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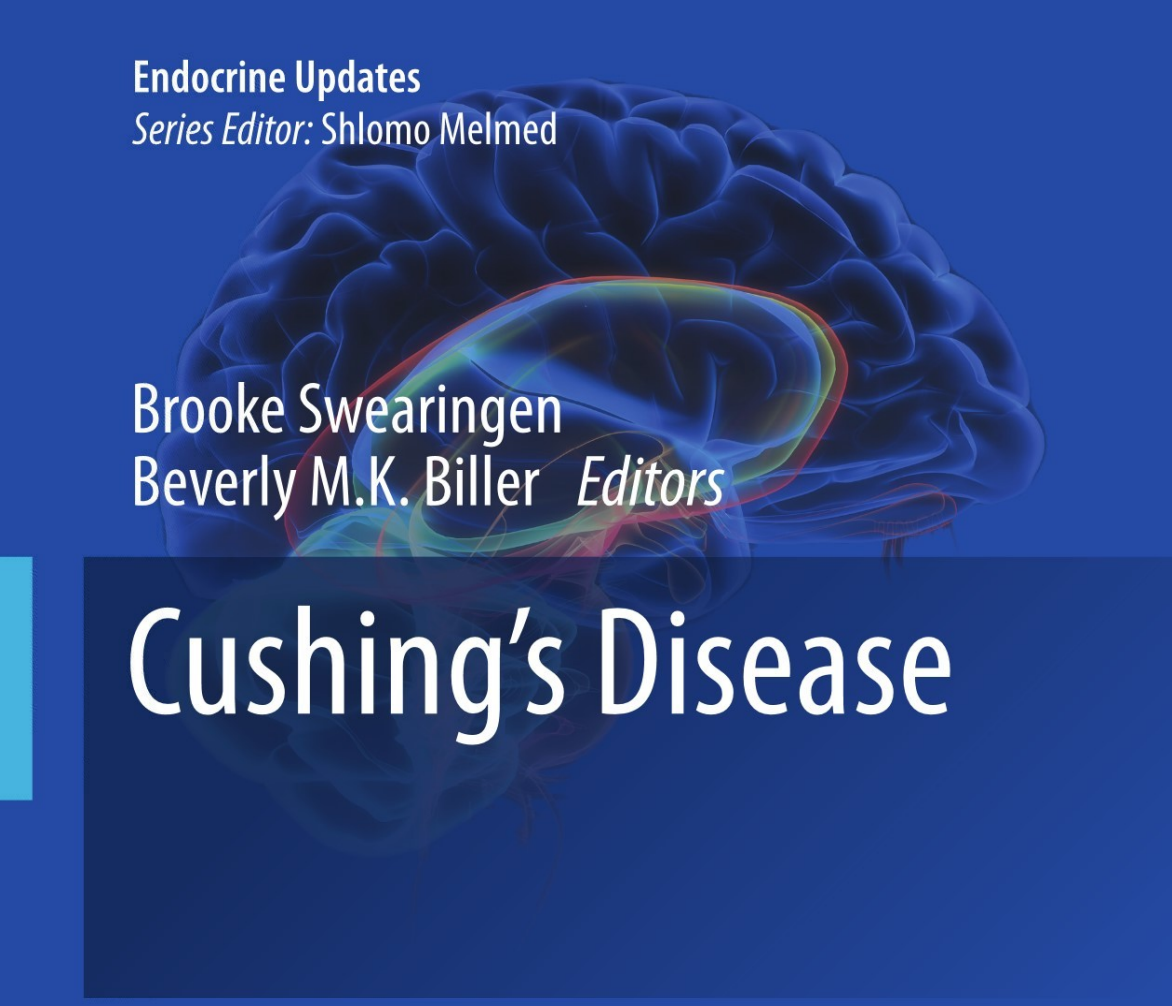

Brooke Swearingen
Beverly M.K. Biller *Editors*

Cushing's Disease

Springer

Endocrine Updates

Series Editor: *Shlomo Melmed*, *M.D.*

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Cushing's Disease

Springer

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Preface

Investigations into the etiology and manifestations of Cushing's disease have served as a model for basic and clinical research in both endocrinology and neurosurgery since Cushing's original monograph in 1932. He worked from careful clinical observation back to underlying pathology; others, including Fuller Albright, elucidated the fundamental hormonal mechanisms. Even today, the complex interrelationships between cortisol dynamics and a wide spectrum of endocrine – e.g., the "metabolic syndrome" – and nonendocrine – e.g., depression – disorders continue to be described.

