Towards a gender-specific medicine

Istituto Superiore di Sanità hosts the first Centro di Riferimento per la Medicina di Genere Convention

Introduction

On the first of January 2017, Istituto Superiore di Sanità (ISS) founded its new Centro di Riferimento per la Medicina di Genere (Hub Centre for Gender-Specific Medicine), directed by Prof. Walter Malorni. The only facility of its kind in Europe, the Centro di Riferimento per la Medicina di Genere pursues three main objectives: to develop training and communication activities dedicated to diffusing gender-specific medicine; to develop a network of Italian centres that deal with gender-specific medicine and to expand it to a European level; to promote research to identify and study the differences between men and women regarding not merely the frequency and way in which diseases occur, but also the response to therapy.

As suggested by the many initiatives promoted by international (UN, FDA and WHO) and national (regional authorities, universities and associations) agencies and institutions, whose aim is to promote health, the interest in gender-specific medicine is growing worldwide, and especially in Italy, and the establishment of the Centro di Riferimento per la Medicina di Genere within the ISS testifies to this fact.

The Convention "Verso una Medicina Genere-specifica" [Towards a Gender-Specific Medicine], which was held on 21 and 22 March 2017, provided the opportunity to present the Centre's work and was the first event it has organised.

The purpose of the Convention was to promote gender-specific medicine and make it known in all aspects of biomedical research and to discuss the political and social actions that could be undertaken in order to favour its introduction into health policy. The Convention therefore provided a qualified opportunity for exchange in order to explore the factors through which the differences associated with sex/gender affect the onset and natural history of many diseases in all phases of an individual's life, as well as response to therapy. The Convention also aimed to stress the fact that dedicating attention to gender differences must become standard practice in health policy as, by opening new perspectives in terms of the appropriateness, effectiveness and equality of prevention and care initiatives, it influences the quality and sustainability of the National Health Service (NHS) by improving its results and cutting its costs.

Members of the scientific, political, institutional and civilian communities and associations attended the two-day event.

The first day of the Convention was dedicated to institutional activities, with presentations by political, academic and industrial stakeholders aimed at creating an inclusive network connecting scientific research, training activities and health policy. This was followed by presentations of a communicative nature dedicated to nutrition, lifestyle, the impact of gender-specific medicine in the health service and the history of gender-specific medicine from Hippocrates through to the current time. The first day closed with the presentation of a consensus document (see pages 37-38) resulting from the work of Thematic Tables dedicated to local government, the associations and false myths. The topic of this last Table is undoubtedly currently of particular interest to the general public, which is all too often led astray by groundless information and fake news. The consensus paper will constitute the basis for the development of gender-specific prevention and treatment strategies over the whole of Italy.

The second day, 22 March, was dedicated to research, with specific presentations on epigenetics, gender differences in paediatrics and old-age and on preclinical trials, which must take into account the differences in gender of the cells and animals used. On the afternoon of the second day, specific presentations on gender differences in various medical fields (from oncology to paediatrics, from infectious and autoimmune diseases to cardiovascular and neurodegenerative ones) highlighted the importance of considering gender/sex when treating male and female patients and the need to create prevention, diagnostic, treatment and care programmes that take gender differences into account in order to guarantee a "patient-oriented approach" and the "protection of health."

The idea was to provide a general overview of the state-of-the-art in

gender-specific medicine in both research and medical practice, placing special attention on the social, cultural and political issues, thereby giving food for stimulation and thought, so that new knowledge may be acquired in scientific research, the biomedical field, innovation and medical practice.

Programme overview

"Italy is proud of its role as a pioneer: since we started talking about gender-specific medicine back in 2006, a great many diverse hotbeds of interest have been generated: women's' rights groups, hospital units, centres, associations and institutions. Over the past few years, we have succeeded in creating a network and a synergistic partnership between the different institutions", stated Giovannella Baggio (University of Padua), and this fact is demonstrated by the participation of representatives from important institutions, even at the highest levels, in the convention.

Health policy and gender. Participants included Emilia Grazia De Biasi, Chair of the Italian Senate's Hygiene and Health Commission, who was quick to point out that gender difference is a topic that should by now be fully accepted in the scientific world, just as it should in the institutional and political worlds and in the organisation of the health service. Paola Boldrini, a member of the Social Affairs and Health Commission, is working to this end. She was the first signatory of the bill "Provisions to favour the application and diffusion of gender-specific medicine" that was filed with Italy's Chamber of Deputies in 2016. The Social Affairs Commission has just approved her amendment to the Lorenzin bill for the introduction in medicine of an approach that is receptive to differences in sex and gender, especially in the research, prevention, diagnosis and care fields.

"It is the health service's duty to implement a gender-specific approach, which means organising services on the basis of clinical care programmes and hospital networks that have protocols that are also identified according to gender".

