The Adrenal Cortex Conference organizers (Bernard P. Schimmer, University of Toronto; Maria L. Dufau, NICHD, NIH, Bethesda and Alexander C. Brownie, University of Buffalo), were very pleased to receive the generous support from the Office of Rare Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The meeting included outstanding presentations by prominent investigators describing new and important developments of major relevance to the general subject of this Conference. The meeting covered basic and clinical aspects of research on the adrenal cortex and brought together scientists from many fields, thereby providing opportunities for interdisciplinary interactions.

An important component of this conference was related to the coverage of rare genetic disorders that affect steroidogenesis and other endocrine and non-endocrine function(s).  

**Familial glucocorticoid deficiency (FDG):** Adrian Clark and Patricia Hinkle presented work on the structure and function of a co-receptor protein, Melanocortin 2 receptor accessory protein (MRAP), which was found by Clark (UK) to be non-functional due to mutations in 20% of cases with ACTH-resistant FDG type 2. This protein was found to form antiparallel homodimers and to associate with the ACTH receptor (melanocortin 2 receptor, MC2R) at the cell membrane through its transmembrane domain (Hinkle, Rochester, USA). These studies also showed that MRAP is required for cell surface expression and trafficking of the MC2R, and that it is a component of ACTH-induced signaling. Moreover, an alanine substitution mutation when expressed was reported to impact exclusively on ACTH signaling function, indicating the presence of specific discrete functional regions. Dai Chida (Japan) generated mice with an inactivating mutation of the MC2R gene that displayed several of the features seen in patients with MC2R mutations that account for 25% of all FGD cases. The MC2R-null mice thus provide a useful model to study FGD.  

**Congenital lipoid adrenal hyperplasia:** The delivery of cholesterol to the inner mitochondrial membrane by the steroidogenic acute regulatory StAR protein is essential for steroidogenesis. Mutations in StAR give rise to congenital lipoid adrenal hyperplasia, the most severe congenital defect in steroid production. Through molecular modeling, circular dichroism, NMR and functional assays Lavigne and colleagues (Canada) demonstrated that the C-terminal α-helix of StAR gates the entry of cholesterol to its binding site. Their studies predicted open (binding and dissociation) and closed (stabilization) states of the gate and concluded that mutations observed in clinical cases of lipoid congenital adrenal hyperplasia promote the open state, causing unstable StAR protein-cholesterol complexes and consequently impaired transport and steroidogenesis. Stocco’s studies (Lubbock, Texas) demonstrated that the A-kinase anchoring binding protein AKAP121 and type II PKA regulatory subunit alpha direct the synthesis of STAR at the mitochondria in response to cAMP. Moreover, Podesta (Argentina), showed that StAR is a substrate of ERK1/2, and that mitochondrial ERK 1/2 is part of a complex that regulates cholesterol metabolism.  

**Adrenocortical carcinoma (ACC):** ACC is a rare and largely untreatable form of cancer. Studies by Hammer et. al. (Ann Arbor, Michigan) demonstrated a role of Wnt/beta-catenin signaling in the self renewal of subcapsular stem progenitor cells of the adrenal cortex, and characterized mechanisms by which disregulation of this pathway contributes to development of adrenal failure or carcinoma. Zambeti and his group established an International Tumor Registry and Tissue bank, a resource that has permitted the identification of a constitutively active TP53 and novel germline mutations and polymorphisms of TP53 and functional partners that predispose carriers or confer tumor risk. Tobias (Michigan) showed that telomere dysfunction in mice resulting from the Acd mutation (protein of the telomere cap complex) leads to senescence of the adrenal cortex that, when rescued by a p53-deficient background, leads to adrenocortical tumorogenesis. Michael Thomas (France) reported that transplantation of bovine adrenal cortical cells expressing Ras and truncated p53 beneath the kidney capsule of adrenalectomized mice triggered ACC development...
and metastasis in several organs. This finding provides a model to investigate novel therapeutic approaches to ACC. Ilpo Huhtaniemi described the genetics and endocrinology of gonadotropin responsive adrenal tumors in mouse models. These could be of relevance to the pathogenesis of macronodular adrenal hyperplasia and postmenopausal adrenocortical tumors. Stratakis demonstrated that the type 1 regulatory subunit of protein kinase A is mutated in most patients with Carney complex, an autosomal dominant disease, and also that phosphodiesterase-11A and -8B mutations were present in patients with isolated adrenal hyperplasia and Cushing’s syndrome. These studies have revealed that PDEs act as tumor suppressors, that when inactivated could lead to tumor development. prkar1a and pde11a null gene mouse models are currently being evaluated to delineate the participation of the cAMP/PKA pathway and associated PKA genes in the process of endocrine tumorigenesis.