In this book, we review the pathogenesis, diagnostic algorithm, and treatment options for this complex disease, as presented by leading experts in the field. Dr. Aron discusses the fascinating history of Cushing's disease as well as its historical significance to both endocrinology and neurosurgery in Chap. 1. Dr. Melmed and colleagues present both their and others' work on the molecular pathogenesis of the disease in Chap. 2 while Drs. Cheunsuchon and Hedley-Whyte illustrate the anatomic pathology in Chap. 3. The diagnosis of Cushing's syndrome remains a major challenge; Dr. Nieman depicts the current diagnostic algorithm in Chap. 4 while Drs. Kaltsas and Chrousos review the differential of pseudo-Cushing's syndromes in Chap. 5. Cyclical hypercortisolemia can be extraordinarily difficult to diagnose; Drs. Tritos and Biller discuss its evaluation in Chap. 6. Dr. Findling and colleagues present their current approach to the differential diagnosis of Cushing's disease in Chap. 7. The source of the hypercortisolemia is localized by a combination of endocrine and radiographic techniques; Drs. Rapalino and Schaefer portray the imaging findings in Chap. 8.

The mainstay of treatment remains surgical removal of the corticotroph adenoma; current techniques and results are described by Drs. Tierney and Swearingen in Chap. 9. Dr. Vance reviews the postoperative management and assessment of remission in Chap. 10. If surgery is unsuccessful, adjunctive treatment is required. Dr. Loeffler and colleagues explain radiotherapeutic options in Chap. 11, and Dr. Petersenn describes recent exciting developments in medical therapy in Chap. 12. Even with initially successful surgical treatment, the disease will sometimes recur; the management of this difficult situation is reviewed by Dr. Kelly and colleagues in Chap. 13.

Although rare, Cushing's disease in the pediatric population is important to recognize, as its clinical manifestations and impact on growth can be severe; Dr. Savage and associates characterize its diagnosis and treatment in Chap. 14. Drs. Kaushal and Shalet review silent corticotroph adenomas as a distinct clinical entity in Chap. 15. The diagnosis and management of Cushing's disease during pregnancy can be especially difficult; this is highlighted in Chap. 16 by Drs. McCarroll and Lindsay. Although bilateral adrenalectomy is less frequently employed in treatment than several decades ago, postoperative progression of the underlying corticotroph tumor remains a potential complication of this approach, and is reviewed by Dr. Bertagna and associates in Chap. 17. Finally, the long-term psychological manifestations of hypercortisolemia can be significant even after disease remission; this important topic is discussed by Dr. Sonino in Chap. 18.

We would like to thank our colleagues for their excellent contributions, Ms. Ellen Green of Springer for her editorial assistance, and Dr. Shlomo Melmed, as senior editor of the series, for his initial invitation. All of us remain students of this fascinating disease.

Boston, MA, USA

Brooke Swearingen
Beverly M.K. Biller

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Chapter 1
Cushing's Disease: An Historical Perspective

David C. Aron

Abstract The history of Cushing's disease exemplifies one of the triumphs of clinical and experimental medicine, as well as some of their limitations. This history can be described in terms of the development of Cushing's disease as a clinical entity, which paralleled the history of medicine and the evolution of endocrinology as a discipline. Advances in endocrinology depended on clinical observations combined with laboratory studies – clinicians and chemists. The description of Cushing's disease and its elucidation depended upon these developments. Not only could treatment be effected by replacing a deficient hormone, but hormone excess could be treated by the removal of the pathologic hormone-secreting tumor, as demonstrated in Harvey Cushing's 1909 report of the successful treatment of acromegaly by the removal of a portion of the anterior lobe of the pituitary. The maturation of the field of endocrinology brought with it the recognition of the importance of feedback control and the development of the radioimmunoassay (among other scientific developments), as well as a shift in focus to hormone action, the rise of molecular biology, and the unification of endocrinology, immunology, and neuroscience into a single discipline.