This is something of which Anna Maria Celesti (Regional Centre for the coordination of Health and Gender-Specific Medicine; Department of Health | Citizen Rights and Social Cohesion Directorate – Tuscany Regional Authority) is convinced and she told us that for some years now, Tuscany Regional Authority has been committed to building a gender-specific medicine network: the Centro di coordinamento regionale per la salute e medicina di genere was established in 2014 and since then, throughout the Region it has established 12 Centres for the coordination of health and gender-specific medicine, four centres in Tuscany's University Hospitals and another within Fondazione Monasterio.

A mention must also be made of the host of the initiative, the chairman of Istituto Superiore di Sanità, Walter Ricciardi, who highlighted the importance of gender mainstreaming, "a practice aimed at making gender equality an essential part of the mainstream on a social level, so that women and men can both enjoy the same benefits. This means examining each step of policy development – planning, implementation, monitoring and assessment – with a commitment to promoting equality between men and women". This is exactly what Istituto Superiore di Sanità is trying to do, with conviction, by striving to provide politicians with the scientific evidence available. Which policies are susceptible to gender mainstreaming?

Table 1: Gender-specific medicine in the community

Francesca Bagni Cipriani, Daniele Biagioni, Anna Maria Celesti, Angelo Del Favero, Angela Goggiamani, Raffaella Michieli, Antonio Saitta, Alessandro Solipaca, Gabriella Tanturri, Paola Sabatini

- Transversal nature of the expertise of Table participants: not just healthcare professionals and doctors with different specialisations, but also other stakeholders
- To make a distinction between health policy connected to the environment we live in, lifestyles, etc. and community health policy, with reference to general practitioners and primary-care paediatricians
- The importance of communication concerning gender-specific medicine, to make it known in the community, including by means of the different Networks (e.g. the Città Sane [Healthy City] network, networks of equal opportunity councillors, etc.)
- To make a distinction between direct evidence-based information for the public and training for healthcare professionals (literacy)
- The importance of statistical information as a support to monitoring and programming, referring to gender, with the most detailed analysis possible
- The data: associated with the single issues, transferable, with gender breakdowns, usable
- Gender-specific programmes: prevention, lifestyles, vaccine cover, therapy compliance, etc.
- Community health policy depends, to a large extent, on the decisions taken at regional level

PROPOSALS (to be put to the Regional Authorities)

1. To collect and input data that is broken down according to gender
2. To introduce training on the gender-specific approach to the individual in regional training schemes for general practitioners
3. To organise, as proposed by the ISS, training courses with CME credits for all health professionals
4. To implement a programme involving all local institutions and the local health authority in order to put local health education policy into practice

Ageing, disability and loneliness; alcohol, smoking, cancer prevention, cardiovascular disease, mental health, medicines: "These are all fields for which the ISS has drawn up a series of proposals, initiatives and research", said Ricciardi, who added "I am certain that the partnership between the ISS and the other stakeholders, academia, scientific societies, industry, professional men and women and the general public, will lead to the creation of an Italian model".

Andrea Lenzi. Medicine degree learning and gender-specific medicine. Andrea Lenzi was one of the attending stakeholders for the education field: in his capacity as Chair of the Permanent National Conference of Presidents of Medicine and Surgery Degree Courses, he reminded those attending the meeting held in Messina in September 2016, that a motion was drawn up urging all medicine and surgery degree courses to modify their structure so that all courses (59 in all) are obliged to tackle the topic of gender-specific medicine.

"This provides us with the guarantee that in academic year 2017-2018, all degree courses will be aligned and will train doctors taking the gender dimension into account in all disciplines".

Simona Montilla. The role of AIFA [Italian Medicines Agency] in the development of gender-based pharmacology. The Italian Medicines Agency was represented by Simona Montilla, who started her presentation by stressing that there is a tendency to consider gender-based pharmacology as a subject dealing with "medicines and women". However, gender-based pharmacology tackles a great number of aspects ranging from research methods, to the effectiveness and equality of treatment through to the loss of knowledge and social discrimination between the genders. Montilla then went on to discuss "gender blindness" in medical (clinical) evidence, a term used to define the lack of research, analysis and publication of data broken down according to gender.

