paternal copy of the X-chromosome. In addition, random X-inactivation in girls contributed to the wide spectrum of severity observed among girls and the same MECP2 mutation. The same mutation in MECP2 also resulted in differential effects on different brain regions and different cells in studies using Rett animal models. The expression levels of MECP2 proteins during early developmental stages are also different in males and females. This is beyond what can be explained by random inactivation of the X-chromosome.

**MeCP2 protein and Rett syndrome in different species**

The genetic sequence of the MECP2 gene is very well conserved in different species indicating orthologous functions and the potential to use different animal models to study Rett syndrome. However, there are obvious differences in disease manifestation in different species. Similar to Rett syndrome in humans, male rhesus and cynomolgous monkey fetuses carrying MECP2 mutations were miscarried, while females did not show any obvious phenotypes at least for the first 4 months after birth during the study period. This is profoundly different from mouse Rett syndrome models where all animals survived, and males, but not females displayed Rett syndrome phenotypes at an early age. Furthermore, Zebrafish has no gender during early development, and mecp2 mutant fish also survived but showed clear behavioural alterations and had a relatively shorter lifespan than wild type fish.

Despite species differences, studies using cells from Rett syndrome patients and different Rett animal models (knockout or knockdown of the MECP2 gene) show common neuronal-specific phenotypes. MECP2-deficient Rett neurons are smaller in soma size, have less extensive neurite outgrowth and have less number of synapses compared with control neurons. These Rett neurons also show deficits in their intrinsic functions and ability to form connections and networks with other neurons.

**Functions of MECP2 protein**

MECP2 was first known to be a repressor of transcription, but was subsequently found to have other functions such as RNA splicing and even transcription activation. For example, MECP2 binding to 5-hydroxymethylcytosine (5hmC) can facilitate transcription in neural cell types, but represses transcription when bound to 5-methylcytosine (5mC) containing DNA. However, it is still not clear why the 5hmC and 5mC content (different modifications...
on genes) in the same genes vary between different cell types. Nonetheless, these variations can therefore explain, at least in part, the very few overlaps in MECP2-dependent regulated genes identified from different studies, especially from studies using different organisms or different cells and different parts of the mammalian brain.

**Treatment for Rett syndrome**

There is no effective therapy for Rett syndrome to date, but efforts are being made on multiple fronts to attempt to reverse neurological defects. Earlier interventional studies for Rett syndrome in animal models focused on correcting mutations in the MECP2 gene where aminoglycoside antibiotics have been shown to suppress nonsense mutations in MECP2 in human cells. Other methods include replenishing downstream targets affected by MECP2 proteins such as insulin-like growth factor-1 (IGF-1) and brain-derived neurotrophic growth factor (BDNF). Although there were some encouraging results, these interventions were still less than ideal. Correction of mutations only works on nonsense mutations and are effective for up to 20% of all animals studied. Moreover, not all MECP2-deficient cells or animals show decreased IGF-1 and BDNF levels. Subsequent effort was then directed to targeting mechanisms affecting neuronal growth and functions. Compounds such as pentobarbital was used to modulate γ-aminobutyric acid (GABA) class A receptor signalling so as to enhance the growth and synaptic functions of neurons. Nutritional compounds such as choline could possibly work by changing the phospholipids composition in cell membranes and enhancing acetylcholine production, which are both affected in Rett syndrome models. Although these potential drugs are still at the experimental stage, using human cells and animal models, these treatment strategies have shown some apparent efficacies, and should go into human trials in the near future. The current treatment for Rett syndrome is only directed towards symptoms, providing support and speech, occupational and physical therapy as well as nutritional support. As Rett patients tend to also have seizure-like activity, sleep disturbance and gastroesophageal reflux (GER), anti-epileptic drugs (AEDs), sedative-hypnotic agents and anti-reflux agents are often prescribed in clinics to treat these symptoms respectively.

**Treatment for ASD**

Similar to Rett syndrome, there is also no cure for ASD. Current interventions for ASD are mainly targeted at behaviour, including speech, occupational and physical therapy. Along the same direction is the applied behaviour analysis (ABA) that uses positive reinforcement techniques to bring positive changes in behaviour. Medication is not the preferred intervention unless there are severe behavioural problems. The level
of the chemical messenger serotonin, has been found to be low in the blood and corticospinal fluid in ASD subjects associated with social behaviour. Thus, selective serotonin reuptake inhibitors (SSRIs) have been used in clinics. Anti-psychotic medicines are also frequently used to treat irritability and associated behaviours including aggression and self-injury as well as hyperactivity and stereotyped behaviour.

Since there is strong gender preference in the prevalence of ASD and biochemical profiles are different in males and females, the future direction of therapeutics for ASD is gearing towards sex hormones. Whether sex hormone-related interventions will be effective for ASD remains to be validated.

Eyleen L.K. Goh is a senior research scientist at the National Neuroscience Institute and an assistant professor with the Duke-NUS Medical School in Singapore. Her research laboratory is studying how neurons grow and functions in normal young developing brains as compared to diseased and adult brains. Their research work aims to understand the fundamentals of brain development and functions, and to search for possible intervention strategies for brain disorders. Besides the usual pharmaceutical approach, they are also exploring nutraceutical approach for the treatment of ASD and Rett Syndrome. Email: Eyleen_Goh@nni.com.sg.

References
Redefining reproduction

Last year was a significant year for reproductive biology research, with the creation of fertile mouse eggs from skin cells in a Japanese lab. Notably, the mouse eggs produced by Professor Katsuhiko Hayashi and his team from Kyushu University went on to form healthy offspring when fertilized and implanted in surrogate mothers - a promising development for the future of in vitro fertilisation technology for people with fertility problems. In another advance, Dr Anthony Perry (University of Bath) and colleagues produced fertile mice offspring by fertilizing abnormal ‘parthenogenote’ embryos, containing only the mother’s genes, created by artificially triggering mouse egg cells to begin dividing on their own. Helen Albert speaks to both researchers about their work and its implications for the future.

Making life

Katsuhiko Hayashi is based at the department of developmental stem cell biology at Kyushu University in Japan. He completed a PhD in Biological Sciences at Tokyo University of Science and then worked as a postdoctoral fellow at the Gurdon Institute, University of Cambridge, from 2005 to 2009. Following this, he spent 5 years as Associate Professor at Kyoto University in the graduate school of medicine before starting his own research group at Kyushu University. His current goals are to understand the basic mechanisms of early oocyte differentiation and to reconstitute oogenesis in culture. He is an expert on the generation of artificial eggs, having worked in this area in collaboration with his fellow researcher Professor Mitinori Saitou (Kyoto University) for a number of years.

Transforming skin cells into viable mouse eggs is a remarkable achievement, can you comment on how you got to this stage?

Our motivation to achieve egg production in culture is that we want to know what happens when eggs are formed (oogenesis). Therefore, we need to carefully see whether oogenesis in culture is really reproducing the events that you see in the body (in vivo) in mice. First, we carefully produced primordial germ cells, the precursor population of all germ cells (cells that can go on to form sex cells such as eggs and sperm), from embryonic (ES) and induced pluripotent stem cells (iPS) cells in 2011, although the preliminary experiments started in 2009. ES cells come from embryos, but iPS cells can be generated from adult non-embryonic cells. Then we produced functional eggs from ES/iPS-derived primordial germ cells by transferring them into an adult mouse ovary, waiting for 4 weeks and then taking cells again from the donor ovary and tissues, collecting the mature eggs from the follicles and then fertilizing them. At that time (2012), we needed to transplant them into the ovaries because the ovary is a very nice environment for growing egg cells. Now, in current work, we have managed to do it in culture. We succeeded in full egg production in culture from these cells in 2016. As you now know, this achievement took us 7 years with a lot of basic experiments.

What proportion of the eggs you created were successfully fertilized and did the resultant offspring have any abnormalities?

This depended on the ES/iPS cells. Fertilization rate is actually not different between the in vitro and the in vivo eggs, but the rate of the development is different. The development potential of the in vitro eggs is actually lower than the in vivo egg. This is probably because of the chromosomes. Some of the in vitro eggs have abnormal numbers of chromosomes. I think there are several reasons, but the possible reason I am now thinking is a chromosomal defect and maybe they need further maturation of the cytoplasm of the cells. So I think that they are immature.

The in vitro eggs largely went through the normal oogenesis pathway, but accuracy was bit inferior to that seen in vivo. For example, gene expression was almost identical in an immature type of egg, but in fully mature eggs there are some differences between those developed in vitro and those produced in vivo. And we saw abnormal chromosome numbers (aneuploidy) in 20% of the in vitro mature eggs, whereas less than
5% of eggs in vivo are aneuploid. We think that the successful rate of oogenesis is still lower in culture due to suboptimal conditions. We are now refining the culture conditions to try and improve this.

Overall, successful fertilization ranged from 0.3–3.4%. ES cell-derived eggs tend to have higher potential (1.2–3.5%), compared to those from iPS cells (0.3–0.9%). We did not see obvious abnormalities sex hormones. All of the pups from the ES cell-derived eggs grew up to be fertile adult mice without any premature deaths and they survived at least a year. For pups born from iPS-derived eggs, two were cannibalized by the nursing mother for some unknown reason, which sometimes happens during maintenance of mice. The rest grew up and all of them became fertile mice.

