Press release

The 12nd *Colloque Médecine et Recherche* of the *Fondation IPSEN* in the Endocrinology series: "Hormones, intrauterine health and programming"

Paris (France), December 5 2012 - A striking association has recently emerged between weight at birth and health in adulthood: adults who had low birth weights are more prone to develop a range of diseases including cardio-vascular disease, type 2 diabetes, poor stress regulation and psychiatric problems. At this year's Endocrinology meeting hosted by Fondation IPSEN, scientists from Europe, North American and Australia explored the influences and mechanisms regulating fetal growth and their long-term consequences for health. Nor are these effects limited to the individual: epigenetic changes underlying this 'developmental programming' can be transmitted to subsequent generations. A better understanding of the impact of environmental factors on fetal development and the complex consequences for both the individual and later generations is in sight. The new knowledge should pave the way to both prevention and early intervention,

The *Colloque Médecine et Recherches* in the Endocrinology series hold on December 3 in Paris opened a window into this young and rapidly expanding research field, which has the potential to improve many aspects of life-long health. The organisers were Jonathan Seckl *(University of Edinburgh, Edinburgh, UK)* and Yves Christen *(Fondation IPSEN, Paris, France).*

Although the fetus developing in the womb may seem to be well protected, its growth is remarkably susceptible to influences from the external environment through their effects on the mother's health: her diet, whether she is lean or over-weight, and her stress levels. Epidemiological studies have demonstrated that these factors affect not only the baby's birth weight but also have life-long consequences for the individual's health and survival (**Johann Eriksson**, *University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland*). Both lower-than-normal and higher-than-normal birth weights are associated with increased likelihood of developing a range of health problems as adults, such as cardio-vascular and metabolic problems, lung disease, some forms of cancer and some allergic reactions, poor regulation of the hypothalamic-adrenal axis and hence stress management, reproductive health, and psychiatric disorders (**Eriksson; Seckl; Michael Meaney**, *McGill University, Montreal, Canada*; **Mark Hanson**, *University of Southampton, Southampton, UK*). Mostly these appear during adult life but some children with low birth weights show signs of poor emotional regulation by 18 months (**Meaney**).

Maternal stress has a significant impact on the fetus. Women in the third trimester of pregnancy who suffered from post-traumatic stress disorder as a result of the 9/11 atrocity in New York had children who showed neuroendocrine changes at one year old, confirming previous observations of increased stress responses in survivors of the Nazi Holocaust *(Seckl)***.** Gluco-corticoids, passing from the mother to the fetal circulation in the placenta, are important as a mediator of maternal stress and a critical factor in developmental programming (**Seckl; John Challis**, *Simon Fraser University, Vancouver, Canada*; **Caitlin Wyrwoll**, *University of Western Australia, Perth, Australia*). Increased glucocorticoid exposure results in reduced fetal growth and premature maturation of tissues, as well as

affecting the development of the nervous system and leading to altered stress and inflammatory responses and a predisposition to type 2 diabetes (**Challis**). Low levels of a molecule known as 11ß-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which regulates the passage of glucocorticoids through the placenta, correlate with low birth weight and raised blood pressure in babies, and raised plasma cortisol in adults *(***Seckl***)*. Mice lacking 11β-HSD2 also show reduced circulation in the placenta and umbilical cord, leading to impairment of the fetal heart beat *(Wyrwoll)*.

The placenta, which is part of the fetus, is the overall modulator of the fetus's responses to the maternal environment, and so has a claim to be the agent that programmes adult susceptibility to disease (**Challis; Claudine Junien**, *UMR INRA ENVA CNRS 1198, Jouy en Josas, France*). As well as regulating glucocorticoid effects, it controls transfer of nutrients from mother to child and responds to external stimuli, such as oxygen levels and availability of nutrients to the mother; it also produces a metabolic hormone, lactogen, and molecules that regulate inflammation (*Challis*). Work in mice fed a diet high in fat, however, shows that the response of the placenta differs between male and female fetuses, implying different life-long health outcomes for the two sexes, even with the same environmental stimuli (**Junien**).