This form of gender-blindness originates from the pretext of gender neutrality, the conventional assumption that the differences between man and woman can be simplified as differences in body weight and those regarding the reproductive cycle. The evidence suggests that this assumption is incorrect, indicating the need to design research and investigations in an appropriate manner, in order to identify the differences and issues relating to gender. The aim of gender-based pharmacology is to investigate and define, where present, the differences in the efficacy and safety of medicinal products in order to overcome the gender bias that has characterised preclinical and clinical pharmacological research in the past. The enrolment of fewer women in studies on medicinal products has resulted in the development of medicinal products and disease models and the definition of physiological parameters built, primarily, on men. AIFA's commitment to gender-specific medicine is testified by the establishment of its working group on Medicines and Gender. Its initiatives included, in 2013, the drafting of a circular titled "Medicines and Gender" aimed at sensitising pharmaceutical companies presenting registration dossiers for new medicinal products regarding the need to process data broken down according to gender, in order to highlight any differences. The document also suggests that the analysis of data for the female population should be stratified by age range, given their significant variations in terms of response to therapy.

Table 2: Exchange between Associations and Monitoring Centres

Giovannella Baggio, Caterina Ermio, Barbara Mangiacavalli, Anna Maria Moretti, Maria Antonietta Nosenzo, Elvira Oliviero Lippi, Andrea Peracino, Pia Petrucci, Cecilia Politi, Cristina Tarabbia, Angela Ianni Palarchio

- The central role of health professional training and population information with continuous quality control. Monitoring regarding the application and effectiveness of university teaching as established by the Council of Presidents of Medicine and Surgery Degree Courses
- Coordination of Italian Scientific Societies through the FISM for the promotion of scientific research and quality training for doctors and all health professionals, especially young ones. Rewriting of the guidelines for all disciplines
- The importance of a multidisciplinary approach in the involvement not merely of medical professionals, but also representatives of the world of art, professions and business
- The need for a correct collection of epidemiological data on which to base the on-going monitoring of economic investments as the fulcrum of appropriate health planning

Table 3: Hoaxes and false myths in (gender-specific) medicine, how can we protect ourselves?

Roberta Chersevani, Paolo Costanzi, Nicoletta Luppi, Francesca Moccia, Tiziana Sabetta, Fulvia Signani, Gian Paolo Zanetta, Michela Molinari, Amelia Ceci, Annarita Frullini, Marina Rizzo

- Inadequate knowledge of the topic/issue/approach (confusion with women's medicine, with the "gender theory")
- Need for a definition that is comprehensible both for professionals and for the general public
- Language that is more comprehensible to the general public (considering also different ethnic groups and cultures) – gender-specific medicine, knowledge regarding gender in health and healthcare as part of the cultural baggage of a well-informed citizen (*empowerment*)
- Training and refresher courses for active doctors and health professionals (distance learning, conventions, scientific literature, etc.)

Presentation of Centro di Riferimento per la Medicina di Genere

On the first of January 2017, as part of its re-organisation, Istituto Superiore di Sanità (ISS) founded the new Centro di Riferimento per la Medicina di Genere (Hub Centre for Gender-Specific Medicine), directed by Prof. Walter Malorni. The only facility of its kind in Europe, the Centre pursues three main objectives: to develop training and communication initiatives dedicated to the diffusion of gender-specific medicine; to develop a network of Italian centres dealing with gender-specific medicine and to expand it to a European level; and to promote research for the identification of the pathophysiological bases responsible for the differences observed between genders. Furthermore, considering the ISS's role as the technical and scientific organ of the Ministry of Health, the Centre will have the duties of connecting the different players that already work in the gender-specific medicine field and promoting this novel approach within the National Health Service (NHS). In connection with this, on a broader level, Centro di Riferimento per la Medicina di Genere will be responsible for coordinating promotion and research activities in the gender-specific medicine field throughout Italy, liaising with doctors' associations, universities, parliament, patient advocacy groups, the Regional Authorities, AGENAS, non-profit organisations, the media, industry, scientific societies and AIFA. The Centre is composed of Units with the task of performing institutional activities, research activities and educational and training activities in the gender-specific medicine field. The basic and translational research activity that the Centre intends to conduct is to promote and coordinate the study of gender differences in those medical conditions that require a clinical programme that is diversified according to sex. The aim of this activity is to improve the preventative, diagnostic, prognostic and therapeutic strategies for all diseases presenting differences between the sexes.