How does your work compare with that of Azim Surani and Jacob Hanna on human sperm and egg precursor cells?
First, the species is different, of course. Second is the stage of germ cell development. Please remember that the precursor cells are really an immature type of germ cell. For example, in mice the precursor cells appear at 6 days after fertilization, whereas it takes 5 weeks to become eggs. And oogenesis needs more complicated processes, such as interaction with surrounding somatic cells and growth of ooplasm (cytoplasm of the egg).

Do you think your process could be successfully applied to humans?
A big obstacle of the application is ‘gonadal somatic cells’. The cells are absolutely essential for egg production in the current culture system. Gonadal somatic cells contain precursors of granulosa cells and theca cells, both of which are known to play critical roles in oogenesis. In the case of mice, we got a number of the cells from fetal ovaries. It seems difficult to prepare gonadal somatic cells from human embryos because the sources of human embryos are limited. But I would say that it is not impossible. At the moment, it also seems difficult to replace the cells by recombinant factors or drugs.

I know that there are several groups that are trying to make eggs from human stem cells. In my experiments, I’m trying to make gonadal somatic cells from the pluripotent stem cells in mice, so if we can do that we do not need the embryos. If such a system is established, that technique could be applicable in humans. Then we will not need to involve human embryos. If we have such a system, we can make both germ cells and gonadal somatic cells from human stem cells. In that case probably making human eggs becomes more realistic, more feasible.

The other factor is that oestrus cycles in the mouse are 4–5 days, whereas in humans of course it’s 1 month. This means it would probably take a longer time to make the egg in humans than in the mouse. In the mouse system it takes 5 weeks to convert the stem cell to the egg. So I can imagine that for humans it could take 2 or even 3 months to convert the stem cells to the egg so it could be much longer than in the mouse and the culture conditions would have to be very good.

This kind of research obviously throws up some ethical questions. Do you think we should be developing this kind of research in humans to help people who are infertile? Or should we steer clear?
In my personal opinion, we need more careful evaluation of such artificial eggs. Again we saw a number of abnormal eggs and indeed the efficiency of producing pups is low (~3.5%, versus 60% of eggs in vivo grew up to pups). So, I think it is too early to apply this technology to humans. We need to find out more about possible problems and side effects first.

Of course you know there is already a technique to screen eggs to see if they are good or bad in humans called preimplantation genetic diagnosis (PGD), so this technique could be used to determine which eggs have abnormal chromosomes and then only use the good eggs. We can potentially get thousands of eggs using the in vitro technique, but we need to use a technique like PGD to select the best eggs. So if this technique in mice was transferred to humans, we could use a selection technique like PGD to choose a safe human artificial egg.

What role do you think regulatory authorities should play? Is it better that they approve this sort of research under strict guidelines (eg, like the recent approval of three-parent embryos by the UK Human Fertilization and Embryology Authority) or should they prevent research on human embryos?
Besides simply using eggs for reproduction, the system will contribute to deeper understanding of basic mechanisms of oogenesis, which may discover genes or factors causing infertility. So, all research for human egg production should not be prevented. Rather, we should control at some point, such as fertilization and implantation of artificial egg research. We are scientists, so our ethics is not to give an empty hope to people suffering from infertility. We need to express precisely the facts of our experiments.
Anthony Perry began his career at the University of Bristol, where he did a degree in microbiology and a PhD in microbial genetics looking at the causative agent of meningitis. He then switched to mammalian reproductive biology research at the University of Bristol in the late 1980s. The mid-1990s took him to Hawaii on a travelling fellowship, to work in the lab of Ryuzo Yanagimachi, a pioneer of assisted fertilization and cloning. There, he worked with Teruhiko Wakayama and together they were the first to clone mice, resulting in a 1998 *Nature* paper. Following a couple of years in the US, at Rockefeller University in New York and at a Boston company, Advanced Cell Technology, Perry moved to Japan to work at the Riken Center for Developmental Biology, Kobe, where he continued in the field of reproductive biology, returning to the UK in 2010. He is now based at the University of Bath where he is head of the laboratory of mammalian molecular embryology.

**What is your current research focus?**

We are continuing with the theme that I started in Hawaii, which is trying to understand the basis, in molecular terms, of the initiation of mammalian development using the mouse as a model. What we work on now, is how it is that when a sperm and an egg combine together in fertilization that they stop being these specialized cells and not only don't die, but give rise to a single cell that is capable of producing an entire individual. This is the most extreme programmed cellular potency change in nature that we know of, from death to the next generation. So we'd like to know what the molecular changes are that influence this in the first hours after sperm and egg union and that's the driver in my lab.

More recently things like genome editing have come into play. We've been able to show that the CRISPR-Cas9 genome editing system works very well in a process called ICSI, or intracytoplasmic sperm injection, where sperm is injected into an egg to artificially induce fertilization.

**Could you explain the rationale behind the research described in your recent research paper on parthenogenotes?**

The rationale is that we are trying to understand this process of reprogramming when the sperm and the egg get together in fertilization. We are changing as many of the different events and parameters as we can, seeing which of them are still consistent with development and which ones prevent development from occurring.

What happens in natural fertilization is that the egg is uniquely arrested in the cell cycle. At this stage, it has still not completed meiosis and when the sperm comes in, it tells the egg that it's arrived and the cell cycle is restarted. Quite quickly, the egg starts to take on the features of an embryo.

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**Parthenogenesis**

Parthenogenesis is a form of asexual reproduction in which growth and development of embryos occur without fertilization. It occurs in many plants, some insects, and a few vertebrates, but not in mammals, where both a maternal and a paternal genome are needed. There are different mammalian aneuploidies (chromosome number abnormalities e.g., Down's syndrome), but these are very unusual and usually when this happens the embryo is not viable. There are some species of geckos and lizards that can reproduce parthenogenetically, some of which live on Hawaii.
was that after 3 hours there was really no development. Toru decided to start his time course later and looked at 7, 10 and 13 hours. He found that after 7 hours if he injected the sperm and transferred those embryos to a surrogate mother he could get some offspring, about 1% (1 in 100). If he waited for 10 hours he could get almost twice as many viable offspring, at 1.8%, but if you waited until 13 hours, it went right up to 8.1%.

**Did the mice born through this process have any abnormalities compared with mice born through normal reproduction?**

These offspring are healthy and as far as we can tell they are normal, although we have not done any real testing apart from looking to see if they are fertile. When we look at them we can tell they are healthy and they seem to be behaving in a normal way.

We didn’t look at their telomeres, but what we did do, was to look at the longevity of these mice. Cloned mice tend to die off a bit earlier than normal mice, but that is not true of these ‘phICSI’ mice (produced from parthenogenotes). If anything, they might live a little bit longer than normal.

**Why is this a key finding for the field?**

For us, it’s key because the reprogramming in terms of DNA modification and histone modification of the parental genomes is different than it is in ICSI and normal fertilization. It’s also interesting, because ever since Karl Ernst von Baer (who discovered the mammalian egg) first knowingly observed a mammalian dog egg, and wrote in his report of 1827 that ‘animals develop from an egg’, this idea has bedded into the narrative of developmental biology and no-one has been able to show that you can fertilize anything other than an egg with a sperm and have full development.

The not particularly logical conclusion that you have to have an egg to support development with a sperm has now been shown in Toru’s paper to be invalid, because what we’ve done is injected a sperm into an embryo. This embryo is a mitotic cell and doesn’t depend upon meiosis. Now, whether it can only occur in that particular mitotic cell, or whether it can occur in other mitotic cells, this is a question that’s open. Whether you can also have a sperm being fully reprogrammed by other mitotic cells at the right stage of the cell cycle is another matter.

It may well be that factors that are inherited from the egg have been masked, or there could be other influences involved. We don’t know what the relationship is, whether it’s the same process or an analogous process that would have occurred in the oocyte that’s now occurring in the embryo, but if that’s the case we’d need to explain why the epigenetic modifications are different between the embryos formed from the parthenogenotes and those formed from normal fertilization or ICSI. We looked at a handful of marks and we found there were five that differed between the parthenogeneote and ICSI embryos, although we haven’t looked at the adult mice to see if they are epigenetically dysregulated.

**If you are suggesting that this process could theoretically take place with a non-gamete, would the amount of genetic information present not be an issue?**

That’s a very good point. So we have to think of ways, or people in the future will have to come up with ways of haploidizing the cell so that when you combine a maternal genome with the existing genome you end up with the right number of chromosomes.

**How do you think this process could become relevant to humans? Could it impact in vitro fertilisation, for example?**

Certainly not immediately. There are some other papers that may be more important in this regard. It’s very difficult to know what will become important without the benefit of 20:20 hindsight.

There was a brilliant paper that was published recently by Mitinori Saitou and Katsuhiro Hayashi, where they have almost recapitulated female meiosis in the lab (*in vitro*) [see Hayashi interview above]. Almost, because they had to use somatic gonadal cells that were derived in live mice (*in vivo*) in order to get this to work. But they have taken a lot of steps and it’s really impressive. So they can make oocytes, apart from that caveat, and this is all in the lab. This starts to answer a little bit your question about how do you haploidize, how do you get cells with one set of chromosomes? Well, they have done it.

People have raised a note that some of these procedures may not be all that easy to reproduce in humans because there have been other advances in the mouse. For example, *in vitro* recapitulation of growth and full development of eggs from very small oocytes to fertilizable oocytes. This has been known in mice for decades, and people have observed that this might be doable in humans, but I think there are other technological (not just ethical) issues that make it difficult to do.

There was a recent paper from a Chinese group in *Cell Stem Cell* that recapitulated male meiosis as well. They produced sperm precursors, spermatids. And they were able to produce healthy offspring when introduced into egg cells at around 4.7% success rate.