Environmental factors affecting the pregnant mother, in particular psychological stress, impact on the development of the fetal nervous system, with later behavioural and mental health consequences (**Meaney; Louise Kenny**, *University College Cork, Cork, Ireland*). Maternal stress is associated with an increased risk of schizophrenia, although the outcomes depend on both the timing of the stress during pregnancy and the sex of the fetus (**Kenny**). Poor maternal diet leading to abnormal birth weight is implicated in behavioural disorders in children, although these can be ameliorated by good quality post-natal care (*Meaney*). Glimpses into the mechanism come from macaque monkeys, where gene expression in the hippocampus, a brain structure involved in memory and emotional regulation, differs significantly between offspring with normal and low birth weights.

Many of these responses to maternal and environmental factors involve epigenetic regulation of gene expression. Epigenetic mechanisms determine which genes will be transcribed into proteins, and when and how much protein is produced, according to the particular needs of the organism at each moment. One way this is achieved is by attaching methyl groups to specific points in the DNA sequence of a gene, which usually prevent it being transcribed. One example is in the sexually dimorphic responses to a high fat diet described above, where the pattern of DNA methylation differs markedly between male and female fetuses (**Junien**). Identifying patterns of epigenetic markers associated with low and high birth weights should serve as markers for later risk. Although these markers are in place early in fetal life, some can later be reversed by diet or by hormonal or pharmacological treatment *(Hanson)*. However, epigenetic mapping is still a young science and consistent parameters have to be established (**John Greally**, *Albert Einstein College of Medicine, New York, USA*). Comparing DNA methylation patterns in a defined cell type found in cord blood from overweight, underweight and normal babies is helping to identify the genes crucial for subsequent susceptibility to disease.

In the β-cells of the pancreas, which produce and secrete insulin, intra-uterine growth retardation causes permanent epigenetic changes, increasing the likelihood of developing type 2 diabetes and obesity. In a rat model of restricted fetal growth, a gene transcription factor essential for β-cell development is silenced by epigenetic modifications, changes that are reinforced after birth and with the onset of diabetes. Similar epigenetic changes are present in human β-cells from patients with type 2 diabetes (**Rebecca Simmons**, *University*

of Pennsylvania, Philadelphia, USA). Abnormal patterns of DNA methylation have been found in disorders of post-natal growth, in the genes coding for key regulators of development and growth (**Yves Le Bouc**, *Hôpital Trousseau, Paris, France*). These changes are present in both overgrowth and growth-retardation syndromes. The increased prevalence of the overgrowth syndrome in children conceived through in vitro fertilisation raises concerns that the conditions created by in vitro fertilisation may be affecting methylation patterns.

One of the most far-reaching discoveries in this field is that the effects of intra-uterine experience extend beyond the life of the individual: the patterns of epigenetic markers set up in response to adverse conditions can be transmitted to the next generation (**Seckl; Mandy Drake**, *Queen's Medical Research Institute, Edinburgh, UK; Anne Ferguson-Smith, University of Cambridge, Cambridge, UK*). Both males and females can transmit these epigenetic changes, although, once again, there is a difference between the sexes. In rats, key genes are expressed to different extents in the offspring of males and females that have been over-exposed to glucocorticoids in utero (**Drake**). The transmission through the male line is particularly intriguing, implying that an epigenetically inherited 'memory' is being carried by a pattern of DNA methylation in the sperm (**Ferguson-Smith**).

.

About the Fondation Ipsen
Established in 1983 under the aegis of the Fondation de France, the mission of the Fondation Ipsen is to contribute to the development and dissemination of scientific knowledge. The long-standing action of the Fondation Ipsen aims at fostering the interaction between researchers and clinical practitioners, which is indispensable due to the extreme specialisation of these professions. The ambition of the Fondation Ipsen is to initiate a reflection about the major scientific issues of the forthcoming years. It has developed an important international network of scientific experts who meet regularly at meetings known as Colloques Médecine et Recherche, dedicated to six main themes: Alzheimer's disease, neurosciences, longevity, endocrinology, the vascular system and cancer science. Moreover the Fondation Ipsen has started since 2007 several meetings in partnership with the Salk Institute, the Karolinska Institutet, the Massachusetts General Hospital, the Days of Molecular Medicine Global Foundation as well as with the science journals Nature, Cell and Science. The Fondation Ipsen produced several hundreds publications; more than 250 scientists and biomedical researchers have been awarded prizes and research grants.

For further information, please contact:
Isabelle de Segonzac, Image Sept
E-mail : isegonzac@image7.fr
Tel. : +33 (0)1 53 70 74 70