The Centre's working groups conduct research in various sectors: from gender-related diagnostic and prognostic biomarkers to gender-based pharmacology, from oncology to diet and lifestyles, from cardiovascular disease to preventative medicine and occupational safety and toxicology. Various lines of research are currently being conducted at the Centre in order to assess gender differences in response to biologics in patients with autoimmune diseases, in the response to immunotherapy in patients with melanoma and in the incidence and severity of chemotherapy-induced cardiovascular damage. Research is also being conducted to study the role of sex hormones, nutrients and lifestyle, as well as genetic and epigenetic factors in the pathogenesis of certain diseases, such as tumours and immunomediated, cardiovascular and metabolic diseases. Lastly, studies are also being conducted on genetic-, metabolic- and behaviour-based gender differences in the response to certain dietary regimes. Special attention will be dedicated to infectious diseases, given the gender differences observed in response to treatments and vaccines. Certain units liaise between the Centre and other ISS facilities, in 6 different areas of interest, namely: Biomarkers in neurodegenerative disease, Transplants, Tumour immunotherapy, Antibacterial immunity, Safety, Stress, mental health and behaviour. The Centre's tasks include intense training and information work regarding all levels, from the general public to healthcare professionals, in order to diffuse the full awareness that gender-specific medicine is not a new specialty of medicine, rather an interdisciplinary dimension of it that studies the influence of sex and gender on human physiology, pathophysiology and pathology. The Centre's aim is to implement the network of partnerships already established with various Italian facilities dealing with gender-specific medicine in order to diffuse a gender-specific culture in the biomedical field.

Massimo Scaccabarozzi. The pharmaceutical industry and gender-based pharmacology. The pharmaceutical industry was represented by the Chairman of Farmindustria, Massimo Scaccabarozzi: pharmaceutical companies support researchers in the development of gender-specific medicine. This applies to both preclinical research, by promoting *in vitro* studies on cells obtained from both male and female specimens and *in vivo* studies on animals of both sexes and to clinical research, by favouring an approach that overcomes the protectionist attitude that characterised the past and an adequate participation of women in trials.

"It is not enough to enrol women in clinical trials. We also need study design to involve analyses broken down according to gender and that takes into account age-gender interactions" and, he added, "in health, the gender dimension is a basic parameter for clinical activity and for guaranteeing the appropriateness of therapeutic intervention. Including the 'gender' determinant in medical practice means redefining the pathways and training processes that influence the organisation and programming of services".

Delia Colombo Industry and gender-specific medicine. "The pharmaceutical industry's relationship with gender-specific medicine is difficult and complex and also involves aspects of an economic nature", stated Delia Colombo, who participated in the Convention in her capacity as researcher, clinician and industry representative. However, the situation is getting better: safety and efficacy studies are beginning to be conducted also on women: "In phase 3 trials we have almost reached equality. It is in phase I studies that women still only represent 30%, a situation that is nevertheless better than in the past". Why is this? It is more difficult to conduct trials on women: "Unless studies are conducted on cells and animals, fertile women cannot be included in phase I studies.

There is a potential risk for the gametes. If a woman enrolled in a phase I study becomes pregnant, this is a problem", Colombo points out, adding that it is also very expensive to

perform studies on female animals, because they have a must cycle every week; in addition, it is not required by law. We must also consider that it is difficult to enrol women in clinical trials because they never have any time to themselves. In 2008-2009, Novartis started taking interest in gender-specific medicine, an interest that led to the Gender Attention study, the first prospective study with a gender approach. About 1,000 psoriasis patients were enrolled and the investigational medicinal product was cyclosporine, the medicinal product with the highest number of publications in the world, about 80 thousand.

Some 50 dermatology centres were involved and although no difference was seen in side effects between women and men, a difference was observed in the side effects between fertile women and menopausal women, with a side effect incidence rate that was approximately 33% lower in fertile women than in menopausal ones. Novartis' commitment continues with other research initiatives, such as the *MetaGem Project*, which involves a post hoc analysis of the gender differences in observational studies already conducted on various conditions, the *Synergy* study on psoriatic arthritis, and that on "wearing off" in Parkinson's patients, all with a gender perspective.

Gian Paolo Dotto. Sexual dimorphism and cancer. Gian Paolo Dotto, University of Lausanne, gave a *lectio magistralis* on sexual dimorphism and cancer. When dealing with the issue of cancer prevention, he emphasised how important it can be in connecting science with politics. Referring to one of his studies published in 2015, he showed that incidence and mortality in the world of tumours of the lung, oral cavity, oesophagus, bladder, liver and kidney are higher in men than in women. There is also a sexual dimorphism for melanoma, with a higher incidence and mortality in the male population than in the female one. Performing research on secondary prevention means interfering in the conversion of pre-malignant tumours into malignant ones. In this sense, Dotto proposed two models that explore this aspect from a genetic and molecular standpoint. The cancer evolution model attributes the cause of malignant tumour onset to an accumulation of genetic mutations. The big bang model of cancer is based on the existence of normal cells, with mutations inside them, that transform into malignant tumours when changes or stressor events occur.

He then discussed the results of the studies in which he was involved into identifying the genetic differences between different races and stressed the difference in the susceptibility to different tumours between the black and white population. He subsequently proposed a model of potential interactions between genetic and epigenetic alterations that may favour the onset and progression of squamous cell carcinomas.