It’s all very promising, but let’s see whether it’s reproducible in humans eventually and if it is how long it takes us to get there.

**Further reading**

6. Cyranoski D. Rudimentary egg and sperm cells made from stem cells. Nature 2014 (http://dx.doi.org/10.1038/nature2014.16636)
Gender Medicine – the heart and mind of the latest findings in our collection from Clinical Science

Emma Pettengale (Commissioning Editor, Portland Press)

Gender Medicine focuses on the impact of gender on human physiology, pathophysiology, and clinical features of diseases. Men and women may have different experiences of the same disease and the pathophysiology of disease may also vary as a function of genetics, epidemiology and biological sex/gender. Translating molecular bioscience and experimental research into medical insights, the journal Clinical Science offers multi-disciplinary coverage and clinical perspectives to advance human health. Together with leaders in the field of gender medicine, we have put together a special themed collection of the journal focusing on this often neglected dimension of medicine.

This special collection of the journal was compiled with Guest Editor Jane Reckelhoff, whose guidance and assistance we are most grateful for. She has also contributed an introductory article to this issue of The Biochemist (see page 4). Professor Reckelhoff is a leading figure in the gender medicine community. She is the Director of the Women’s Health Research Center at the University of Mississippi¹, her research focusing on the role that sex steroids play in control of blood pressure and renal function, and the mechanisms responsible for postmenopausal hypertension. Serving on multiple editorial boards for respected journals, she is also an active member of the American Physiological Society, chairing the Women in Physiology Committee (2008–2011). Following this she was elected to Council, organized several conferences related to sex and gender differences and women’s health, and in 2016 she became the 89th President of the American Physiological Society².

The collection includes several contributions from key members of the gender medicine research community, not least from members of the Board³ of the International Society for Gender Medicine (IGM), including Giovannella Baggio, Marianne J. Legato, Virginia M. Miller and Vera Regitz-Zagrosek.

Beginning with ‘Gender-specific medicine in the genomic era’³ by Marianne Legato. Reviews the history of gender-specific medicine, and how our perception of the nature of biological sex has changed, particularly in light of expanding genomic discoveries. She explores questions such as: How has our concept of gender-specific medicine evolved? What is the impact of the genomic era on gender-specific medicine? Are “Male” and “Female” two distinct categories or a continuum? Legato is a globally recognized expert on the sex-specific aspects of men’s and women’s health and is the founder and director of the Partnership for Gender-Specific Medicine⁴ at Columbia University. In 2008, she established the non-profit Foundation for Gender-Specific Medicine⁴, devoting much of her research to the subject of women and heart disease.

Sex differentiation is controlled by complex molecular signalling pathways, including the development of the ovaries and testes in utero. Disorders of sex development such as 46,XX disorders can arise when gonadal differentiation
is disrupted, and Ingrid Knarston, Katie Ayers and Andrew Sinclair review some of the molecular and genetic mechanisms involved here.

**Ageing**

Professor Giovannella Baggio, Chair of Gender Medicine at the University of Padua, is the Founder and President of the Italian Research Centre for Gender Health and Medicine, a not-for-profit association established to investigate the ways in which sex and gender impact on normal human functions, patient-physician relationships, health organizations, and health policies. Worldwide, women live longer than men, and in her review on ‘Gender, aging and longevity in humans’ **7**, Baggio focuses on centenarians and their offspring as a model of healthy aging to explore possible gender differences which may impact on longevity, such as the influence of sex hormones on the immune system (see Fig 1).

**Immunology**

Women are more susceptible to HIV-1 infection, have lower viral loads during acute infection and exhibit stronger antiviral responses than men. Oestrogen receptor signalling could represent an important mediator of sex differences in HIV-1 reservoir size and may represent a potential therapeutic target. Marcus Altfeld is a Professor of Medicine at Harvard Medical School, where he is also Director of the Harvard University Center for AIDS Research **8**, and is recognised as an exceptional researcher in the field. In his review **9**, he discusses the impact of hormonal contraceptives on HIV-1 acquisition, how hormones may affect preventative measures, sex differences in the adverse events rate of ARV drugs, and the potential role of IFNα. A better understanding of the underlying mechanisms of HIV-1 infection, could improve preventive and therapeutic strategies.

**Kidneys**

Juan Jesus Carrero is a Senior Researcher in Renal Epidemiology at the Division of Renal Medicine (CLINTEC) and Center for Molecular Medicine (MMK), both at the Karolinska institutet. He sits on the Council of the International Society of Renal Nutrition and Metabolism (ISRNM) and is the founder and secretary of the European Renal Nutrition working group at the European Renal Association – European Dialysis and Transplant Association **10**. The effects of sex and gender on chronic kidney disease (CKD) have been poorly explored, and the field is not as developed as in other disciplines such as cardiology, discussed later. Carrero highlights the key sex- and gender-specific evidence in the field of CKD **11**, starting with a critical appraisal of the lack of inclusion of women in randomized clinical trials in nephrology, and thereafter revisits sex/gender differences in kidney pathophysiology, kidney disease progression, outcomes and management of haemodialysis care.

**Neurology**

The brain is the most complicated organ in the human body and the ultimate goal in neuroscience is to understand the connection between brain structure/ function and behavioural outcomes, with sex differences shown to affect the structure and function of the brain. Gregor Majdic and Neza Grgurevic are neuroendocrinologists from the University of Ljubljana, researching the interplay between genes and hormones in neurodevelopment, and they have reviewed the current understanding of sex differences.
Pre-eclampsia

Pre-eclampsia is a disorder of pregnancy characterized by high blood pressure and often a large amount of protein in the urine, affecting around 5-7% of pregnancies worldwide and is the leading cause of maternal morbidity.

The aetiology of pre-eclampsia originates from abnormal remodelling of the maternal spiral arteries, creating an ischaemic placenta that releases factors that drive the pathophysiology. It has been hypothesized that during pre-eclampsia, placental ischaemia occurs as a result of shallow trophoblast invasion which is associated with an immune imbalance where pro-inflammatory CD4+ T-cells are increased and T-regulatory cells are decreased. The role of inflammation in the pathology of pre-eclampsia is reviewed in detail by Babbette LaMarca, a leading researcher focusing on the interactions between lymphocytes and autoantibodies in the pathophysiology of hypertension in response to placental ischaemia. You can also read about pre-eclampsia in a feature on page 22 by Eric George.

An initial neurological outcome of pre-eclampsia is the absence of the autonomically regulated cardiovascular adaptations to pregnancy, which combined with sympathovagal imbalance and a blunted baroreceptor reflex sensitivity leads to life-threatening neurological outcomes. Gene L. Bidwell III, is an Associate Professor at the University of Mississippi, with a dual interest of glioblastoma and pregnancy. Together with colleagues Omar Logue and Eric George, he addresses the neurological consequences of preeclampsia that present in females both during and after pregnancy in their review.

Sandra T. Davidge is the Director of the Women and Children’s Health Research Institute (WCHRI), a Canada Research Chair in Maternal and Perinatal Cardiovascular Health, and a Professor in the Department of Obstetrics & Gynecology and Adjunct Professor in the Department of Physiology at the University of Alberta. Her lab investigates potential
mediators for vascular endothelial cell dysfunction in both aging and oestrogen deficiency as well as pre-eclampsia. In her research paper, she shows that circulating factors in pre-eclampsia contribute to endothelial dysfunction by increasing oxidative stress, decreasing nitric oxide bioavailability and increasing prostaglandin H synthase-dependent vasoconstrictors17.

**Diabetes**

Maternal obesity is a predisposing factor for gestational diabetes (which in turn increases the risk of pre-eclampsia), and increasing maternal obesity is associated with significant reductions in placental mitochondrial respiration. In their research paper, Muralimanoharan et al. show that down-regulation of miR-143 might be at least partially responsible for mitochondrial dysfunction in women with gestational diabetes controlled by medication18.

**Hypertension**

Hypertension (high blood pressure) affects one-third of adults in the Western world, is the most common independent risk factor for cardiovascular disease and there are important sex differences in the onset and rate of hypertension in humans. Compared with age-matched men, pre-menopausal women are less likely to develop hypertension, however after age 60, the incidence of hypertension increases in women and even surpasses that seen in older men.

Jennifer Sullivan is a pharmacologist and physiologist at the Medical College of Georgia at Georgia Regents University. She was the 2015 Chair of the American Physiological Society Sex and Gender-Related Research Interest Group19, and is currently working on research that will help determine some of the mechanisms of gender differences in hypertension with the goal of improving treatment for the condition. While there is evidence that T-cells have a role in the pathogenesis of hypertension, and that there are distinct sex differences in the presentation and pathology of the disease, the majority of this research has been conducted in males. In her review, Hay surveys the current understanding of the role of increased SNA in the risk factors contributing to hypertension21 and the role of oestrogen receptors in the brain on the regulation of SNA (Figure 3). Understanding the mechanisms by which oestrogen acts at key sites in the brain for the regulation of SNA is important for the development of novel, sex-specific therapies for treating hypertension.

Studies have shown that exposure to adverse influences during foetal life, birth weight, growth during infancy and childhood, all contribute to the developmental programming of increased cardiovascular risk. There is also a strong sex difference in the developmental programming of blood pressure, leading to increased blood pressure in males (Figure 4). The review from John Henry Dasinger and Barbara T. Alexander highlights the current data about sex differences in the developmental programming of blood pressure and cardiovascular disease22.