Adrenal insufficiency: Miller (California) addressed the genetics of P450 oxidoreductase, a protein that contains FAD/FMN and transfers electrons from NADPH to microsomal (type II) cytochrome P450 enzymes and participates in the biosynthesis of steroids (17α-hydroxylase/17,20 lyase, 21-hydroxylase, aromatase), sterols, fatty acids and eicosanoids and hepatic drug metabolism. Patients with POR deficiency have a broad range of steroidogenic disorders. Sequence variation in 842 individuals of four ethnicities were presented (SPN, missense) The activities of all sequence variants gave different results in the four POR activity assays employed. Also, differences were observed in the support of the activities of P450c17, P450c21 and P450aro by a single POR mutant. These studies underscore the importance of assessing each POR mutant for each target P450 enzyme. Tomlinson addressed the topic of cortisone reductase deficiency and showed mutations in 11β-hydroxysteroid dehydrogenase type I or in hexose-6-phosphate dehydrogenase impaired cortisol formation and promoted ACTH-mediated androgen excess, resulting in a condition that resembles polycystic ovary syndrome. These studies also suggest that hexose-6-phosphate is an important source of reducing potential for the 11β-hydroxysteroid dehydrogenase type I and a potential target for drug development. Congenital adrenal hyperplasias (CAH) are defects of cortisol biosynthesis that occur in 1:10,000 to 1:15,000 of live births. The most common form of CAH is 21-hydroxylase deficiency. In its most severe form, 21-hydroxylase deficiency causes prenatal virilization of female external genitalia. Maria New addressed aspects of early prenatal diagnosis and treatment to reduce genital ambiguity and associated problems. She concluded from her extensive data and also from studies of other groups that treatment in the early prenatal period is effective and without adverse effects during the follow-up period so far. Subjects exposed to prenatal treatment continue to be monitored for adverse reactions. New strategies for earlier diagnosis of CAH are being investigated to avoid treatment of unaffected fetuses as necessitated by current protocols.

Other talks in the program described post-translational modifications that modulate the activity of Ad4BP/SF1, a member of the nuclear receptor family that regulate genes essential for steroidogenesis, and of CYP17 an steroidogenic enzyme regulated by SF1. Morohashi (Japan) demonstrated that SUMO modification of SF1 suppresses it transcriptional activity by recruiting a newly-characterized chromatin-like remodeling factor that in turn modulates chromatin structure and transcriptional activity. Sewer (Atlanta, GA) reported that the specific phosphorylation of p54nrb by phospho-PKA6 in response to cAMP regulates its association with CYP17 and its binding to SF1 and CYP17 pre-mRNA, and thus modulates the transcription and splicing of CYP17. Cidlowski (Research Triangle, NC) described new mechanisms for tissue specific actions of glucocorticoids resulting from his findings on multiple receptor isoforms produced by alternative mRNA splicing and alternative translational initiation. The various forms regulate specific subset of genes that selectively control cellular functions. Parker (Dallas, TX) generated mice with a specific SF1 null mutation in the central nervous system, that display anxiety-like behaviour. This was attributed to decreased expression of brain derived neurotrophic factor, and several receptors that control anxiety.

Overall, the meeting provided an excellent environment for interactions within a diverse group of basic and clinical scientists interested in the Adrenal Cortex, and covered a wide array of
topics that generated vigorous and informative discussions. The attendance was excellent (101 participants) and included a number of trainees and young scientists at the beginning of their independent careers who benefited from the discussions of their work with expert and seasoned scientists. Many of the leading research groups from the USA and abroad were represented. Scientists from 13 foreign countries, including the UK, Germany, Norway, Canada, France, Taiwan, Argentina, Italy, Switzerland, Japan, Israel, Australia and South Africa, attended and participated in the meeting. There was a consensus among attendees that the meeting was a major success. The outstanding presentations elucidating the modalities and mechanisms of several rare genetic diseases placed this important subject at a prominent level in this highly successful conference.