Paolo Marchetti. Gender and cancer therapy. Gender differences are grossly underestimated in clinical practice, as regards treatments for the main types of cancer: this is something of which the oncologist Paolo Marchetti of Sant'Andrea Hospital (Rome) is convinced. We need to improve knowledge in this field in order to identify the variables that may influence "prevention, treatment choices and their possible toxicity". These differences include, for example, the case of colorectal tumour: on average, women are affected five years later than men, they are diagnosed later and the most common site is the right colon. Non-small cell lung cancer affects non-smoking women more often than non-smoking men and occurs at a younger age. However, women respond better to therapy. As regards melanoma, women have a better survival and a lower risk of progression and metastasis. Another field to be explored, says Marchetti, is that of gender differences in the response to pharmacological and other intervention for pain, including the tolerance of opioids and side effects, as well as the different perception of pain and treatment-related preferences.

Teresita Mazzei. Gender-based pharmacology. Teresita Mazzei of Department of Health Science, Clinical Pharmacology and Oncology Section], University of Florence, and coordinator of FNOMCeO's Gender-Specific Medicine Commission.

Women are greater consumers of many classes of medicinal products (e.g. analgesics, antidepressants and antibiotics) and respond to medicines in a different way to men (physiological, anatomical and hormonal differences). One of the differences with the most significant repercussions regards adverse reactions: women have a 1.5 to 1.7 times higher risk of developing adverse drug reactions (ADRs) than men: 59% of hospital admissions for ADRs are women. The factors that can favour a higher frequency and greater severity of ADRs are women's greater susceptibility to certain drug-induced pathological conditions; pharmacokinetic and pharmacodynamic differences and greater drug-drug interactions in the case of polydrug use; in addition, posologies are studied for male subjects (often healthy young volunteers) with an average weight of around 70 kg. Hormone changes associated with the different phases of reproductive life should be considered. Lastly, there is still a lack of gender-based preclinical and clinical studies. Women use more medicines and are often prescribed more medicines, including antibiotics "although we do not know exactly why: women are not more prone to bacterial infection than men, although they do suffer from urinary tract infections more often than men do (acute cystitis, after birth, etc.)", said Mazzei, "however, women, especially over 20 years of age, are prescribed more antibiotics, a difference that doesn't exist anymore by the age of 60". This issue deserves to be made an absolute priority: Italy is the third country in Europe for the prescription of antibiotics and bacterial resistance doubled in this country between 2005 and 2014. This issue needs to be tackled also from a gender-specific perspective.

Lucia Migliore. Epigenetics and gender. Lucia Migliore, University of Pisa, spoke about epigenetics and gender. Genomic imprinting and X chromosome inactivation in females are cell processes caused by epigenetic mechanisms and they can have implications in gender differences.

The alteration of these processes may lead to pathological conditions and an altered sex-ratio for certain illnesses. The brain is one of the main targets of genomic imprinting and many neurological disorders can originate from defective signalling during the development of the brain. The differences in gene expression between the two sexes can be regulated by both genetic factors, such as X-linked micro-RNAs, and by hormonal factors such as sex steroids. The X chromosome contains approximately 10% of the micro-RNAs of the whole genome that often have an important function in immunity and cancer. Furthermore, approximately 15% of X-linked genes escapes inactivation on the X chromosome and their continuous expression may be responsible for women's different sensitivity to certain diseases.

Anna Teresa Palamara. Viral infections and gender. Anna Teresa Palamara (Sapienza University, Rome) spoke about viral infections and gender, placing special emphasis on influenza. Her presentation revealed the extreme complexity of this constantly-evolving area of research. The researcher reminded participants that, just a few years ago, we were all convinced that men were more prone than women to bacterial, fungal, parasitic and viral infections, on the basis of a series of stringent publications that did not, however, take into account many of the variables that came to light later, which over time vary in the different types of infection. A bacterial infection is dramatically different to a viral one; each one has its own story and different characteristics. For now, we can state that the data and results of the most recent research indicate, as regards influenza virus infection, that males and females respond differently. There are many factors that may condition this difference: different immune response activation, different host metabolism conditions and, lastly, females have a greater anti-oxidising power than males.

The topic of *immunity and autoimmunity* with regard to gender was discussed by Maurizio Cutolo (Università di Genova), during his presentation.