In this research paper, Brett M. Mitchell, from the Texas A&M Health Science Center, shows how human placenta-derived stromal cells decrease inflammation, placental injury and blood pressure in hypertensive pregnant mice23.

**Cardiology**

Virginia M. Miller is a member of the International Gender Medicine Society Board, Director of the Mayo Clinic Women’s Health Research Center, and Director of the Mayo Clinic Specialized Center of Research on Sex Differences24, and a leading voice in the study of sex differences in cardiovascular disease. Over the last
was thought of as a “man’s disease”, and Dr Wenger was among the first physicians to focus on coronary heart disease in women. She called attention to the fact that coronary heart disease in women was ubiquitous, often overlooked, and usually inadequately managed. She chaired the U.S. National Heart, Lung, and Blood Institute Conference on Cardiovascular Health and Disease in Women, and remains today one of the most outspoken and best known champions for women with cardiac disorders.

Women and men share many similarities in the pathophysiology and manifestations of heart disease, but as research advances we learn more about gender differences between the female and male heart. Further understanding of gender differences in the heart is crucial for advancing our ability to maintain a healthy population and identify and treat heart disease in both women and men. In her review she discusses specific examples within the spectrum of heart disease, and proposes areas for further research, including female-specific risk calculators.

Currently a member of the Board of the International Society for Gender Medicine and leading voice pushing for the consideration of sex in cardiovascular disease, in 2002, Vera Regitz-Zagrosek became the first and only German Professor of Cardiovascular Disease in Women at the Charité Berlin/Humboldt University. The following year, she founded the Berlin Institute for Gender in Medicine (GiM), the working group on cardiovascular disease in women at the German Cardiac Society, the German and International Societies for Gender in Medicine (DGesGM, IGM) and served as founding president in both. She is Task Force leader of the European Society of Cardiology on cardiovascular diseases in pregnancy. Research from her lab showing cardiomyocyte-specific overexpression of oestrogen receptor β improves survival and cardiac function after myocardial infarction in female and male mice is included in the collection.

As Nanette Wenger states, “Substantial morbidity and mortality can be attributed to our lack of focus on the prevention and treatment of cardiovascular disease in women. We cannot afford to lose more ground for one-half of the world’s population.” You can also read about the role of biological sex in cardiovascular disease in a feature on page 18 by Georgios Kararigas and Andrea Rodrigues Sabbatini.

During a career spanning over 50 years, Nanette Wenger’s steadfast dedication to reducing women’s disability and death from cardiovascular disease has made her one of the world’s most-respected experts on coronary heart disease in women. Half a century ago heart disease was thought of as a “man’s disease”, and Dr Wenger was among the first physicians to focus on coronary heart disease in women. She called attention to the fact that coronary heart disease in women was ubiquitous, often overlooked, and usually inadequately managed. She chaired the U.S. National Heart, Lung, and Blood Institute Conference on Cardiovascular Health and Disease in Women, and remains today one of the most outspoken and best known champions for women with cardiac disorders.

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To find out more about the sex and gender differences in cardiovascular disease, and other pathologies, please visit the full collection from Clinical Science, available online here: http://www.portlandpresspublishing.com/cc/gender-and-molecular-medicine.
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35. Schuster et al. Cardiomyocyte-specific overexpression of oestrogen receptor β improves survival and cardiac function after myocardial infarction in female and male mice Clinical Science 2016, 130 (5) 365-376; DOI: 10.1042/CS20150609
Citizen science is a concept that has developed over the last 40-years and is broadly defined as the engagement of the general public in scientific research. Although its roots go back much further to the days of the gentleman scientists, self-funded or amateurs such as Sir Isaac Newton, Charles Darwin and Benjamin Franklin. However, the definition can be made much broader to include ‘the engagement of non-scientists in decision making about policy issues that have technical or scientific components’ and the general public certainly have an important role to play in guiding science policy over the next few years.

Today’s citizen science projects are broadly composed of three main areas. Firstly, searching vast amounts of data, typically using personal PC’s such as SETI@home and folding@home. These are largely passive projects with little involvement for the volunteer after the initial setup. Secondly, the emergence of computer gaming that allows non-scientists to become actively involved in complex research problems that have been re-imagined as online multiplayer computing games e.g. eterna and Foldit. This type of gaming project has been a huge success. Finally, the largest contributors to citizen science are the data collectors who go out into the field to collect information on plants, animals and their environment. One of the biggest initiatives of this type being Open Air Laboratories (OPAL), which has more than a million participants in environmental and wildlife projects.

Brexit and the current changes in the global political landscape have huge implications for citizen science projects. The EU has been a major provider of funding for these initiatives and the UK has been a major beneficiary. Numerous citizen science projects involve data collection for biological science studies and many of these initiatives cross numerous national boundaries, migratory behaviour of wildlife being an obvious one, and as such are attractive to EU funders. A loss of EU funding, or at the very least a restriction...
in access to Horizon 2020 funding, would limit future opportunities for EU collaborative projects. This seems likely given that free movement of people will be an obstacle to negotiating access to EU funding streams. However, other national funding opportunities may yet present themselves and we should not forget that sources of money for public engagement in science within the UK are widely available for local projects. Only recently the Big Lottery provided £1.2 million to the UK focused OPAL citizen science network. A refocussing of citizen science projects within local communities also represents a real opportunity to engage with the British public on science/environmental issues that are most relevant to them. This is surely an opportunity worthy of further exploration, given all the concerns that the general public and professional scientists have regarding the UK’s place in the world, post BREXIT. Clearly, there has never been a better time to engage with the public on local/national issues, which matter to them and to infuse their support for UK science as the country finds its feet outside of the European Union. Global opportunities for funding may also be envisaged for citizen science and perhaps by turning our back on Europe we may have inadvertently opened the UK up to worldwide crowd science.

I have saved perhaps the most unlikely definition of citizen science till last, which is ‘the engagement of research scientists in the democratic and policy process of government’, now even professional scientists are part of the world of crowd-sourced science! Given the extremely low level of involvement of professional scientists in steering government policy, is it any surprise that obvious mistakes in government decision making are being made time and time again? Government policy failures are publicised daily, along with broken promises and the annoying use of cherry picked statistics by politicians at all levels of government.

There are thousands of scientists in the UK, but most prefer to keep politics at arm’s length. With Brexit looming large it is more important than ever that scientific researchers, both amateur and professional, play their part in guiding UK policy makers as valued citizen scientists.

The Biochemical Society is looking for members at all levels (from undergraduate students to senior scientists) to join our Policy Network. This is a great opportunity to feed into the Society’s policy activities and get your voice heard. For more information, please email our Policy Officer, Gabriele Butkute (gabriele.butkute@biochemistry.org)

Further reading:
- SETI@home website https://setiathome.berkeley.edu/
- Folding@home website https://folding.stanford.edu/home/
- Eterna game website http://www.eternagame.org/web/
- Foldit puzzle website https://fold.it/portal/
- Open Air Laboratories website https://www.opalexplorenature.org/
Biochemical Society announces Diversity in Science Grant winners

The Biochemical Society is committed to fostering diversity and equal opportunity for entry and progression in our discipline. In addition to funding a Daphne Jackson Fellowship, Stay-Connected bursaries and supporting In2Science placements for young people from disadvantaged backgrounds, the Society offers a Diversity in Science grants scheme to support our community in their activities to deliver a more inclusive environment for all.

The Diversity in Science Grants scheme was launched in 2014 and provides grants to support and address issues relating to diversity in science. We have been thrilled with the quality and creativity exhibited in the projects proposed in the latest round and are pleased to announce the following winners:

- **Joana Moscoso**, Native Scientist, Project: “Native Biochemists”
- **Bashira Chowdhury**, Auburn University, US, Project: “Bee a Biologist: Empowering Alabama’s Aspiring Biologists Through Pollination”
- **Eva Sharpe**, Institute for Cancer Research, UK, Project: “Who we are”
- **Jess Wade**, Imperial College London and King’s College London, UK, Project: “Hidden Women Wikithon”
- **Larissa Paver**, freelance science communicator, Project: “Kitchen Table Science”
- **Matthew Lee**, University of Bristol, UK, Project: “Big Bang Bristol”

Commenting on the grants, Dr David Pye, Chair of the Biochemical Society’s Policy Advisory Panel said: “Issues related to the underrepresentation or participation of groups in science are being addressed in the community, within educational establishments and in the workplace like never before. However, much still remains to be done if we are to offer better support individuals from poor socioeconomic backgrounds, women, ethnic minorities, LGBT and others who have an interest, or are employed in scientific activities globally. Over the years the diversity grants offered by the Biochemical Society have supported activities that reach out to people and highlight issues related to Diversity in Science. It was a real pleasure to be able to offer the diversity grants again this year, and to have received such an interesting and exciting range of proposals. I am sure that this year’s awards will enable the recipients to send out the message that science is for everyone and that discrimination in science is set to become a thing of the past in the not too distant future.”

The next round of Diversity in Science grants will open on 1 September 2017. For more examples of previously funded projects, please visit our website.

