HIGHLIGHTS

Fondazione
Internazionale
Menarini

HIGHLIGHTS

Welcome to Matera!

"Welcome to the city of Matera where we are going to address topics and research that are both topical and unusual, just like this city, which is so topical and unusual. Of extremely ancient origins, Matera is now writing a new page of history for itself, full of traditions and culture in a stimulating environment in which all its inhabitants feel involved. A convention on Gender Medicine is inevitably exclusive, unique and universal, just as the city of Matera is exclusive, unique and universal!" With these words Dr. Raffaello Ruggeri, Mayor of Matera, and Prof. Flavia Franconi, Chairman of the convention, opened the congress works which was attended by some of the leading international researchers in Gender Medicine.

Raffaello De Ruggeri (Matera, Italia)
Flavia Franconi (Sassari, Italia)
Andrea Lenzi (Roma, Italia)

To follow the presentations in this convention just click on this link: www.en.fondazione-menarini.it/... and after logging in, access the multimedia material.

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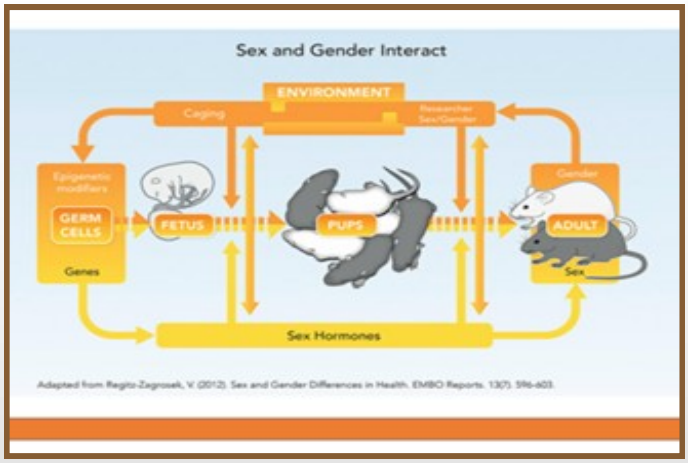
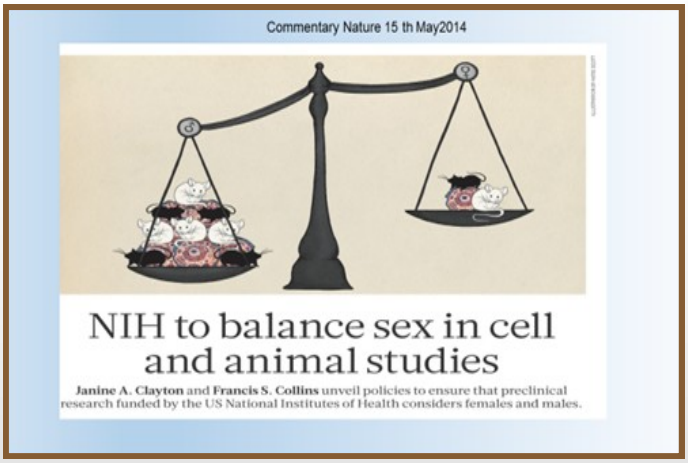
Gender medicine: a new opening for the appropriateness and sustainability of healthcare

Flavia Franconi
(Sassari, Italy)

Prof. Franconi from Potenza presented very interesting data based on the main differences between men and women in terms of healthcare procedures and involvement in clinical research projects. Women are historically less involved in clinical studies. The examples in literature are innumerable and very stably present in the various medical disciplines. What is the meaning of this different involvement between sexes-genders? Underlying this phenomenon are specific sex-gender dependent differences that start from birth. Prof. Franconi presented a whole series of data where, in different pathological conditions, the pharmacological treatment of men and women has produced profoundly different effects in terms of effectiveness and safety. We just need to think of the two particular moments in the life of a woman, such as pregnancy and menopause, in order to understand how the female response to pharmaceutical products is radically different to that of males. The differences in response to drugs linked to sex and gender start early in life and depend on a woman's age and hormonal condition. Starting from the preclinical stage, clinical research is carried out principally on male subjects. This is valid for animals involved in preclinical research and also for humans enrolled in clinical studies, right from the early stages. This situation is anything but optimal, since the pharmacodynamics and pharmacokinetics of a wide variety of pharmaceutical products differ significantly between men and women. Another extremely interesting aspect is linked to the different sensitivity to drugs in terms of adverse events in men and in women. Normally women tend to show a greater prevalence of adverse effects to drugs compared to men. In several studies the women proved to be more sensitive to developing specific adverse effects when treated with particular molecules, but not with others belonging to the same pharmacological class.





When do sex-gender differences usually start in terms of response to pharmaceutical products? Are there any differences between men and women in the incidence of diabetes mellitus during treatment with statins? How does the access to healthcare change based on sex-gender differences? Can the sex-gender differences in the research team influence the results of the research itself?

In order to answer these and other questions click on the link www.en.fondazione-menarini.it/... and after logging in, access the multimedia material.