Claudio Gasperini. Multiple sclerosis and gender-specific medicine. In his presentation, Claudio Gasperini of S. Camillo Forlanini Hospital (Rome) discussed the way males and females differ in multiple sclerosis. MS is a multifactorial disease whose aetiopathogenesis involves both genetic and epigenetic factors. The latter can, in turn, be conditioned by environmental factors. These include, most importantly, factors related to lifestyle and infection (for example, Epstein-Barr virus infection). The disease's increased incidence in women has risen over time, as shown by the increase in the sex ratio (from 1.9 to 3.2 over 50 years), pointed out Gasperini. A number of hypotheses have been formulated to explain this phenomenon. The increase may originate from behavioural factors, such as a shift in the reproductive cycle towards older age; the increased incidence of cigarette smoking in women and a reduction in the exposure to sunlight. The latter factor (and the associated vitamin D deficiency) causes a more marked pro-inflammatory effect in women than in men as it acts in synergy with 17-beta-oestradiol, through the oestrogen receptors; lastly, exposure to light under 15 years of age was associated with a lower risk of developing the disease; vitamin D would appear to have a protective role that combines with that of oestrogen hormones.

Stefano Savonitto. Cardiovascular disease. Cardiology is the discipline that for the longest time has dealt with gender differences and that has undertaken to do away with stereotypes associated with heart disease.

As was pointed out by Stefano Savonitto (A. Manzoni Hospital, Cardiology Division, Lecco) the WHO data on causes of death in Europe show that more women die of cardiovascular causes than men (2,220,000 women versus 1,863,000 men), and that cardiovascular disease is the first cause of death for both genders, although early death (before 65 and even before 75 years) is far higher in men. The study of cardiovascular disease in women is therefore, in part, connected to studies in old age. It should also be stressed that many of the treatments that women require at each age are poorly studied in ad hoc studies. One ad hoc study was the "LADIES ACS" study (study on women with myocardial infarction), published in the *American Journal of Medicine*, coordinated by Savonitto. The data collected clearly show that, for each age class considered (up to over 85 years), women have less severe coronary disease than men. The extent of coronary disease increases progressively with age in both sexes, whereas the age of menopause is not in any way related to the extent of the coronary disease. Savonitto concluded by focussing attention on a number of key points: women have approximately 10 years' advantage over men as regards atherosclerosis; however, this advantage disappears gradually after the menopause; so far, the efforts to prolong the benefit of hormones with hormone replacement therapy have been unsuccessful. The myocardial infarction mechanism is similar in both sexes and similar reductions in mortality have been obtained with the same treatments in men and women. It would appear that higher age-adjusted mortality rates after acute myocardial infarction persist in women, due to the more frequent and severe cardiogenic shock.

Alberto Villani, Isabella Tarissi de Jacobis. The differences start in the cradle. Whereas cardiology has played a pioneering role in medicine, the same cannot be said of paediatrics, an area in which the importance of a gender-specific approach only recently came

to light. As was explained by Alberto Villani and Isabella Tarissi de Jacobis of Ospedale Pediatrico Bambino Gesù (Rome), in paediatrics, there is data available in literature, albeit still limited, that indicates the presence of specificity in both sexes, even in the prepubescent age. As early as the foetal age, gender, male or female, influences the possibility of developing various abnormalities or the risk of a premature birth or need for a C-section and from birth differences can be seen in the prevalence of certain congenital diseases. Villani and Tarissi de Jacobis reported on a series of examples. Overall, congenital heart diseases are distributed in a fairly even manner between males (48.7%) and females (51.3%); however, the most severe heart diseases are rarer in the female population. For many infectious diseases, incidence is higher in males. However, evolution would appear to be worse in females (greater immunoreactivity and risk of immunopathogenetic effects). There are differences in vaccine response between the genders at all ages. The female gender is more prone to developing autoimmune diseases, even in the paediatric age. "The use of different diagnostic and therapeutic pathways in these conditions that take into account gender differences, would permit better prevention thanks to targeted screening and a reduction in the severity of the diseases and complications due to specific and individualised treatment", concluded Villani and Tarissi de Jacobis.

Claudio Franceschi. Longevity and gender: beyond the first 100 years. We took a radical change in age range with Claudio Franceschi (University of Bologna), who provided an overview of the studies, many written by Franceschi himself, considering the relationship between longevity and gender.

In 2015, life expectancy at birth was 80.1 years for men and 84.7 years for women (ISTAT data, 2017): in just a century, life expectancy at birth has more than doubled, "an incredible demographic revolution". More specifically, in 2015, in Italy, there were 19,095 people over 100 years of age, of whom 878 were over 105 years of age and 17 were over 110. And the Italian population continues to age. In particular, as regards the centenarians, as has been demonstrated by a number of studies, the male/female ratio in Italy varies greatly from region to region, where we go from two women for every man in the south to more than 8 women for every man in certain regions of the north of the country. Of the many studies he mentioned, we would like to recall that published in the journal *Demographic Research* (Caselli et al. 2014), on the relationship between maternal longevity and the infantile mortality of the offspring. The most important fact, stressed Franceschi, is that for those women who go on to become centenarians, the infantile mortality of the offspring was 79/1000, whereas in women, in the same cohort, who die between 60 and 70 years of age, the infantile mortality of the offspring was between 118/1000 and 172/1000.