Research Excellence Framework consultation

Building upon Lord Stern’s Independent Review of the Research Excellence Framework (REF), the four UK higher education funding bodies are carrying out a consultation to propose an overall approach for the assessment in 2021. The inquiry looks into many areas of concern, including a potential administrative burden, portability of outputs, the definition of impact and the use of metrics. We have been gathering the views of our Committees and wider membership and will be contributing to the Royal Society of Biology’s consultation response. Higher education institutions and any other groups and organizations with an interest in the conduct, quality, funding or use of research, as well as, individuals are invited to respond to this consultation via the link below. The deadline for responses is Friday 17 March 2017. You can find more information on the HEFCE website: www.hefce.ac.uk/rsrch/refconsultation
The future of public engagement: Biochemical Society and beyond

Last November, the British Science Association held its inaugural Huxley Summit, titled Trust in the 21st Century. Named for Thomas Huxley (Darwin’s Bulldog), who was instrumental in bringing Darwin’s theory of evolution to the general public, the event aimed to capture the spirit of public debate, engagement, and interest in a high profile arena – and, crucially, involve people from beyond the boundaries of science. In a period of time when, apparently, “people in this country have had enough of experts” how do we as scientists rebuild this trust?

Engagement, but if you’ve never done any before, where do you start? A good place to begin your journey into the realm of PE would be to sign up for one of our free training events. In collaboration with the Royal Society of Biology, we are running a public engagement primer at 10 locations around the UK and Ireland. The aim is to give undergraduate and early career members the opportunity to learn about the principles and practicalities of engaging the public along with hands-on experience of running activities. Delivered by PE experts, Science Made Simple, the courses will give you everything you need to get started. If you can’t make it to one of the events, you can still access the Society’s archive of outreach and PE activities via our website.

When the Committee on the Public Understanding of Science (COPUS) was formed in 1985, much of its work was founded on the deficit model; suggesting that the public’s mistrust of science came from a lack of understanding of the current work being done. Thankfully, this rather condescending, top-down, didactic approach has been replaced with the more modern sounding ‘public engagement’. More than just a change in terminology, this has been a shift towards a two-way dialogue between research and the public, which benefits both sides and aims to inform, consult and collaborate. And I’m pleased to report that public engagement is in rude health. The range of opportunities for members of academia and industry to engage the public is vast, with a different approach suitable for almost every conceivable taste.

This year the Biochemical Society is taking a themed approach to its public engagement, with that theme being genome editing. We will be running activities at festivals and events, as well as holding public debates and lectures on the rise of these new technologies. As the Nuffield foundation has highlighted in its recent work on the subject, genome editing is a perfect example of the need for a dialogue with the public about current research. As scientists make rapid and potentially game-changing progress, it is crucial that we as a society discuss openly the limits to how we wish to use this technology. The ethical debate is one that cannot be confined to scientists.

But public engagement (PE) shouldn’t be seen as a service expected of researchers; when done correctly it is beneficial to both sides. As well as developing improved communication skills, researchers are able to get feedback on their work, gain new perspectives and ideas, collaborate with people from different fields, make connections, strengthen the pipeline of future scientists, demonstrate impact, and build public trust, accountability, relevance and responsiveness.

So, we know it’s important, and I know from personal experience that there is a lot of enthusiasm about public engagement, but if you’ve never done any before, where do you start? A good place to begin your journey into the realm of PE would be to sign up for one of our free training events. In collaboration with the Royal Society of Biology, we are running a public engagement primer at 10 locations around the UK and Ireland. The aim is to give undergraduate and early career members the opportunity to learn about the principles and practicalities of engaging the public along with hands-on experience of running activities. Delivered by PE experts, Science Made Simple, the courses will give you everything you need to get started. If you can’t make it to one of the events, you can still access the Society’s archive of outreach and PE activities via our website.

Helping out with Medicine Makers at Big Biology Day in Cambridge
to run for yourself. If you're looking for a bit more of a guided start, look out for when the education team will be attending events in your area (on the website or social media), we're always happy to have volunteers or even just a chat about public engagement. Check our website's public engagement page for a list of events and resources or send us an email at education@biochemistry.org.

For many researchers, running stands at science festivals and open days will be a regular occurrence. So, how can you take it to the next level? The first stage is to step away from the comforting environment of the science literate and to head to those audiences which don't often engage with science. The ASPIRES 2 project being run by Professor Louise Archer at King's College, London shows the importance of engaging with audiences of low science capital; those members of the public who have had little contact, interaction or experience of science in their everyday lives. (If you've not come across this principle, look at the further reading section to find out more) Taking your science activity to shopping malls, food festivals, book fairs, art galleries, music festivals, football matches, pubs, air shows and national parks, can really bring you to an audience who you might ordinarily miss. To help you with this, the Society’s Scientific Outreach grants offer up to £1000 for activities that communicate the excitement of molecular bioscience to young people and the community. There are two rounds a year which close in April and September, and we are always looking to fund novel and innovative PE activities. Details of these can be found on the grants section of the Biochemical Society webpage.

This of course, means that you might have to think carefully about how you are going to engage with these audiences. The first thing to consider is how you’re going to reach the audience; it’s likely that you will have to go to them. Instead of science festivals and museums, try going to food festivals and football matches! Could you run activities at a vacant shop in the local mall for a day? How could your research link into an air show? Could you demonstrate the science of sun protection at the beach? Do you have a talent for comedy or drama? Are you musical? How can you communicate your work in a different light?

Of course, in the spirit of proper public engagement, the planning of your activity should be a collaboration which includes members of the community that you are targeting. Every audience will be slightly different; working with them to understand their particular needs and challenges will ensure an effective interaction.

And really, that’s the key. It doesn’t matter so much what your PE activity is, the important aspect is that it starts a conversation; a two-way dialogue between you, the researcher, and a member of the public. This is where the real magic happens; it’s unpredictable, surprising and when everything is going right, absolutely joyous.

Remember, you’re not alone on this journey. There is loads of help and guidance out there; check the further reading list for inspiration and read on below to hear about how you can get involved with the British Science Association.

**British Science Association**

**Christina Fuentes Tibbitt**
(Engagement Manager, British Science Association)

The British Science Association (BSA), previously known as the British Association for the Advancement of Science, is a charity that was founded in 1831, and works to create a world where science is seen as a fundamental part of our society and culture.
The BSA organizes major initiatives across the UK. These include British Science Week, the largest grassroots celebration of science in the UK, and the British Science Festival, Europe’s longest-standing national science event which connects people with scientists and engineers from across the globe.

In addition, they support regional and local events through their network of volunteer branches and organize programmes for young people in schools and colleges, including the CREST Awards. They also run specific activities and training for professional science communicators; undertake research and policy work; and seek to influence and collaborate with stakeholders, including policy makers and opinion formers.

Through these programmes there are many ways in which you can get involved and make a difference to the BSA and its vision. The BSA believes that volunteers are the best people to connect with a broad range of audiences. Volunteers contribute time, energy and talent, as well as generate enthusiasm and help extend the BSA’s vision across the UK. In return, the BSA ensures that their volunteers’ contributions are recognised and supported, for example, by providing funding opportunities, promotion of their events, and rewards and recognition.

The annual Sir Walter Bodmer Award for Volunteering and the Branch of the Year Award both publicly acknowledge the contributions that specific volunteers and branches have made to the BSA. The volunteering opportunities available at the BSA are outlined online at: www.britishscienceassociation.org/volunteer. Examples of how you can get involved include advising the BSA on scientific developments, mentoring students doing a CREST science project, or speaking at the British Science Festival. You can also register as a speaker on their new event platform, Science Live (www.sciencelive.net). Science Live connects event organizers, science speakers and event volunteers together, making organizing and participating in science events that much easier.

“What I enjoy most about volunteering with the British Science Association is being involved in promoting science in the community through a well-respected organization – with easy access to support and funding.” – anonymous feedback from the BSA 2015 Volunteer Satisfaction Survey.

In addition to volunteering, you can also become a BSA member for just £3 per month. Your membership will support major initiatives across the UK, giving people from all ages, backgrounds and communities the chance to explore, investigate, and discuss science. As a member, you will receive a whole host of benefits including: exclusive opportunities to get involved with their work throughout the year, special offers with selected partners, and priority booking for special events. More information on membership can be found at: www.britishscienceassociation.org/membership.

So, if this has sparked your interest and you’d like to find out more, visit the websites mentioned above or contact the BSA directly at: info@britishscienceassociation.org They would love to hear from you!

Further Reading
- National Co-ordinating Centre for Public Engagement (NCCPE) - https://www.publicengagement.ac.uk/
- British Science Association - http://www.britishscienceassociation.org/
- Wellcome Trust - https://wellcome.ac.uk
- Royal Society Partnership grants - https://royalsociety.org/grants-schemes-awards/grants/partnership-grants/
- Bright Club - http://brightclub.org/
- FameLab - http://www.cheltenhamfestivals.com/about/famelab/
- Dance your PhD - http://gonzolabs.org/dance/
- Pint of Science - https://pintofscience.com/
- BiG STEM Communicators network - http://www.big.uk.com/
- Big Bang Fairs - https://www.thebigbangfair.co.uk/
- ASPIRES 2 - http://www.kcl.ac.uk/sspp/departments/education/research/ASPIRES/index.aspx
In the UK, social mobility is lower than in any other nation in the Organisation for Economic Co-operation and Development and in Britain people who are born to a poor family usually die poor. Experts say that education, education, education is key, but textbook science and a lack of science teachers compounds the problem. A new report just out shows that bright young people from low income backgrounds face major barriers when pursuing science degrees and careers, leading to their under-representation in the sector (Laurison and Friedman, 2016). A good science education, which dispels young people’s reliance on post-truth while promoting diversity and attracting the brightest regardless of background, is vital to drive innovation and success in the scientific community.

How do we encourage under-represented groups to enter into careers in science? By leveraging the science community to give those most in need a real science experience, role models and careers guidance.