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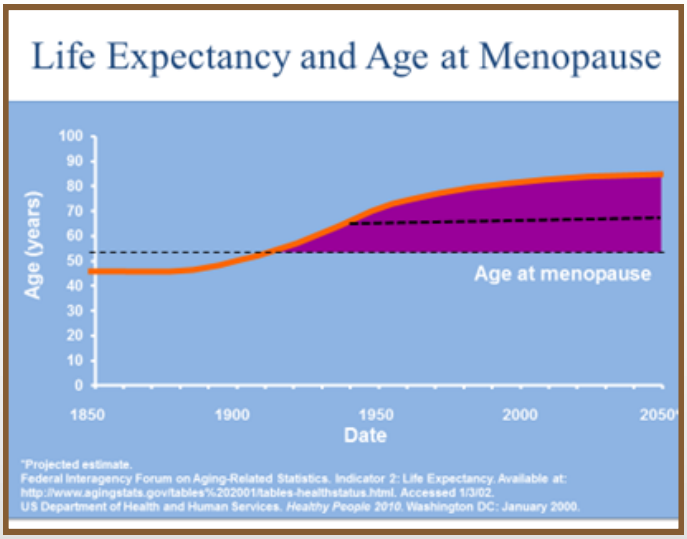
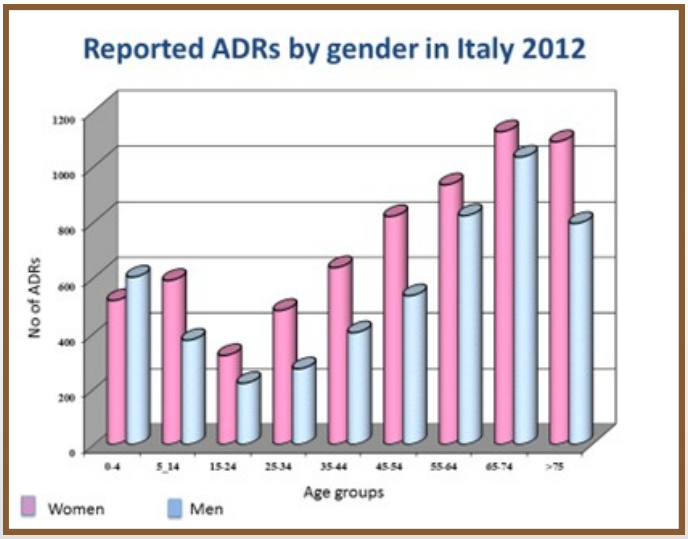
Drugs for the cardiovascular system and gender differences

Giuseppe Rosano
(London, UK)

Prof. Rosano from London addressed this extremely current theme due to the still very high prevalence of cardiovascular diseases. More specifically, he talked about the aspects linked to the safety profile of cardiovascular drugs viewed in terms of gender differences. From a pharmacodynamic and pharmacokinetic point of view there are important differences between men and women. Since the 1960 till today there was an increase in the prevalence of cardiovascular diseases in women. This phenomenon is closely linked to the increase in the average life expectancy which in turn has given rise to a significant increase in women in post-menopause conditions. The drop in female hormones is the main cause of the increased prevalence of cardiovascular diseases in females. Another problem has emerged in this context: the insufficient involvement of patients of the female sex in clinical studies conducted with cardiovascular drugs. In fact, from an analysis of the data of clinical studies it has emerged that the risk of developing adverse events has increased more in women than in men. Female patients are more exposed to the risk of developing arrhythmias: the incidence of *torsades de pointe (wave-burst arrhythmias)* has at least doubled in women compared to men. What is the explanation of this phenomenon? From studies conducted on the populations of both sexes in different phases of their bodily development, the role of the oestrogen hormones as membrane stabilisers becomes evident. Therefore, due to their specific hormonal-metabolic setup, women react differently to drugs than men, in particular drugs designed to treat cardiovascular diseases.





What are the main gender differences in terms of pharmacodynamics and pharmacokinetics of Dofetilide? Why do women have a greater lengthening of the QT than men? What is the mechanism that determines greater susceptibility to develop arrhythmias in women than in men?