This, it is suggested, could mean that either the mothers are genetically stronger, or they have healthier lifestyles that they pass on to their offspring.

Rita Biancheri. The sociological approach to gender in the medical setting. "Gender is a prism that breaks down the male neutral and makes the differences visible" is the suggestive metaphor proposed by the sociologist Rita Biancheri of University of Pisa, who gave a presentation on the sociological approach to gender in the medical field from a multidisciplinary perspective. Disease is not just a clinical and biological event, but also a biographical and social one: in the organisation of services, according to the speaker, there is ever-greater attention to management, effectiveness and quantitative indicators that can only be partly justified by cuts to resources and financial sustainability and poor integration in terms of public health. The purely clinical response loses what is known as the "conjunctive character" of the disease. The current debate on health, on the other hand, has to measure up against the complexity of the concept of equality and apply it to health pathways.
The sociologist hopes for a switch from gender-specific medicine to a gender-based perspective in health. Nowadays, a new vision, that takes into account living conditions, social and economic status, academic

achievements and ethnic and geographical origin, is fundamental for favouring a biographical and phenomenological approach rather than a merely medical and therapeutic one.

Roberta Pacifici. Addiction and gender. The study and management of addiction also benefits from a gender-based approach, as demonstrated by Roberta Pacifici, director of the ISS National Centre on Addiction and Doping. The consumption of illegal substances is higher in males. Men are 2-3 times more likely than women to encounter substance abuse/dependence; however, this difference in gender could reflect differences in opportunities rather than in the vulnerability to substance use. Important gender differences can be seen in all abuse drugs. As far as alcohol is concerned, the starting age is later than in men and use is more modest (in quantitative terms); however, in women the evolution towards dependence is faster and the alcohol-related consequences are more serious. Furthermore, the risk of death in the female alcoholic population is 5 times greater than amongst the male one and suicidal behaviour is also prevalent amongst women.

"Generally speaking, a gender-based approach to dependence is recent. It requires a complete reworking of treatments; more specifically, no gender-oriented studies have been performed on the pharmacological treatment of dependence. There are no dedicated centres in the facilities dealing with these issues. Substitute medicines have never been studied in the female compared to the male populations. All the studies regard dependence in women", concluded Pacifici.

Roberta Masella. Eating habits and gender. Women follow healthier diets and eat foods that are less dense with energy, guaranteed Roberta Masella (Centro di riferimento per la medicina di genere, Istituto Superiore di Sanità) in his presentation. Women eat more fruit and vegetables, wholefoods and yoghurt, but they also eat more sweet foods. Men, on the other hand, eat more proteins and fats, they drink more fizzy soft drinks, more spirits, wine and beer, they eat more snacks, eat fast food more often and they more frequently skip breakfast. Women are more likely to follow a dietary regime and, therefore, to adjust their habits in order to adopt healthier diets, but they tire sooner and are more likely to transgress. Men, on the other hand, maintain the change for longer and are more constant. The adoption of adequate diets brings more obvious results in men than in women.

Why? Probably because men have more unbalanced diets than women to start with and therefore the change that follows dietary intervention is more pronounced. Other factors exist, however, such as differences in the capacity to metabolise fats: men use fat to produce energy faster than women.

Giovanna Badalassi. NHS budget and gender. The contribution of Giovanna Badalassi, Istituto di Ricerche economico-sociali del Piemonte (IRES), who spoke on the subject of "NHS budget and gender", was an original one. For many years now, the Piedmont region has used gender-based budgets: part is dedicated to the interpretation of health policy, connected to an economic dimension, in order to establish how much is spent on health for women and for men. The idea is not so much to consider "how much", rather "how", in an attempt, through these analyses, to promote the efficacy and effectiveness of health expenditure, in order to treat everyone better. These results show that various behaviours, various lifestyles, reflect on health services and their cost. In this perspective, the expenditure required to manage road, domestic or occupational accidents, traumas or other accidents, are all variables with different gender components that therefore have a different impact, especially when they are associated with behaviour that can be modified and intervention can be taken also on a cultural level, in order to obtain a better care of the self. Badalassi stressed that at the heart of gender differences lies a different education in terms of care: women are brought up to be sensitive, to create a relationship with others, to care, they are the first "family doctor"; whereas men are brought up to manage wealth. This has a multitude of implications, all stemming from the different attitude towards caring for the self and others, ranging from the adoption and promotion of healthy lifestyles, to more or less risky behaviour and prevention, to mention just a few examples.