In2scienceUK is an award winning charity founded by research scientists with the mission to target young people from poor and under-represented backgrounds to help them to progress to science degrees and professions while promoting diversity and equal opportunities. The programme puts researchers at the heart of the solution enabling the selected students to work alongside researchers on cutting edge science. High quality skills days provide invaluable advice and information. This year in2scienceUK teamed up with Abcam, a leading global life science research tools company that produces antibodies, kits, reagents and other research tools, to launch the Abcam Image Competition. Students entered images into one of three categories. The results were stunning.

We are passionate about providing inspiring opportunities for our participants and we are really keen to find new ways to develop industry links which engage our students in a creative way. The Abcam image competition did just this and our students loved making the images and showing them to their friends, families and teachers.

Commenting on the collaboration, Alan Hirzel, CEO of Abcam, said: “We are thrilled to be involved with In2science and look forward to the launch of Abcam’s bespoke mentoring programme in 2017. As a business that has always closely collaborated with the scientific community, we believe inspiring the next generation is critical to advancing future scientific research”.

Evaluation of the In2ScienceUK programme and students shows that over 70% of participants progress to university to study a science degree. The images and student testimonies reflect the measurable positive impact and transformational difference communities can make.

As part of the in2scienceUK experience, students also take part in a blog competition and submit a report on their lab experience. This year the blog winner was Benjamin Simpson. He wrote his blog during his placement in Professor David Attwell’s group at UCL where he carried out his placement. “There are so many small things that you learn in class that seem to make little difference but out in the industry are absolutely vital. I am very grateful for the experience and took a lot from it” he commented. Ben’s blog has been published on the Biochemical Society blog (https://biochemicalsociety.wordpress.com/).
To be eligible for the in2scienceUK programme students must fulfil the below categories:

- Year 12 student
- Receive free school meals
- Have parents who do not hold a higher education qualification

In 2017, there is an additional focus on supporting those from white working class and black backgrounds.

In2scienceUK has expanded and supported:

- 552 students
- From 147 schools
- Supported by over 252 volunteer scientists

78% of in2scienceUK students proceed to university
54% of in2scienceUK students proceed to a top university

Mouse cochlea section under a confocal microscope. Student: Fabiola Hauwel, Supervisor: Dr. Katie Smith, Lab: UCL Ear Institute

Getting to grips with a micro-pipette. Student: Ilhaam Ibrahim, Supervisor: Luis Pacheco/Roberto Lopez, Lab: UCL Biochemical Engineering

Injecting DNA For electrophoresis. Alice Cummings, Supervisor: Katherine Trevers, Department: Kings College London. Centre for Developmental Neurobiology
Social mobility (the income gap between the richest and poorest in society) continues to drop, with our earnings more likely to reflect our parents’ than any other country (OECD, 2010). A recent study has shown that science follows this relationship and bright students from the poorest backgrounds are unable to pursue their interest in science due to the lack of information, opportunities and role models they have compared to students from wealthier backgrounds. (Laurison and Friedman, 2016). This starts at university with students from poor backgrounds six times less likely to progress to university than their more affluent peers.

The Biochemical Society is proud to support in2scienceUK. In addition to sponsoring five students each year, the Society also gives delegates attending our events the opportunity to donate to the scheme. In 2016 this allowed us to provide an additional £600 in funding.
Royal Society of Biology News

Working with Government to ensure support for UK research

The Royal Society of Biology has been working to represent the views of its members and Member Organizations in our policy work, as the Government approaches the challenging Brexit negotiations ahead.

We set out our position in a policy briefing on ‘Arguments in favour of public investment in UK research and innovation’, and were pleased to see the importance placed on research and development (R&D) in the Autumn Statement. The Chancellor said that the UK “does not invest enough in research, development and innovation” and that to amend this, the UK will build on its strength in innovation in science and technology, to ensure the next generation of technological discoveries are made and developed in the UK. The announcements of funding and regulatory support built on the new substantial investment in R&D worth £2bn per year by 2020, revealed shortly beforehand by the Prime Minister.

We welcome the Government’s commitments to helping the UK maintain its leading role in R&D. The RSB is keen to continue working with and advising Government to ensure that global collaboration and the international flow of talented people is enabled and supported, and the right regulatory environment created, in order to truly benefit from the financial investment in UK R&D.

In December, representatives from the RSB took part in discussions with Robin Walker MP from the Government Department for Exiting the EU, along with other scientific and conservation charities. The discussion included topics such as funding for research and innovation, continent-wide collaborative programmes, talent recruitment in the science community and the importance of maintaining international environmental standards, as the UK leaves the EU. We look forward to ongoing discussions with Government and others, and to building on collaborative and joint working approaches across the sector.

The provision of scientific advice is a key activity for the RSB and our members. So we were very pleased that the Cabinet Office withdrew from the proposed ‘anti-lobbying clause’ in their grant standards, which would have restricted publicly funded scientists and researchers from using their expertise to advise MPs and Ministers. As an early intervention in March 2016, I, along with chief executives of eight member Learned Societies, including the Biochemical Society, wrote to the Cabinet Office Minister Matt Hancock to highlight community concern and seek a solution. We are relieved that Government has listened to the concerns of the community, removed uncertainty, and officially acknowledged that informing policy and public debate is an integral part of the research process.

The RSB’s public engagement work brought food experts to Cardiff for a ‘Come Dine with the Future’ event in November. Five researchers outlined strategies including urban farming, insect eating, GM livestock and rice grown using recycled sewage, in order to create a menu of the future which could sustainably nourish our growing population. We also crowned the hedgehog the Favourite UK Mammal with a huge majority of the 5,000 votes in our public poll; which aimed to highlight population decline and conservation of diverse UK mammals, especially during the winter months.

During World Antibiotic Awareness Week the RSB worked with the Biochemical Society and the Society for Applied Microbiology to run a live tweet chat with AMR experts. The hour-long Q&A was a great success with questions pouring in on everything from farming to diagnostics, to vaccines and phage therapy. It was great to work across audiences to increase engagement and understanding of this important and complex topic.

Dr Mark Downs CSci FRSB  
(Chief Executive, Royal Society of Biology)
Upcoming Events

- Using e-learning to improve student engagement in the biosciences: a workshop for HE educators
  20 March 2017, London, UK
- ROS and Mitochondria in Nervous System Function and Disease
  27–29 March 2017, London, UK
- Effective teaching strategies for Cancer Biology
  29 March 2017, London, UK
- The 1st Biochemical Society and Against Breast Cancer Glyco Oncology Workshop
  6 April 2017, Oxford, UK
- Protein modelling and its applications in current science
  6–7 April 2017, Keele, UK
- Quantitative Proteomics
  22–23 May 2017, London, UK
- Non–Coding RNA: Recent Insights into the Mechanisms of Action
  22–23 June 2017, Edinburgh, UK
- Deubiquitinases – From Structure to Physiology
  26–28 June 2017, Oxford, UK
- A Breath of Fresh Air: Helminth Protection From Chronic and Acute Lung Diseases
  5–6 July 2017, Winchester, UK
- Translation UK 2017
  6–7 July 2017, Nottingham, UK
- EMBO Conference – Helicases and Nucleic Acid-Based Machines – Sponsored by Harden Conferences
  23–28 July 2017, Banberg, Germany
- Extracellular Electron Transfer: Mechanisms and Opportunities
  21–23 August 2017, Norwich, UK
- The Pleiotropic Nuclear Envelope
  22–25 August 2017, Edinburgh, UK

Meeting Reports

Cardiovascular Disease and Diabetes

5–6 September 2016, University of Leeds, UK

The rising global epidemic of diabetes is a major healthcare concern. Given that the leading cause of mortality in these patients is cardiovascular disease, the British Society for Cardiovascular Research BSCR) autumn meeting on Cardiovascular Disease and Diabetes, supported by the Biochemical Society, could not have been more pertinent. The meeting had over 150 delegates and contributions from the UK, The Netherlands, Sweden, France, Japan and the USA.

The scientific programme was fascinating and included sessions on ‘Vascular signalling in diabetes’, ‘The diabetic heart’ and ‘Molecular mechanisms towards novel therapeutics’. All the speakers presented cutting edge data, giving the delegates a taster of the exciting scientific advances that will be emerging in the next few years. Attendees were also treated to an invited lecture from Dr Shin Yajima from the Osaka University School of Medicine. The meeting offered an exceptional display of current and future-thinking research, inspiration and context that will undoubtedly lead to fruitful collaboration driving future research into the cardiovascular complications of diabetes.

Kirsten Riches and meeting co-organizers

Victoria Mascetti, winner of the Marshall Young Investigator Prize, receiving her award from Colin Berry, Chairman of the BSCR, at the event

The 4th International Biennial meeting on La and Related Proteins

14–17 September 2016, Stockton House, Wiltshire, UK

This Independent Meeting, supported by the Biochemical Society, brought together 38 scientists working on La and Related Proteins (LARPs), including 20 principal investigators and 18 graduate students and postdocs. The talks and poster presentations at the conference conveyed a broad spectrum of topics in RNA biology and presented exciting new aspects of LARPs’ mechanisms and functions, featuring predominantly unpublished results.

The 23 talks were divided into 5 themed sessions and 8 young scientists were given the opportunity to give oral presentations. Four Faculty of 1000 prizes were awarded to John Brogie (University of Iowa, USA), Daniele Hasler (University of Regensburg, Germany), Emily Baldwin (King’s College London, UK) and Sandy Mattijsen (National Institutes of Health, Bethesda, USA) for giving the best young scientists talks on a variety of topics in the LARP area.