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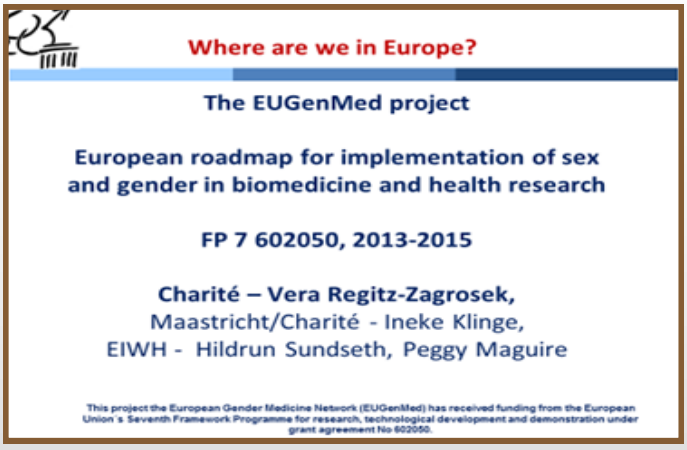
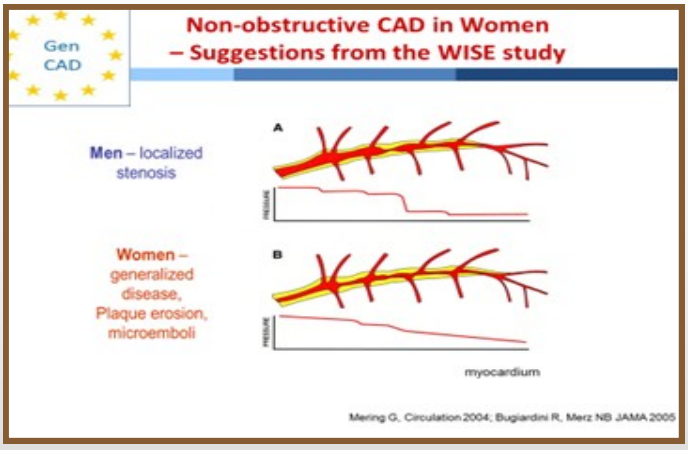
Cardiovascular diseases in women and men: differences & similarities

Vera Regitz-Zagrosek
(Berlin, Germany)

Prof. Regitz-Zagrosek from Berlin addressed this topic by presenting data taken from the work group of the EugenMed Project and from literature. At what point are we at in Europe? In answer to this question the speaker outlined a picture that has alarming contours: the risk of cardiovascular morbility and mortality is on the rise in patients of the female sex compared to males. More specifically, the prevalence of systolic arterial hypertension, angina, left ventricular hypertrophy and diastolic heart failure are increasing. The presence of diabetes in women exacerbates the outcome of the disease to a greater extent than in men. Of crucial importance is the fact that the same physiopathological mechanisms underlying the development of the major cardiovascular diseases, such as angina, differ in a significant manner between men and women. Angina in women is triggered principally by the so-called microvascular coronary syndrome, and spontaneous coronary dissection can be observed with a significantly greater prevalence than in men. The angiographic picture is often normal in a higher percentage of women than men with retrosternal pain. This is indicative of a greater prevalence of coronary spasm in women compared to men. Unfortunately, there are other differences between men and women linked to the healthcare times and measures: in women, the latency time between the manifestation of the symptoms and the beginning of therapy is longer than in men; in addition, the same reperfusion starts later in women than in men. This is a problem connected to the greater difficulty in diagnosing cardiovascular disease in women compared to men. In addition, the physiopathological mechanisms underlying the symptoms of heart failure differ in a significant manner between women and men. In the presence of heart failure with a reduced ejection fraction, women show an improved outcome compared to men and they adapt better to the pressure load. As far as heart failure with a conserved ejection fraction is concerned however, its prevalence is significantly greater in women than in men.





What is meant by the Takotsubo (broken-heart) syndrome? What is the prevalence of the Takotsubo syndrome in women? What are the reasons underlying the prevention and treatment of the cardiovascular diseases in men and women? What is the prevalence of heart failure with conserved ejection fraction in women and men?

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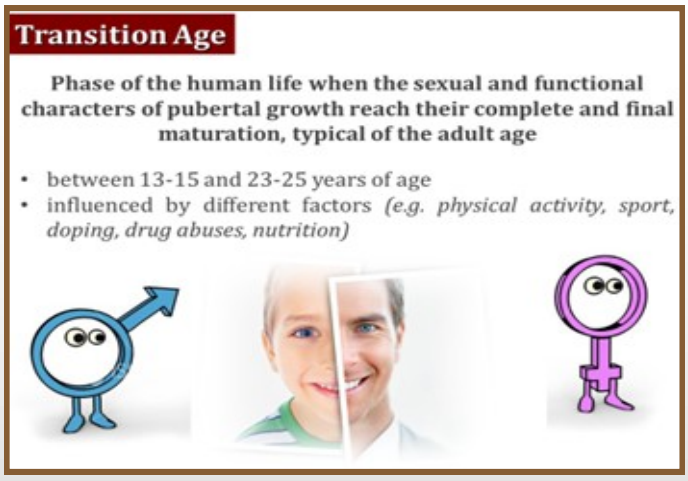
Sport and doping at the transition age: gender differences

Fabio Pigozzi
(Rome, Italy)

