Cushing’s syndrome was first described by Harvey Cushing in 1912 at a time when the detection of ACTH as the cause of corticotroph adenomas was still decades ahead. He reported on a 22-year-old woman, Minnie G., who suffered ‘from a 7-year history of painful adiposity, hypertrichosis and amenorrhea.’ (1). The circumstances of the case description and the natural course have been reconstructed due to the detailed work of Carney (2) and Pendleton et al. (3). It took Harvey Cushing 20 more years to firmly verify the hypothesis that this syndrome is caused by basophile (corticotroph) adenomas of the pituitary (4).

Progress in diagnosing and treating Cushing’s syndrome has been slow following the first few decades after Cushing’s seminal description. For years, it appeared to be an orphan disease with relatively few advances in diagnosis and treatment. This is mainly attributable to the rarity of Cushing’s syndrome: an incidence of one to three new cases per million has been reported consistently from several countries (5). Therefore, many advances have been the result of medical spillovers from other more frequent but related pituitary or adrenal diseases, and it took 100 years to develop, approve and license the first drug specifically addressing Cushing’s disease – pasireotide (6).

Since 2008, the scientific number of articles addressing Cushing’s syndrome is steadily increasing in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/?term=Cushing’s+syndrome). This development reflects both the recent progress in diagnoses and treatment and the increased awareness that orphan diseases receive in our days. In 2014, we felt that the progress in Cushing-directed research has been so significant that a meeting dedicated only to Cushing’s syndrome might be justified. The main goal of the meeting was achieved by summoning the world experts of Cushing’s syndrome to reflect the current state-of-the-art diagnosis and treatment, discuss challenges and unsolved issues and develop collaborative projects by combining forces to develop more effective and targeted approaches. The conference Improving Outcome in Cushing’s syndrome (IMPROCUSH) was held from the 12th to the 14th of October 2014 in the beautiful surroundings of the Carl Friedrich von Siemens Foundation in the vicinity of Nymphenburg Palace in Munich. Over 100 scientists from around the world attended the meeting and discussed a broad spectrum of topics ranging from pathophysiology to treatment.

This special issue includes 13 invited articles summarizing main presentations given at the symposium. The topics covered in this issue are broad and can be divided into three categories. First, there are articles addressing the pathophysiology and the genetics of Cushing’s syndrome. The genetic basis of micronodular adrenal hyperplasia and Carney complex was elucidated 15 years ago by the Stratakis group at the National Institutes of Health (7). With the advent of whole-exome sequencing in endocrine tumors over the last 3 years, this was followed by the recent discovery of ARMC5 germ line mutations as the cause of primary bilateral macronodular adrenal hyperplasia in 25–50% of cases (8). In early 2014, the genetic basis of sporadic cortisol producing adenomas was uncovered (9). Finally, we and others identified recurrent hotspot mutations in the ubiquitin-specific protease 8 (USP8) in corticotroph adenomas (10). These mutations result in a gain of function of USP8 increasing epidermal growth factor receptor deubiquitination. As a result, activated epidermal growth factor receptor, instead of being degraded in the lysosome, is recycled from the early endosomes back to the plasma membrane, increasing proopiomelanocortin gene transcription and ACTH.
release. Aberrant adrenal receptor expression, in contrast to these very recent discoveries, is a pathophysiologic mechanism of adrenal cortisol excess established more than 20 years ago. This topic is covered by review of Lacroix et al. who have made seminal contribution to the field (11). However, it remains to be seen whether the identified new adrenal driver mutations such as ARMC5 are associated with illicit receptor expression.

Secondly, diagnostic aspects of Cushing’s syndrome, including clinical presentation and biochemical screening, were addressed. Early identification of patients affected by Cushing’s syndrome is the ultimate goal of every endocrinology unit. Distinguishing subjects with the very frequent metabolic syndrome from rare Cushing’s cases by clinical and biochemical means remains a challenge as outlined by the review of Lynette Nieman (12). Several new approaches, such as automatic face recognition and cortisol determination in hair, are covered by competent reviews from Kosilek et al. (13) and Wester & van Rossum (14) respectively. Localization of corticotroph adenomas by PET-based techniques is a more recent topic addressed by the Cambridge group around Gurnell et al. (15).

A third topic of the symposium was co-morbidities and therapeutic advances of Cushing’s syndrome. Despite surgical resection inducing biochemical remission, it is well known that comorbidities are not immediately reversible, and the patients remain at increased risk for adverse cardiovascular long-term outcome. The comprehensive reviews of Ferrau & Korbontis (16) and Coelho et al. (17) cover the important topics of metabolic complications and coagulopathy. Is subclinical hypercortisolism really a disease? Three independent retrospective case control series from Italy and the UK give strong evidence for an increased adverse cardiovascular outcome. The conclusions to be drawn from these and other studies are reviewed by Di Dalmazi et al. (18). Finally, the last review addresses bilateral adrenalectomy in ACTH-dependent Cushing’s syndrome as a safe and effective procedure (19). We hope that the review articles published in this special issue of the European Journal of Endocrinology will inform the clinician about state-of-the-art science in Cushing’s syndrome research and will guide those involved in patient care with relevant up-to-date information. It is obvious that progress in Cushing’s syndrome continues at a rapid pace. Because of this dynamic new data, biomarkers and molecules for the treatment of Cushing’s syndrome may arrive soon in clinics and will further improve patient care.

Declaration of interest
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