A Nucleic Acids Research (NAR) prize was also awarded to Roni Lahr (University of Pittsburgh, USA) for her talk and poster “LARP1 interacts directly with 5’UTRs encoding translation machinery”.

Attendees expressed their pleasure with the excellent science presented and the many opportunities to socialize, network and discuss potential collaborations in the stunning surroundings.

Maria R Conte, Cécile Bousquet-Antonelli and Sarah Blagden

Stockton House (from http://www.larp-society.com/meeting-2016-information/)
Local Ambassador Focus – David Whitworth

David Whitworth did his first degree Biochemistry at the University of Oxford and then went to the University of Warwick to do a PhD in molecular microbiology. After a couple of postdocs and a fixed-term lectureship at Warwick, he moved to a lectureship at Aberystwyth University in 2007. He currently co-ordinates undergraduate Biochemistry provision at Aberystwyth and was recently promoted to Reader.

What motivated you to become a scientist?

I was fascinated by science subjects at school, particularly chemistry. At A-level I was introduced to the molecular basis of transcription and translation, and from then on was determined to become a biochemist. I like knowing how and why things happen - what the mechanisms are that underpin phenomena we can see. And it is a real privilege to have a job which involves discovering such knowledge.

What inspires you about molecular bioscience?

The subtlety and the stochasticity of life. The plasticity of genomes, coupled with probabilistic interactions with the environment, give rise to reproducible, robust and yet highly improbable biological phenomena.

What are you reading at the moment?

I don't read for pleasure any more. There always seems to be something more robust and yet highly improbable biological phenomena.

What's on your lab bench/desk right now?

I don't really have a bench anymore. I didn't use it for months at a time, so decided to give it up. On my desk are three disorganized piles of paperwork. I favour a temporal filing system - how high things are up the pile is dictated by how recently I last needed them. There are also a couple of Star Wars spaceships dangling off my monitor - pure frivolity which makes me smile.

What's been the greatest challenge in your career so far?

Getting a permanent lectureship was the greatest and most stressful challenge. I didn't get any papers published during my PhD and only one in my first postdoc, which put me on the back foot compared to most of my peers. Luckily my supervisor indulged me taking a few tangents wduring my postdocs which allowed me to catch-up on the paper count.

What is your advice for someone who would like to pursue a career in molecular bioscience?

Try not to lose the enjoyment of biology when focusing on the details of research. It's very easy to get obsessive about tiny things - a particular experiment, a potential application, Serine-135, etc. Always keep in mind the bigger biological picture.

Take responsibility for your own career trajectory early on and plan strategically. Take every opportunity that comes your way, and if none do, create your own.

What do you do in your spare time?

I love photography. Having two young children I don't have as much truly free time as I used to, so painting has gone by the wayside for a few years. With photography though, you can be creative and get some really good results without having to invest a huge amount of time in it.

Ambassadors are a key group of members that help us to raise awareness of the Biochemical Society, promote its activities, recruit new members and act as the Society's point of contact at their institution. If you would like to get involved as an Ambassador please contact: membership@biochemistry.org

Second EMBO Workshop - Actualizations in Membrane Trafficking in Health and Disease

4–9 September, La Serena, Chile

The Biochemical Society supported the Second EMBO Workshop ‘Actualizations in Membrane Trafficking in Health and Disease’ held in September 2016 in La Serena, Chile. The meeting gathered 97 attendees from Europe, USA and South America who exchanged novel ideas and evidence about the molecular organization of the cell with an emphasis in membrane traffic.

Three major themes and conceptual breakthroughs emerged during the meeting. First, there was a collective realization that traditional boundaries of organelles are blurring through interorganellar contacts, signaling mechanisms and metabolic pathways coordinating organelles as distinct as the endoplasmic reticulum and mitochondria.

Second, sequentially organized organelles such as the endoplasmic reticulum and the Golgi apparatus establish molecular dialogs that coordinate responses of the whole exocytic route to diverse physiological challenges. Finally, the advent of novel microscopy and genomic editing approaches is opening unprecedented access to mechanisms traditionally explored in cells in culture, now in whole organisms such as zebra fish and Drosophila.

An intense intellectual and collegial atmosphere characterized the meeting. Graduate students and post-docs actively participated in prolonged and enriching discussion during talks, poster sessions and social events. The meeting fostered collaborations, exchange and visits, achieving its goal of reducing geographic barriers among scientists in three continents.

María Paz Marzolo and meeting co-organizers

Membership News

The annual Local Ambassador Day took place at Charles Darwin House in London on 17 November 2016. Local Ambassadors (LAs) form a key part of the Society’s network in attracting, recruiting and retaining members, we have Local Ambassadors at universities in the UK and worldwide and now have two Local Ambassadors within companies as part of our industry strategy. Approximately 30 LAs attended and heard updates on the Society’s activities and discussed new initiatives to be taken forward into 2017. Following the LA Day, the 2016 GlaxoSmithKline award lecture on Cancer Diversity and Evolution was given by Charles Swanton.

To find out more about the Local Ambassador program please email: membership@biochemistry.org
Looking forward to the year ahead – as I’m sure many readers will have done recently – it is encouraging to see that 2017 is set to be another busy, and hopefully fruitful, year for all at the Biochemical Society and Portland Press. This year, we welcome Professor Anne Dell of Imperial College, London, as the Society’s incoming Chair. The arrival of 2017 also marks the second year in which the Society continues to pursue its three-year objectives, and I look forward to working with Anne, our President, Professor Sir David Baulcombe, and the Council of Trustees, to drive forward our strategy.

As you will have read in previous issues, the recommendations of the governance review were approved by the membership last July, and following this we are implementing a new and improved governance structure that will help to support the continued dedicated work of the Society’s Trustees, who will meet as the newly formed Council of Trustees for the first time this month. Without a doubt, the Society draws its greatest strengths from its membership, and in this new structure we are therefore eager to maximize opportunities for members at all career stages to engage with the Society, its governance and its strategy. To this end, I would strongly encourage all of our members to consider stepping forward to help shape the future of the Society in the round of nominations which will open soon. The closing date for nominations is Friday, 3 March; if you’re interested in getting involved and would like further information, please get in touch with Zoe Halbert, Executive Assistant (zoe.halbert@biochemistry.org).

We continue to champion the molecular biosciences during this pivotal time, channelling the views of our membership to the government through our ongoing work with the Royal Society of Biology (RSB) and, following the UK’s decision to leave the European Union, we have responded to several consultations on the implications of this for UK science. We have also been gathering the membership’s views to feed into the RSB’s response to the consultation on the implementation of the Research Excellence Framework (a topic which will be covered in more detail in the next issue of The Biochemist). In March, we will attend the Voice of the Future event, organized by the RSB, in Parliament. We will be joined by up to six of our early career members, who will have the opportunity to ask science policy questions of prominent scientists and politicians.

Nurturing collaborations with sister societies also remains a strategic focus across the breadth of the Society’s activities. This is especially important as part of the Society’s meetings strategy and I am pleased to update you on several exciting collaborative events. In April, the Society will attend the Experimental Biology 2017 conference in Chicago (22–26 April). Following the success of our joint mixer with the British Pharmacological Society and The Physiological Society at last year’s meeting, I am pleased to announce that this year we hope to continue this new tradition with the additional involvement of the Nutrition Society (which last year celebrated its 75th anniversary). Our new Honorary Meetings Secretary, Professor Stefan Roberts, will co-host this event which we hope will raise the profile of UK biosciences, as well as each of our respective societies. A little closer to home, the Society is sponsoring a symposium, ‘Epigenetics: causes and consequences in neurological disorders’ at the British Neuroscience Association 2017 Festival of Neuroscience which will take place in Birmingham (10–13 April).

2017 will also see the launch of the Society’s first new journals since 1981, one of which, Emerging Topics in Life Sciences, is jointly owned with the RSB. The first issue, (which will explore the pertinent theme, ‘Antibiotics of the Future’) will be published later this year. Don’t forget to also keep an eye out for our other new, online-only and fully Open Access journal, Neuronal Signaling – you can access the first articles online at http://www.neuronalsignaling.org/.

Building upon our successful repertoire of public engagement collaborations, this year we are developing a new public engagement activity, ‘Scientific Scissors’, an exciting project in collaboration with the British Society for Gene and Cell Therapy which will explore genome editing. In addition, to support those of our student and early-career members who are interested in developing the skills to run their own public engagement activities, we have collaborated with the RSB to produce a programme of free public engagement training days delivered by public engagement experts, Science Made Simple, at locations across the UK.

We are also in the early stage of exploring a collaborative activity with CDH co-owner societies which would take the form of a scientific meeting and public engagement event to be held in the Autumn.

Working with our sister societies has never been more important to secure a strong future for the life sciences – I’m sure readers aren’t strangers to the benefits of collaboration – and I’m pleased to be able to report on so many exciting projects lined up for 2017.
Introducing the Chair and President

Chair of the Executive Management Committee – Anne Dell, Imperial College London

I am delighted to have taken up my position as Chair from 1 January 2017. I am aspiring to bring as much to the Society as Ida Smedley MacLean did. She was the first woman to Chair the Society (1927–1928) and you may have read about her in Robert Freedman’s Historical Feature in the December issue. If not, I urge you to read Robert’s article now – Ida’s life is an inspiration to us all.