Prof. Pigozzi from Rome addressed this topic, which is generally little known. The playing of sport is very important for the physiological development of the bodies of young people of both sexes. The problem arises when the sporting activity reaches levels entailing particular intensity and stress that are capable of producing paraphysiological phenomena linked above all to delays in pubertal development, especially in athletes. One particularly important problem surrounds the use of doping methods in athletes of both sexes at the transition age. The most widely used substances are anabolic agents, mainly testosterone, but not only: we can also find the β_2 agonists, the cannabinoids and the generic stimulants with double-figure percentages. The speaker went on to describe the principal effects that these substances have on the growing organisms of athletes who make use of the same, and more specifically, on their body composition, nervous system, growth and the sex hormones, with frequent symptoms deriving from conditions of hypogonadism, high blood pressure, liver cancer, cardiovascular diseases, rhabdomyolysis, and mood swings, to name just a few of the pathologies caused by these substances in growing organisms. Especially dangerous is the use of stimulant substances such as cocaine which, in addition to phenomena linked to addiction, can also give rise to encephalic haemorrhage. Another decidedly dangerous substance is EPO which thanks to its stimulating effect on the erythropoiesis, consequently gives rise to an increased viscosity of the blood with an increased risk of cerebral thrombotic and cardiovascular events. The derivatives of Cannabis are in turn responsible of an increased incidence of cancer, memory disorders and psychoses in young athletes of both sexes. Another dramatic pathology linked to the abuse of these substances is sudden cardiac death. The problems of doping at the transition age are therefore of vital importance and must be seriously addressed by the medical class, especially via the application of effective educational strategies targeting young athletes and their families.



What are the main problems linked to the use of doping substances in young athletes? What are the main effects of anabolic hormones on the bodies of young athletes? What are the effects of EPO? What are the links between the use of doping substances and sudden cardiac death? How healthy are the so-called nutritional supplements?

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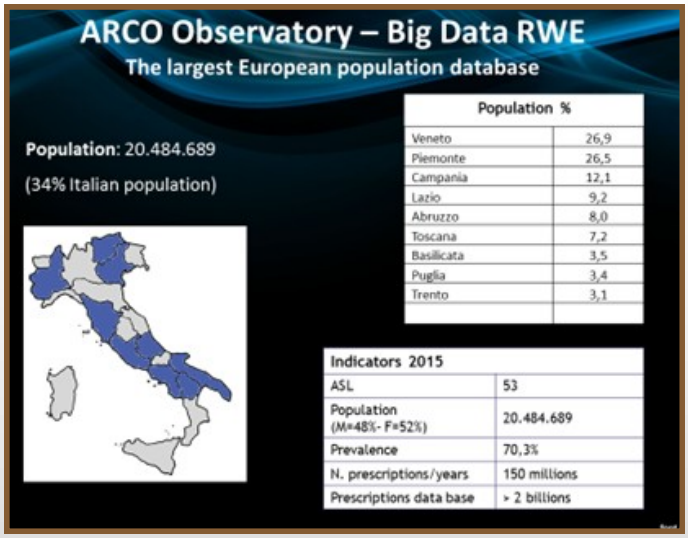
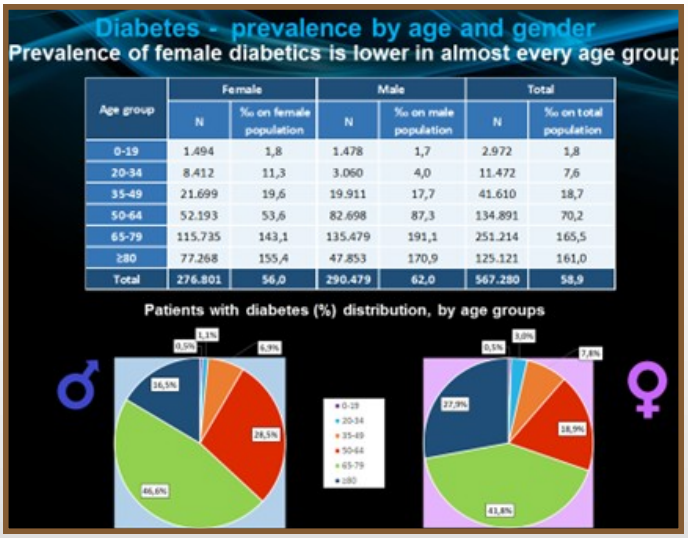
Gender medicine and the "big data": a pathway for implementing correct healthcare policies

Nello Martini
(Rome, Italy)

Prof. Martini from Rome addressed the issue of gender differences in terms of the "big data"; that is, the data collected not so much from clinical studies as from the treatment of diseases in clinical practice. This type of data is essential for the health system in order to launch appropriate strategies for sustainable healthcare at a local level for real patients in real life conditions and with real treatment. These data are also fundamental for implementing correct reimbursability strategies of the health-care costs, since they are capable of giving specific indications also in terms of gender differences. The speaker then presented the data of the AR-CO database, which is really representative of the Italian population. Over the age of 65 women have a higher prevalence than men. Women in general take more drugs than men, they have a higher percentage of hospitalisation, and they avail of the territorial health services more than men. By analysing these data it has been possible to establish the real costs of the Italian healthcare expenditure and the costs linked to hospitalisation are approximately half of the total expenditure. It is interesting to note the fact that women, despite using the services of the healthcare services more than men, generate lower costs than men. This fact is a direct indicator of the importance of Gender Medicine as an essential tool for evaluating the sustainability of the healthcare expenditure. Moreover, Gender Medicine is also a reliable indicator of the cost differences in the health management of chronic diseases like diabetes mellitus, acute coronary disease and osteoporosis, in which there are significant differences in terms of morbility and outcome between men and women.