This chapter is divided into three parts: (1) development of Cushing's disease as a clinical entity, a process that has moved from bedside to bench and back again, (2) further elucidation of the pathophysiology of Cushing's disease as the discipline of endocrinology moved from the organism to the organ to the cell, and (3) related developments that apply to issues in healthcare delivery.

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Introduction

The history of Cushing's disease exemplifies one of the triumphs of clinical and experimental medicine, as well as some of their limitations. This history can be described in terms of the development of Cushing's disease as a clinical entity, which paralleled the history of medicine and the evolution of endocrinology as a discipline [1–4]. A discipline includes, among other elements, a paradigm, modes of inquiry, a community of scholars, an epistemology (requirements for what constitutes new knowledge), and a network for communication, e.g., learned journals and professional societies. This evolution has been described in part by Dr. Jean Wilson in his Plenary lecture at the 12th International Congress of Endocrinology [3]. He dates the birth of endocrinology to the presentation of a paper in 1889 to the Société de Biologie in Paris by Charles-Edouard Brown-Séquard, introducing the concept of chemical messengers secreted into the blood to exert systemic effects [5–8]. This is the essential paradigm. However, prior to this birth there was a long prenatal period during which many disorders now known to be endocrine in nature were described. For example, Thomas Addison described adrenal insufficiency in his book *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules*, first published in London in 1855 [9]. At about the same time, Brown-Séquard's study of the effects of adrenalectomy indicated that the adrenals were necessary for life, though the reason remained unknown for many years. Endocrinology's adolescence was somewhat stormy; along with proof for the existence of multiple chemical messengers and astounding experiments involving administration of gland extracts, e.g., Murray's treatment of a case of myxedema and the discovery of insulin by Banting and Best; there were also extravagant claims for "organotherapy" [10–12]. However, the scientific approach to the generation of medical knowledge prevailed, and the importance of pathology in linking certain disorders to specific glands became evident. During this adolescence, the principles of hormone characterization were formulated by Doisy: (1) Identification of the tissue that produces a hormone; (2) Development of bioassay methods to identify the hormone; (3) Preparation of active extracts that can be purified, using the relevant bioassay; and (4) Isolation, identification of structure, and synthesis of the hormone [3, 13]. Advances in endocrinology depended on clinical observations combined with laboratory studies – clinicians and chemists. The description of Cushing's disease and its elucidation depended upon all of these developments. Not only could treatment be effected by replacing a deficient hormone, but hormone excess could be treated by the removal of the pathologic hormone-secreting tumor, as demonstrated in Harvey Cushing's 1909 report of the successful treatment of acromegaly by the removal of a portion of the anterior lobe of the pituitary [14].

The growing community of scholars' need for a professional society and journal was recognized with the founding in 1917 of The Association for the Study of

Internal Secretions (changing its name in 1952 to The Endocrine Society). The maturation of the field of endocrinology brought with it the recognition of the importance of feedback control and the development of the radioimmunoassay (among other scientific developments), as well as a shift in focus to hormone action, the rise of molecular biology, and the unification of endocrinology, immunology, and neuroscience into a single discipline. Paradigms were changing. Wilson stated: "The shift of focus to hormone action moved molecular endocrinology into the mainstream of cellular and developmental biology, and advances of several types have eroded the separations between endocrinology, neurobiology and immunology … There is probably no arena of medicine in which collaboration between the clinical and basic sciences has been more productive" [3]. In fact, the elucidation of the etiologies and pathophysiology of Cushing's disease has continued along with, and contributed to, these developments. Questions have been raised whether endocrinology is still a discipline or whether it has been reduced to molecular/cellular biology, but it is useful to view the development of Cushing's disease more broadly in context of health care delivery.