The beginning of 2017 marks a number of governance changes for the Society. These will be coming into effect as a result of the recent review of the Society Governance, the outcomes of which were approved by the membership at the Annual General Meeting in July 2016. More information about the Society’s governance can be found on our website at www.biochemistry.org/AboutUs/CommitteesGovernance.

The key aims of these changes are to introduce clearer, more transparent and responsive governance structures, policies and procedures and to encourage collaboration amongst our Committees and with other Learned Societies. Another important outcome of the review is an agreement to ensure a more proportional representation of the Society’s membership amongst its Trustees.

A significant change arising from the review is that a new Executive Management Committee has been formed, along with a new Council of Trustees. Also, committee structures have been streamlined and terms of reference have been updated to ensure they are fit for purpose. I will chair the Executive Management Committee, which will be working hard to implement our strategy as set by the Council of Trustees under David Baulcombe’s leadership. This Committee will meet regularly and will act to efficiently evaluate and govern Society activities as outlined by the scientific, community and operational strategy set by the Council of Trustees. We will report to the Council on how these activities are progressing according to the relevant strategies.

President of the Biochemical Society – David Baulcombe, University of Cambridge

As a new year begins, I welcome Anne to her new role at the Society and reiterate my thanks to outgoing officers including Steve Busby, our outgoing Chair of the Executive Committee. One of Steve’s achievements was to oversee changes to the Society Governance that will help us to become more efficient and allow us to achieve more towards raising the profile of biochemistry and molecular bioscience and to give better support for students and colleagues in the scientific community.

A consequence of these changes is that the President will now chair the newly constituted Council of Trustees. This is an expanded role in which the President will oversee the formulation and evaluation of the overall strategy for the Society working in collaboration with the area-specific committees such as the Science Activities Committee. I look forward to this challenge.

Both Anne and I would welcome any feedback or questions you may have about governance changes or other aspects of the Society. Please contact us at info@biochemistry.org.

Exciting activities to look out for early in 2017 include the launch of two new journals by Portland Press. The first articles in Neuronal Signaling have just been published and the first issue of Emerging Topics in Life Sciences will appear in April. The 2017 Science Communication Competition has just opened for entries. This is a great opportunity for all the students among you to practise your science communication skills. The Society’s second scientific meeting of the year - ROS and Mitochondria in Nervous System Function and Disease – takes place at Charles Darwin House at the end of March. Places are still available if this is an area of interest for you. There are also a number of conferences taking place over the summer that have recently opened for abstract submissions. You can find information about these and other events on the Society website.
Green Technologies for the Environment

2016, Edited by Sherine O.Obare and Rafael Luque, American Chemical Society, ISBN: 978 0 841230 18 7

There is an ever growing demand to provide the chemical building blocks of our future in a sustainable manner. Green chemistry is used to describe processes which neither hinder human health or the environment. It is driven by the desire to avoid disasters and damage in the chemical industry: a stepping stone to more sustainable future practice.

This book, inspired by three symposia organized by the editors, contains sections on new solvent systems; advances in materials and chemical reactions; waste valorisation and biomass conversion. Across 13 chapters, experts in the fields of biotechnology, toxicology, chemical and environmental engineering discuss advances in green chemistry.

Many of the processes described focus on low-cost, renewable alternatives to their unsustainable counterparts. The development of solvent systems to replace toxic organic chemicals forms the first part of the book. Solvents are used daily, with widespread application from cosmetics to the production of electronics. The authors provide a comprehensive review of the applications and hazards of traditional solvents, before assessing alternative options.

Following this, are advances ranging from green oxidation to chemical reactions in the absence of a solvent. Photocatalytic oxidation of toxic compounds is presented as an increasingly important technology for combating environmental pollution. As would be expected, many of the techniques still have barriers to overcome relating to efficiency, cost or energy use.

The magnitude of food wasted each year is highlighted, as technologies are suggested which use waste as a feedstock for sustainable chemical and biofuel production. Energy storage is explored through the production of budget friendly, re-usable batteries made from carbon fibres. Finally, the book explores biomass conversion processes ranging from the role of nanoparticles in the production of liquid fuels, to the use of agricultural by-products to generate added value: the opportunities for green technologies are seemingly endless.

Perhaps owing to its nature, as a collection of original research and review papers, the book contains a wealth of figures depicting chemical reactions, mechanisms and analytical results. The wide ranging topics are inevitably targeted at a niche audience. The format, and depth of content, is likely to favour postgraduate readership. Retailing at £97.00, it is an affordable option for academic libraries.

A timely collection, well referenced and succinctly published, this book provides a snapshot into the variety of green innovations under development, as we strive to achieve a sustainable future. The book is best approached as a collection of individual papers on like-minded topics: a pick’n’mix selection of technologies to be dipped into, and enjoyed, separately.

Sarah. E. Cotterill (Newcastle University, UK)

Where Science and Ethics Meet

2016, Chris Willmott and Salvador Macip, ABC-CLIO-LLC, ISBN: 978 1 4408 5314 6

Where Science and Ethics Meet provides an exploration of moral questions arising at the frontiers of medicine and biology.

Willmott and Macip begin by offering an overview of reproductive technologies, and they touch upon the difficult issue of selecting embryos on the basis of parental preferences for certain traits. They make a considerable effort to go beyond the reductive ‘designer babies’ label and to present heuristics of reproductive decisions and technologies that do not rely on this overly simplified account of the complexities of assisted reproduction. The authors continue by reflecting on the challenges of cloning non-human animals and humans. Considering the long-lasting debate on cloning, and the often dystopian and utopian scenarios that proliferate in this debate, the authors astutely separate science fiction and reality. Human enhancement is also tackled by the authors, using examples from track and field to show the potential of performance-enhancing drugs and therapies. Willmott and Macip also offer an insightful account of how techniques for analysing DNA, storing genetic information in biobanks and new techniques for analysing automated neuronal responses, can have an impact on forensics. Other topics addressed in the book include stem cell research, and synthetic biology.

The last chapter discusses some bad practices in science and scientific research including fabrication, falsification and plagiarism; the possible effects of these behaviours (i.e. loss of trust into the scientific community); and strategies used to avoid them (e.g. peer review). Despite an accurate portrayal of such practices, the authors fail to acknowledge their pervasiveness beyond natural science research. These bad practices represent a much more widely spread phenomenon in academic research. It is likely that morally questionable behaviours taken are often the result of structural conditions. For example, trying to secure grants to finance one’s own research, while at the same time trying to publish satisfactory results in order to get more funding and to find a new (often temporary) academic position.

Overall, the book represents a valuable contribution to the ethics of new developments in medicine and biology. Despite the multiplicity of competing views regarding the moral standing of new biotechnologies and practices, Willmott and Macip fulfil their promise of providing epistemologically balanced tools to the reader. The authors begin each chapter by presenting an everyday story that exemplifies the challenges, limits and questions raised by the technology or practice. This approach catches the reader’s attention from the outset. Finally, the dialogical style of presenting the story earns the reader’s sympathy, certainly a useful tool to begin ethical reflection. While the book may lack depth of analysis in certain parts, it certainly represents a valuable tool for teaching ethics at the undergraduate level and for engaging a wider audience in the challenges arising from scientific and biotechnological developments.

Giulia Cavaliere (King’s College London, UK)
People in white coats

By Benoît Leblanc

(http://peopleinwhitecoats.blogspot.co.uk)

The male seahorse’s battle against ignorance must be fought every day.
Prize Crossword

N.A. Davies

Across
3. Gland, site of most common male cancer (8)
7. Condition where the lining of the uterus (13)
8. Having both X and Y chromosomes (4)
9. Neurodegenerative disease, more prevalent in women (10)
10. Sum of characteristics that define organisms based on reproductive function (3)
11. Stone-like biliary masses, more prevalent in women (10)
14. Urinary infection, prevented by cranberries (8)
15. Porous, brittle bones (12)
16. Night time vibration of the soft palate (7)

Down
1. Hormone promoting ‘maleness’ (12)
2. Female reproductive gland (5)
3. Scar tissue build up leading to a male directional problem (9)
4. Developmental disorder more prevalent in male children (6)
5. Either of oval male reproductive glands (6)
6. From the greek word for ‘acorn’, painful inflammation affecting males (9)
12. Autoimmune disease, predominantly affecting women, that devours the afflicted parts (5)
13. Most common cancer in women (6)
14. Constricted area of the uterus (6)


Crossword Competition

Win

This month’s crossword prize is The End of Sex and the Future of Human Reproduction by Henry T. Greely. Simply email the missing word, made up from letters in the highlighted boxes to biochemist@biochemistry.org, by Friday 3 March 2017. Please include the words ‘February crossword competition’ in the email subject line.

Congratulations to December's winner:

Caroline Barwood from the University of Nottingham
The missing word from last issue's competition was BIOLUMINESCENCE.
Caroline received a Mpow® 3 in 1 Clip-On lens kit for smartphones.

Terms and conditions: only one entry per person, entrant must be a current Biochemical Society member; closing date Friday 3 March 2017. The winner will be drawn independently at random from the correct entries received. The winner will receive The End of Sex and the Future of Human Reproduction. No cash alternative available. No employee, agent, affiliate, officer or director of Portland Press Limited or the Biochemical Society is eligible to enter. The winner will be notified by email within 7 days of the draw. The name of the winner will be announced in the next issue of The Biochemist. The promoter accepts no responsibility for lost or delayed entries. Promoter: Biochemical Society, Charles Darwin House, 12 Roger Street, London WC1N 2JU; do not send entries to this address.