Why are the "big data" essential in determining the expenditure of the health system?
What is the AR-CO database? What are the main data collected in this database?
What costs are linked to the treatment of diabetes in women and men?

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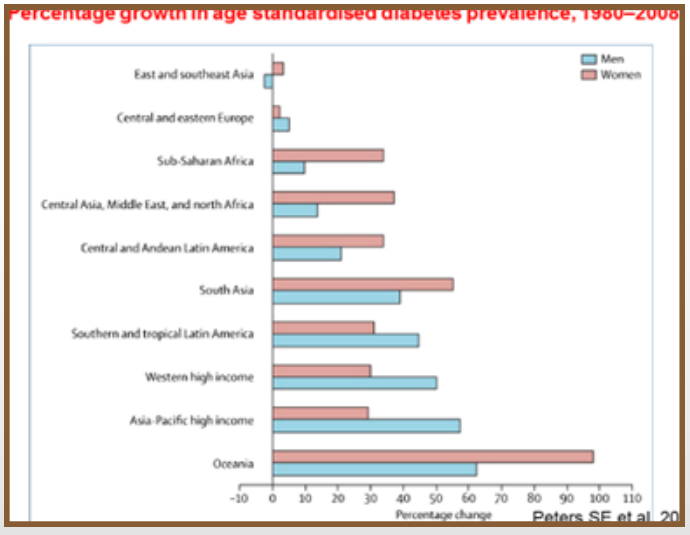
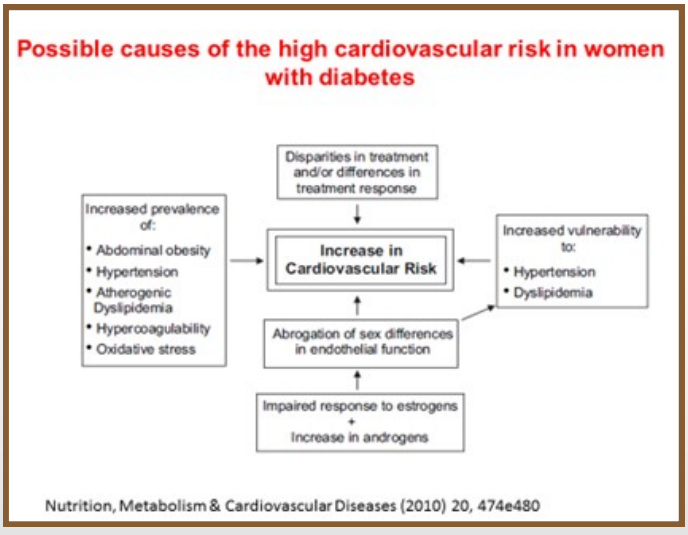
The relationship between Gender Medicine and diabetes mellitus

Giuseppe Seghieri
(Pistoia, Italy)

Prof. Seghieri from Pistoia presented data on the relationship between diabetes and Gender Medicine. An initial aspect is represented by an increased prevalence of diabetes in women compared to men at a worldwide level. With respect to men, women also show higher levels of blood pressure, plasmatic lipids and other risk factors such as the VIII Factor. In addition, diabetic women have higher BMI levels than men. Another extremely interesting factor is represented by the prevalence of cardiovascular disease that is four times higher in diabetic women than diabetic men. Finally, diabetic women show a significantly higher risk compared to men of developing clinical situations of dementia. Why are women more likely to develop these complications than men? The answer seems to lie in the different hormonal setup of women during the post-menopausal phase with respect to the fertile phase. In other words, the oestrogen hormones play an essential role as protection factors in fertile women. Their reduction after menopause exposes women to the aforementioned risks. The oestrogenic deficiency seems to expose women to a higher risk of developing the typical cardiovascular complications of diabetes than men, both at a peripheral and kidney and a retinal level. There are also important differences between women and men with regard to the response to drug treatment of diabetes. Women in particular, are more likely to develop side effects to the use of Metformin and the sulphonylureas.





What are the average blood pressure levels in women suffering from diabetes mellitus? What is the incidence of cardiovascular events in diabetic women? Why are women more likely than men to develop cardiovascular complications in the presence of diabetes mellitus? What are the main complications of Type 1 diabetes in female patients?