Although the emphasis in the current research paradigm as illustrated in the NIH Roadmap is conveniently described as being the linear progression of knowledge from bench to bedside to practice, the reality has always been far more complex [15]. The advance of medical practice depends on the interactions among the clinical practice, healthcare delivery, and biomedical research enterprises, all of which occur in a context with social, political, scientific, and philosophical aspects. For those interested in a detailed chronology of the events in the advance of knowledge of pituitary and adrenal anatomy, physiology, biochemistry, and pathophysiology, there are standard works and recent reviews [2, 3, 16–18]. This chapter is divided into three parts: (1) development of Cushing's disease as a clinical entity, a process that has moved from bedside to bench and back again, (2) further elucidation of the pathophysiology of Cushing's disease as the discipline of endocrinology moved from the organism to the organ to the cell, and (3) related developments that apply to issues in healthcare delivery.

Development of Cushing's Disease as a Clinical Entity

The description and elucidation of Cushing's disease has paralleled developments in medicine at large. Thomas Sydenham (1624–1689) became known as the English Hippocrates because of his idea that diseases were distinct and should be classified based on their clinical features and course. Critical to Sydenham's work (and the future of medicine) was his attention to accurate clinical observation and comparison of case with case and type with type. Thus, advancement in medicine proceeded following a clinical description, which consisted of a complex of signs and symptoms that were recognized as sufficiently different from other disease entities or syndromes to merit a new designation. The title of an essay from a book about the advancement of basic science is "By Their Diseases Ye Shall Know Them – The Endocrines" [19]. As knowledge accumulates, it helps us to understand the condition, how it came into being, how it relates to various other factors, various other

Fig. 1.1 Harvey Cushing http://webapps.jhu.edu/namedprofessorships/professorshipdetail.cfm?professorshipI D=125 accessed 11-28-04

states, i.e., it provides an "explanation" for a set of symptoms [20]. With time, it may prove valuable in the care of the patient and might also force us to modify the original concept of the clinical entity [20]. Although theories to explain the pattern (the science of medicine) may change through the ages, the clinical entity bridges the gap between theories, e.g., Cushing's disease due to hyperpituitarism versus hyperadrenalism. However, theories may broaden or narrow that clinical entity. For example, we now consider Cushing's disease to represent a spectrum from full blown Cushing's disease as it was initially described to a state of "sub-clinical" autonomous cortisol hypersecretion manifest solely by glucose intolerance or obesity [21]. The clinical entity is the persistent thread among the shifting theories and offers a way to examine the development of biomedical knowledge in ways that have implications for today. Following the clinical description of Cushing's disease some 300 years after Sydenham, the evolution of Cushing's disease as a clinical entity occurred in three periods: the description of the clinical syndrome, the explanation of the syndrome as hypercortisolism, and the delineation of three causes of hypercortisolism. In their 1969 article, Liddle and Shute recognized that this evolution was continuing to include the identification of atypical forms [1]. In the first two periods, the primary actors – Harvey Cushing (Fig. 1.1) and Fuller Albright (Fig. 1.2) combined clinical and experimental expertise. As consummate clinician–investigators, they were able to combine their knowledge and skills from each of these domains and the interactions were synergistic.

Harvey Cushing's Interest in the Pituitary and the Clinical Description of the Syndrome

Knowledge of the physiological role of both the adrenals and the pituitary began with recognition of clinical disorders. Bartolomeo Eustachius is the first person known to have described the adrenal glands, what in 1563 he termed the "*glandulae*

Fig. 1.2 Fuller Albright, from: Biographical Memoirs V.48 (1976) National Academy of Sciences, http://books.nap.edu/books/0309023491/html/2.html (NAS) accessed 11-28-04

renibus incumbentes" and his drawing in the *Opuscula Anatomica* is the first known representation [2, 16, 18]. Virtually nothing was known about their function until the middle of the nineteenth century when Thomas Addison stated that "at the present moment, the function of the suprarenal capsules, and the influence they exercise in the general economy, are almost or altogether unknown" [9]. However, in this 1855 work, he described a series of patients with a variety of adrenal lesions – tuberculosis, metastases, and atrophy, some of whom clearly suffered from adrenal insufficiency. In fact, Addison's interest in the adrenals began with his observation of adrenal abnormalities in a form of fatal anemia (pernicious anemia). At around the same time, Brown-Séquard performed adrenalectomies and sham operations on dogs in the form of a controlled study and demonstrated that the adrenals were indispensable to life [2, 16, 18]. Tumors of the adrenal had been recognized at least since the eighteenth century and were associated with a variety of symptoms, particularly virilization [22, 23]. Individual cases, which fit the clinical picture of Cushing's disease, had also been described. However, the distinctness of the syndrome was not yet recognized.