Giovannella Baggio. From gender medicine to gender-specific medicine. We conclude with the appeal made by Giovannella Baggio (Chair of Gender Medicine, University of Padua) who,

Gender differences in history

Eva Cantarella

According to historian Eva Cantarella the idea that personal identity is "sexualised" appears to be clear and well consolidated from the origins of the Greek civilisation. In her presentation, she traced the history of this idea starting from the mythical formulation of the female "difference", through Hesiod's tale of the birth of Pandora, who is considered the Greek Eve. She went on to discuss the attempts to provide a logical explanation for it starting from the birth of Ionian philosophy (7th century BC), commenting on the contribution of Hippocratic medicine (with relative diagnosis and therapies), which identified the inferiority of the female gender in this difference. Using a number of examples of theories formulated in different fields, including the cosmological, linguistic and historical sectors, Cantarella closed by demonstrating how – especially thanks to the authority of Aristotle – the identification between gender difference and female inferiority influenced western culture through the ages, taking us almost to the threshold of the contemporary age.

Independent biomedical research and gender-specific medicine

Walter Malorni

In the second presentation concerning independent biomedical research, Walter Malorni, director of the new Centro di riferimento per la medicina di genere, discussed some of the areas being studied by the Centre's working groups. The aim of research activities in the "oncology" area is to study the molecular bases associated with gender differences in the various types of cancer. In the immunity, autoimmunity and infection area, the general aim is to assess the possible use of sex-specific determinants (sex hormones, genetic and epigenetic factors) as both prognostic markers and markers predictive of response to therapy, vaccine prophylaxis and treatment targets. Studies are currently on-going regarding the identification of prognostic markers and markers predictive of response to therapy in patients with rheumatoid arthritis treated with TNF-inhibitors and on the role of the natural oestrogen receptor beta ligands (e.g. phytoestrogens) in regulating immune response and on the assessment of protective immune response to infection vaccination. In the cardiovascular area, the general aim is to study gender differences in heart failure and in pathological neovascularisation. Research is ongoing into blood flow modulation, cardiac function and the expression of cardiac contractile proteins, including the cardiotoxicity of anti-cancer chemotherapy in murine models. Work in the toxicology area is also very intense: the aim is to assess the toxicological risk of chemical substances (e.g. contaminants, nanomaterials, pesticides) of importance for human health, highlighting factors of exposure and gender-specific effects, through in vivo, in vitro, and population studies. Biomonitoring studies are being conducted on plastifiers (phthalates and bisphenol A) in boys and girls in Italy, assessing the association between exposure and related disorders (obesity in boys and girls, late development in girls, Life Persuaded project); in vivo experimental models are being devised in order to identify and characterise the risk of nanomaterials, such as the Lazio Regional Authority project on nanomaterials, NANoREG; study on the effects of bisphenol A on placental development using a gender-specific in vitro model (trophoblast cells from human placenta). A specific area has also been dedicated to lifestyles, nutrition and associated conditions: the general objective of the studies is to fight the onset of obesity and chronic degenerative disorders caused by an inadequate diet and a sedentary lifestyle. On-going studies are investigating, in the Individualised Dietary Prevention sector, the interaction between dietary components and genetic makeup and the mechanisms responsible for the difference in response between men and women, as well as chronic inflammation and immunosuppression in disorders associated with incorrect lifestyles: the role of gender and the impact of diet. On the other hand, in the targeted (age- and gender-specific) dietary education field, initiatives have been launched regarding the school-age populations (primary and lower secondary schools) to promote healthier lifestyles amongst students and their families.

in her presentation, stressed that gender medicine has to cross three bridges, in order to be understood. The first bridge consists in not identifying it with the study of female health, "gender-specific medicine is a dimension that aims to focus attention on health and sickness in men and women and, where possible, to make comparisons and understand the differences in both the diagnostic approach and in therapy and, even more importantly, in prevention". The second bridge will have been crossed once it has been understood that gender-specific medicine is a transverse dimension that all specialties have to deal with.

Gender-specific medicine must not be a niche of medicine: the whole of medicine must be gender-specific. It is also important to add another dimension, and here comes the third bridge, which is that of a gender-based approach to health, "because health is something to protect both in the prevention of disease and in the loss of health, and it is in this perspective of a gender-based approach to health that all the social policy issues, the attitude to prevention, the doctor-patient relationship and economic investments originate". She concluded: "And so, gender-specific medicine on the one hand and a gender-based approach to health on the other must remain closely connected in order to finally find a correct dimension in our everyday life as doctors and to protect the health of a population".

A fundamental contribution will be made by the new Centro di Riferimento per la Medicina di Genere set up within Istituto Superiore di Sanità that, Malorni guaranteed, aims to become "a service to make sure that all the players present in Italy, wherever they may be, create a network and try to communicate, because it is in the network that the strength lies".

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This account, which is intended to provide a brief overview of the topics discussed, was compiled on the basis of convention slides and recordings.