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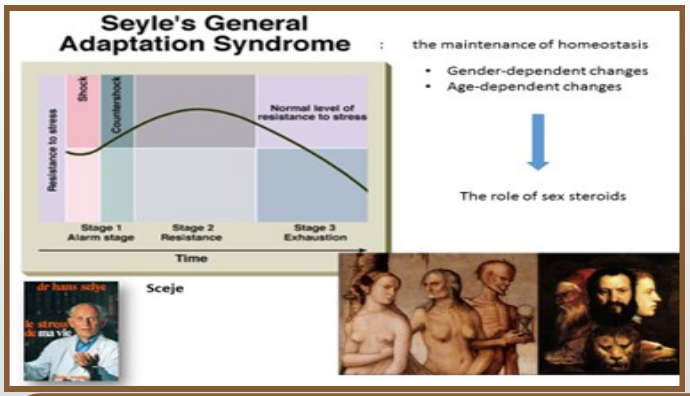
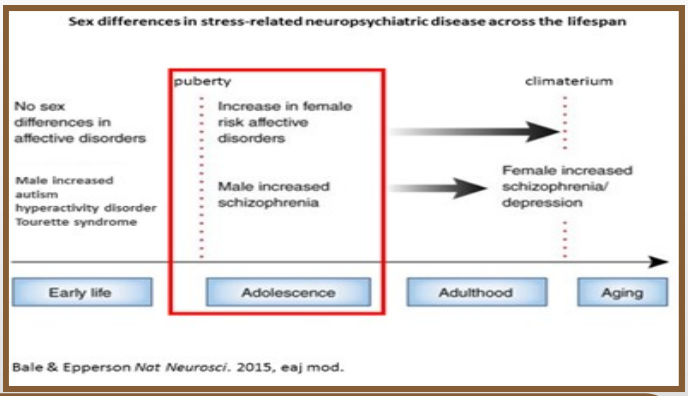
Differences between the sexes and response to stress throughout life

Emmanuele Jannini
(Rome, Italy)

Age, sex and stress were the keywords in the talk by Prof. Jannini from Rome. In endocrinological terms, the starting point is represented by the synthesis of the gonadic hormone in response to a stressful event. The difference between the male and female genders in the response to stress is evident at every moment in life, right from the prenatal stage when the response of the foetus is fundamentally linked to stressful events experienced by the mother. In actual fact, stress that has an impact on the individual during the foetal phase will have a significant influence throughout the course of this person's life. A good example of this is represented by the increase in the births of males compared to females who later on showed signs of schizophrenia in the 1940's in the Netherlands following the invasion of the country by the German army. It seems that this phenomenon was determined by the stress experienced by the young women during their pregnancies. Another moment in the life which is extremely delicate is the period of puberty. The precocity of the start of puberty, a phenomenon that was observed in a stable manner during the last decades of the twentieth century, was determined not only by the enhanced lifestyle, in particular in terms of nutrition, but also by the different modes of exposure to stress occurring during the second half of the nineteen hundreds. As far as reproductive life is concerned, the speaker gave examples of three models: the menstrual cycle, the perception of beauty, and the disorders related to so-called post-traumatic stress. The oestrogenic peak during ovulation significantly changes a woman's preferences towards a certain facial profile desired in the other sex, with more or less masculine features. In other words, in relation to the female gender, it is not the sexual orientation that determines the preferences for facial types in the other sex, but rather, their specific hormonal condition. This phenomenon does not exist in males. As regards the disorders linked to so-called post-traumatic stress, these are handled in completely different ways by men and women. A striking example of this emerged from data published in a study conducted on the population of L'Aquila following exposure to the earthquake that struck this city in 2009.





What is meant by Seyle's adaptation syndrome? What are the "biological production mechanisms" of stress? What are the mechanisms that give rise to the dimorphic development of the cerebral circuits in both sexes? Which is the stronger sex: the female or male one?

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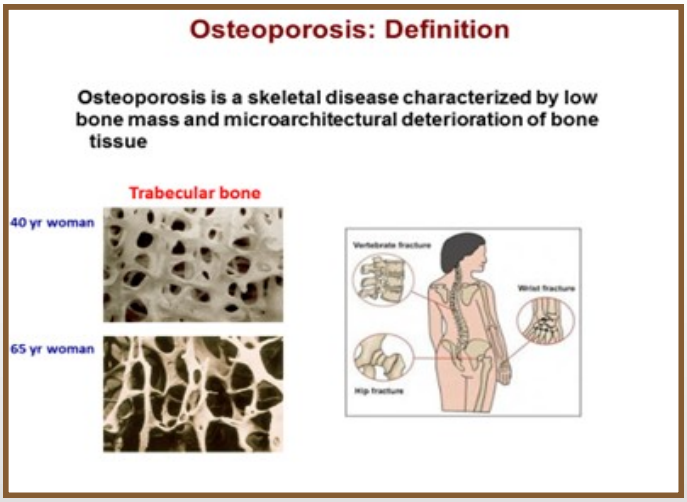
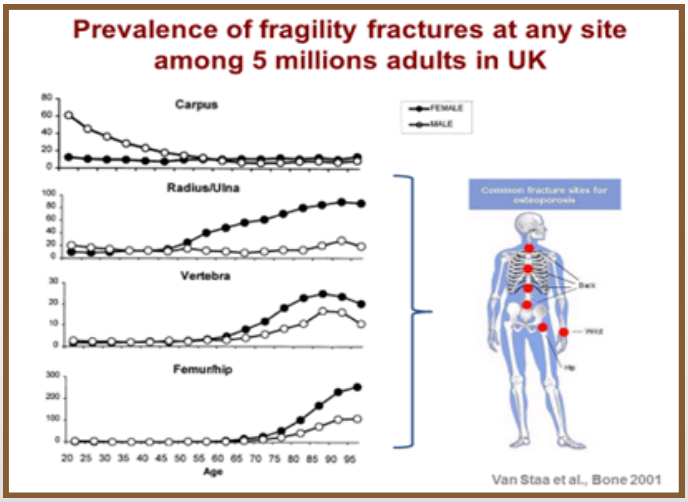
The gender differences in the physiopathology of osteoporosis

