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 Mississippi, 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 Society. The collection includes several contributions from key members of the gender medicine research community, not least from members of the Board 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’ 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 Medicine at Columbia University. In 2008, she established the non-profit Foundation for Gender-Specific Medicine, 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 testis 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', 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, and is recognised as an exceptional researcher in the field. In his review, 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 (ISRNRM) and is the founder and secretary of the European Renal Nutrition working group at the European Renal Association – European Dialysis and Transplant Association. 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, 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 Grisurevic 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.
The conventional view is that masculine or feminine organization of the brain depends on the presence or absence of early gonadal steroid exposure (Figure 2), however studies suggest that in addition to the neonatal period, later adolescent periods, sex chromosome complement and the involvement of epigenetic effects may all play a crucial role. If you are interested in how sex and gender affect the brain, be sure to watch out for a forthcoming review on the potential cellular mechanisms of sex differences in ischemic stroke, from nationally recognised neuroscientist Dr Louise McCullough, coming in Clinical Science in early 2017.

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 vasoconstrictors\textsuperscript{17}.

**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 medication\textsuperscript{18}.

**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 Group\textsuperscript{19}, 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\textsuperscript{20}, Sullivan summarises the available literature regarding sex differences in T-cells in hypertension, and then goes on to highlight the potential pathways that may result in sex-specific effects on T-cell activation and differentiation.

Meredith Hay, Professor of Physiology at the University Arizona College of Medicine, is a leading expert in gender physiology and the differences in males and females in neurocontrol of the cardiovascular system. One of the key mechanisms involved in the development of hypertension in both men and women is an increase in sympathetic nerve activity (SNA). In her review, Hay surveys the current understanding of the role of increased SNA in the risk factors contributing to hypertension\textsuperscript{21} 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 disease\textsuperscript{22}.

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 mice\textsuperscript{23}.

**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 Differences\textsuperscript{24}, 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 Women27, and remains today one of the most outspoken and best known champions for women with cardiac disorders28.

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 calculators29.

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 Charite Berlin/Humboldt University30. The following year, she founded the Berlin Institute for Gender in Medicine (GiM)31, the working group on cardiovascular disease in women at the German Cardiac Society32, the German and International Societies for Gender in Medicine (DGesGM 33, 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 collection35.

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.

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.