



Press release

## **10<sup>th</sup> Colloque Médecine et Recherche of the Fondation Ipsen in the Endocrinology series: “Multi-system Endocrine Disruption”**

**Paris (France), November 30, 2010** - Many man-made chemicals are now known to have deleterious biological effects: they disrupt essential hormone functions. Because substantial amounts of such chemicals have accumulated in the environment, their side effects are potentially disastrous for humans and many other species. The tenth *Colloque Médecine et Recherche* in the Endocrinology series of the *Fondation Ipsen* was dedicated to an exploration of the effects of these substances. International leaders in this field have discussed both the effects of chemicals such as polychlorinated biphenyls, bisphenol A and phthalates on human and animal nervous, metabolic and reproductive systems, and the underlying molecular mechanisms. The meeting has been held in Paris on Monday November 29<sup>th</sup>, 2010 and has been organised by Jean-Pierre Bourguignon (*Université de Liège, Belgium*), Bernard Jégou (*Inserm U 435, Rennes, France*), Bernard Kerdelhue (*Centre Universitaire des Saints-Pères, Paris, France*), Jorma Toppari (*University of Turku, Finland*) and Yves Christen (*Fondation Ipsen, Paris, France*).

Endocrine-disrupting chemicals range from naturally occurring molecules, such as the oestrogen-like compounds found in plants, to synthetic products that include DDT, various chemicals used in the plastics industry, such as bisphenol A and polychlorinated biphenyls. Some of the man-made compounds are now widespread in the environment and the oestrogen mimics used as contraceptives are common in the surface layer of bodies of water. Some chemicals are so ubiquitous that it may be difficult to find people to serve as controls for tests who have had no exposure. Epidemiological studies are identifying likely correlations between chemical exposure and specific human diseases (Phillipe Grandjean, *University of Southern Denmark, Odense, Denmark and Harvard School of Public Health, Boston, USA*; Jégou; Toppari and Niels Skakkebaek, *Rigshospitalet, Copenhagen, Denmark*). The physiological and molecular mechanisms of their actions are being tracked in mice, rats and zebra fish.

For a long time, the focus of research into endocrine disrupters has been their effects on reproduction, in particular fertility (Jégou). In recent years attention has widened to include other systems and endocrine disrupting chemicals are now suspected of contributing to a range of human pathologies, including diabetes (Grandjean; Angel Nadal, *Universidad Miguel Hernández de Elche, Elche, Spain*), obesity (Retha Newbold, *National Institute of Environmental Health Sciences, Research Triangle Park, USA*) and bowel disorders (Eric Houdeau, *INRA, Unité de Neuro-Gastroentérologie et Nutrition, Toulouse, France*), as well as reproductive dysfunctions and hormone-dependent cancers (Toppari and Skakkebaek; Richard Sharpe, *University of Edinburgh, Edinburgh, UK*). Because the disrupting chemicals mimic the actions of oestrogen and thyroxin, which are essential for embryonic development, exposure *in utero* can have serious life-long consequences for brain structure and cognitive performance (Anne-Simone Parent, *GIGA Neurosciences, University de Liège, Liège, Belgium*; Olivier Kah, *UMR CNRS 6026, Université de Rennes 1, Rennes, France*), the onset of puberty (Andrea Gore, *University of Texas at Austin, Austin, USA*; Manuel Tena-Sempere, *Universidad de Córdoba, Córdoba, Spain*), weight regulation (Newbold), as well as reproductive functions (Gore).

Population studies can be used to identify possible causes of health problems. For example, twenty years ago sperm counts were much higher and the incidence of testicular cancer lower in Finland than in Denmark but a prospective study shows a marked decline in sperm count in Finland in the past ten years, correlating with increased industrial pollution (Toppari and Skakkebaek). Androgens are essential for male reproductive development and the experimental disruption of their actions with

dibutyl phthalate results in reduced testis size and level of sperm production in adult rats, provided they are exposed to the chemical both *in utero* and neonatally (Sharpe).

Hypotheses about the actions of particular compounds can also be tested in populations known to be at risk. Evidence that polychlorinated biphenyls contribute to type 2 diabetes is equivocal but has received support from an analysis of a group of 70 year-old Faroe Islanders, who have continued to eat a traditional diet that includes whale blubber high in fat-soluble polychlorinated biphenyls (Grandjean).

Polychlorinated biphenyls also have effects on the development of the hypothalamus in rats if they are exposed as fetuses, through their actions on oestrogen and androgen receptors. Onset of puberty depends on the correct sexual differentiation of the brain in response to the actions of sex steroid hormones during critical developmental periods. The resulting problems differ in the two sexes: in females, puberty is early and adult reproductive behaviour is disrupted; in males, puberty is delayed (Gore). Certain hypothalamic neurons containing the peptide kisspeptin are central to determining the onset of puberty. Maternal exposure to compounds, such as bisphenol A, that mimic the actions of the sex steroids alters the production of these neurons and the postnatal activation of gonad-stimulating hormones (Tena-Sempere).

At the cellular level, in rats, the disrupters affect the differentiation of neurons from their progenitor cells and the radial glial cells that are essential for the organisation of the cerebral cortex; in mice the formation of synapses in the hippocampus is disturbed (Parent). In zebra fish, radial glia and the consequent migration of hypothalamic neurons are sensitive to water-borne synthetic oestrogens that derive from the contraceptive pill (Kah). Embryonic exposure to bisphenol A disrupts differentiation of fat cells and gut endothelial cells, with life-long consequences (Newbold; Houdeau), and causes glucose intolerance in young male mice (Nadal). Adults are also vulnerable to bisphenol A, showing increased insulin resistance and decreased permeability of the gut wall.

The disrupting compounds may mimic the functions of particular hormones by inappropriately stimulating their receptors; antagonise the hormone's actions by interfering with the intracellular signalling pathways; or interfere with the delivery of the hormone to its target cells. To understand these actions, more needs to be known about the signalling pathways stimulated by hormones. The genes activated by thyroid hormone are being identified and previously unknown actions of this hormone are being explored in genetically altered mice (Thomas Zoeller, *University of Massachusetts, Amherst, USA*). The reprogramming of genes in the adult rat hypothalamus revealed after fetal exposure to polychlorinated biphenyls may provide a model for other endocrine disruptors (Gore). In zebra fish, synthetic oestrogens increase the expression of kisspeptin and its signalling pathway, which may provide a sensitive assay for the actions of oestrogen mimics (Kah).

As the actions of endocrine disrupting chemicals are better documented and more details of their mechanisms become known, it should become easier to identify the health disorders caused by these compounds and to take the necessary preventative steps.

### **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, in 2007, the *Fondation Ipsen* started three new series of meetings. The first series is an annual meeting organized in partnership with the Salk Institute and *Nature* and focuses on Biological Complexity; the second series is the "Emergence and Convergence" series with *Nature*, and the third with *Cell* and the Massachusetts General Hospital entitled "Exciting Biologies". Since its beginning, the *Fondation Ipsen*



as organised more than 100 international conferences, published 70 volumes with renowned publishers and 213 issues of a widely distributed bimonthly newsletter *Alzheimer Actualités*. It has also awarded more than 100 prizes and grants. Please visit [www.fondation-ipsen.org](http://www.fondation-ipsen.org)

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