Claudio Marcocci
(Pisa, Italy)

Prof. Marcocci from Pisa addressed the topic linked to the gender differences in the physiopathology of osteoporosis. Bone metabolism is based on the balance between the synthetic activity of the osteoblasts and the catalytic activity of the osteoclasts. This continuous activity of synthesis and destruction of the bone tissue represents the so-called "bone remodelling" which is typical of adulthood and is present in both women and men. In the case of the prevalence of the bone catabolism phenomena over those of the synthesis, then we talk about osteoporosis. The sex hormones play a key role in maintaining the balance between the resorption and synthesis phenomena. In women, the drop in the plasma levels of the oestrogen hormones that takes place as of the pre-menopause phase is the main factor determining the significant reduction in the bone density typical of menopause and which can also give rise to the onset of osteoporosis in the cases in which this is particularly accentuated. This clinical picture may also be present in men but with a decidedly lower prevalence, especially after the age of 50. The studies conducted on fractures linked to particular bone fragility confirm this datum. Right from puberty, males have a different deposition of bone tissue compared to women. More specifically, thanks to the action of the androgen hormones in the male sex, the deposition of bone tissue increases at the cortical level, while in the female sex, thanks to the effect of the oestrogen hormones, the deposition of bone tissue increases at the trabecular level. The bone loss mechanisms are also different between women and men: in particular, with respect to men, in women there is an increased resorption phenomena at the level of the bone trabelculae, which is responsible for the greater bone fragility typical of postmenopausal females.





What are the main mechanisms that give rise to the synthesis and resorption of bone tissue? What is the role played by the androgen and oestrogen hormones in regulating bone metabolism? Are the drugs approved for treating osteoporosis equally effective in both women and men?

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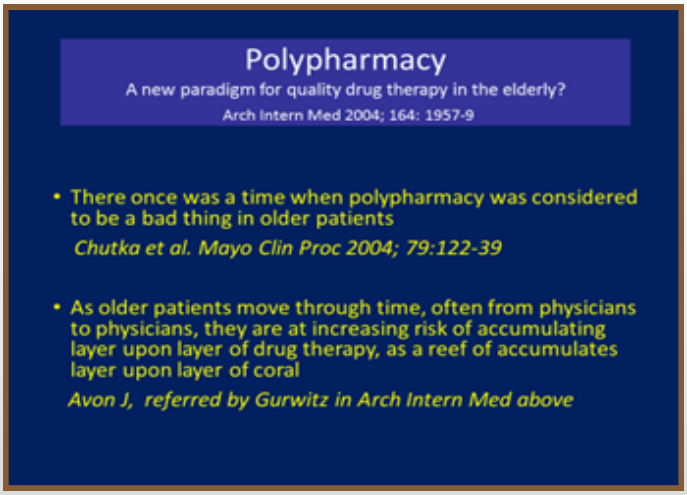
Gender Medicine and polypharmacy

Achille P. Caputi
(Messina, Italy)

Prof. Caputi from Messina addressed the issue of polypharmacy in elderly subjects and the differences observed between women and men. Right from the start of this century, elderly patients have been the subject of a constant increase in prescription drugs to be taken daily or the occasional prescription of at least one drug, and the prescription of a chronic polypharmacy. The latter in particular has given rise to an increase in prevalence equal to 50%. Women take more drugs than men, whereas men have a higher percentage of polypharmacy. In Italy, 73% of patients over the age of 85 take more than 10 drugs a day. In the United States for example, the most frequently prescribed drugs in women belong to the anti-inflammatory classes as well as drugs for the central and peripheral nervous system. Another important aspect is represented by the increase in prescription not only for drugs but also for dietary supplements. At this point the speaker examined the problems linked to polypharmacy prescription. The greater the number of drugs prescribed, the higher the risk of prescription errors and an increased incidence of adverse events connected to the administration of a variety of different pharmaceutical products. Another fundamental aspect that tends to be underestimated is the drastic reduction in compliance with the treatment due to the increase in the number of drugs prescribed. Also representing a problem is the so-called "drug to drug" interaction which in turn is responsible for the onset of specific adverse events. Finally, we must not underestimate the problem linked to the so-called "prescription cascade" which derives from the prescription of an additional pharmaceutical product in order to treat a pathology caused by a previously prescribed drug. A possible solution to the problem of polypharmacy is the application of the practice of "de-prescribing", that is, by reducing the number of drugs prescribed via the discontinuation of those that are not strictly necessary. Nevertheless, this practice is not easy to implement due to not being supported by specific guidelines. The speaker then described the clinical situations in which the discontinuation of one or more pharmaceutical products can have positive effects on the patient's health.



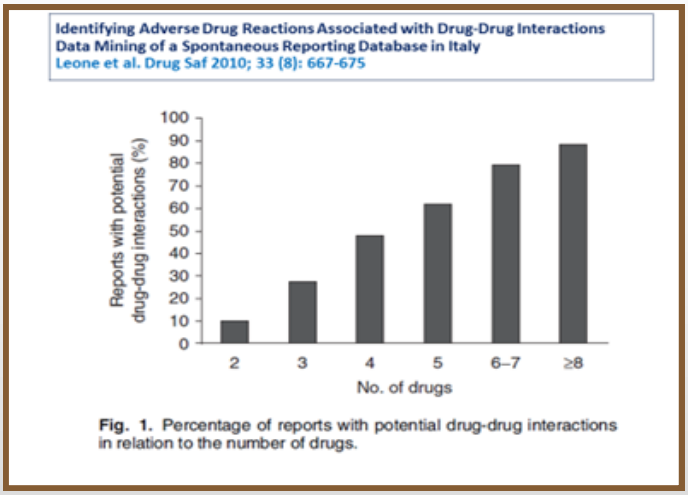


Fig. 1. Percentage of reports with potential drug-drug interactions in relation to the number of drugs.

What are the main problems linked to polypharmacy? What is the effect of polypharmacy on the health of patients, especially in the very elderly? What are the principal conditions in which it may be necessary to implement the practice of de-prescribing?

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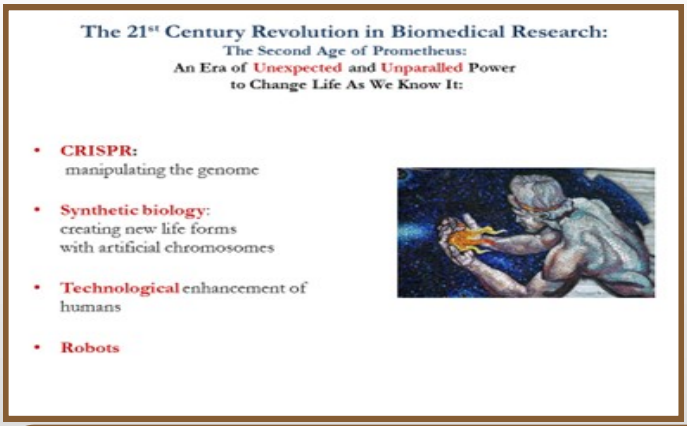
The future challenges of Gender Medicine

Marianne J. Legato
(New York, USA)

Prof. Legato from New York spoke about the future of Gender Medicine and its new challenges that commenced at the beginning of this century with the synthesising of the human genome. From that time on there has been a radical change in the vision of physiology and human physiopathology and the twenty-first century will be remembered as the era in which biomedical research underwent a 360° revolution. The manipulation of the human genome represented the start of this revolution. In fact, thanks to this method it has been possible to synthesise artificial chromosomes used to create new forms of life for the purpose of improving the human species. This is the era in which biology is compared to a computer process, where with appropriately upgraded software it becomes possible to manage the billions of cells making up the human body. Prof. Church, also known as the "doctor of genomics" declared that we humans have arrived at the point in which we have the opportunity of reduplicating and improving what nature has created. Faced with these problems she posed the following crucial questions: Is it ever possible to separate what is hard-wired into the organism by virtue of biological sex and what is the result of the impact of development, hormones and environment on the phenotype? What will be the consequences of our ability to modify the human genome? What is the impact of biological sex on gene expression? Will we be able to change that impact? What role will synthetic biology play in the nature of life on this planet? Lastly, how will our exponentially increasing ability to use technology to alter human competence and prolong life span impact the physician's role? The speaker expressed a whole series of considerations without giving absolute answers and instead invited the researchers present to contribute with their own findings in answering these questions. The destiny of the human species is brought into play here in the sense that within the space of a few years, technology will allow us to implant authentic computers inside our bodies that are capable of changing and improving the biological indicators of life, almost as though the machines we have invented were transformed into extensions of our own bodies. Research on the manipulation of the human genome will allow us to profoundly modify the sexual dimension of human beings and to interfere with human evolution, to the point of changing the very nature of created life. The speaker thus concluded her talk by explaining that we are at the crossroads where it becomes essential to make responsible decisions in order to manage our new technological capabilities that are potentially able to change the fate of the universe. All will depend on the decisions we make over the next ten years.



What are the main challenges that Gender Medicine will have to face in the 21st century? What are the advantages and the limits of the new technologies? How far is it possible to modify the human genome in order to enhance the human species?

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These are just a few of the topics addressed during the congress works.
For a more in-depth analysis please visit the website of the **Fondazione Internazionale Menarini** which also contains the full version of the congress talks.

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