The pituitary gland was identified earlier than the adrenals [24]. Galen, the court physician to the Roman Emperor Marcus Aurelius (third century CE), recognized the existence of the pituitary gland, and the conception of the pituitary as the source of phlegm was attributed to him; the pituitary was thus named (Latin *pituita* = "phlegm"). Andreas Vesalius, the pioneering Flemish anatomist, named the structure *glandula pituitam cerebri excepiens* ("in the little phlegm acorn drawn out of the brain"). This was consistent with the Galenic concept of a structure necessary to eliminate waste products or residues generated in the brain. The English anatomist

Richard Lower suggested in his 1672 *Dissertatio de Origine Catarrhi* what might today be considered an endocrine function of the pituitary: "For whatever Serum is separated into the ventricles of the brain and tissues out of them through the Infundibulum to the Glandula pituitaria distills not upon the Palate but is poured again into the blood and mixed with it" [25]. By the turn of the twentieth century, apart from the clinical description of acromegaly and its association with a pituitary tumor, relatively little was known. In fact, in his classic monograph *The Pituitary Body and its Disorders,* Cushing contrasted the progress in investigation of the functions of the thyroid and adrenal glands: "The other glands have notably lagged behind, with the pituitary body at the tail of the procession. For though this structure was added to the group of so-called ductless glands by Liegeois some 50 years ago, its inaccessibility has been sufficient to discourage investigation even were there no other difficulties to be encountered" [26].

Harvey Cushing's interest in the pituitary gland may find its origin in a misdiagnosed case [27]. In 1901, Harvey Cushing returned to the USA from a European tour and began to develop his surgical career. Among his first cases was a sexually immature 14-year-old obese girl seeking treatment for progressive visual loss and headache. He was unable to localize the lesion clinically and rather than perform an exploratory craniotomy, he performed palliative decompressions. Although the headache improved, the girl's vision deteriorated. Cushing then explored the posterior fossa in the hopes of finding a cerebellar tumor, but to no avail and the girl died postoperatively of pneumonia. An autopsy revealed a pituitary cystic tumor. The misdiagnosis was made even worse because Cushing had recently spent time learning about brain tumor localization in the laboratory of one of the leading neurologists of the day, Charles Sherrington. Furthermore, several months after this case, Cushing earned of a similar case from someone who had studied with him in the same laboratory, Alfred Frohlich. Frohlich described a case of "adiposogenital dystrophy" in a boy with a pituitary tumor and sent a reprint to Cushing. Frohlich not only made the correct diagnosis, but also convinced a surgeon to operate. It may well have been wounded pride as well as intellectual interest in an intriguing case that set Cushing on the course to studying the functions and disorders of the pituitary gland. Cushing recognized the importance of clinical issues pointing the way in research. In his 1914 Weir Mitchell Lecture, Cushing emphasized the importance of tumors to the process of clarifying the function of an endocrine gland: "It may be recalled that much of our knowledge of pituitary disorders has revolved around the question of tumor-using the term *in* a comprehensive sense. It was the presence of a tumor which first led Marie, and subsequently Frohlich, to couple with this comparatively obscure gland the syndromes which bear their names. And for the most of us to-day manifestations of tumor continue to be a necessary guidepost, so that those who venture to predict pituitary disease in their absence do so with misgivings, and merely on the ground that similar constitutional symptoms have been known to arise in conjunction with a growth" [28].

Cushing's skill as neurosurgeon and his development of new techniques gave him an advantage over other experimental physiologists. When pituitary disorders were first being diagnosed, neurosurgery as a subspecialty had not yet come into

being and the thought of surgical approaches to the deeply seated pituitary gland was a daunting prospect. This is illustrated in the words of a late twentieth century textbook: "Where the growth lies in contact with the base of the skull, that is, springs from the inferior surface of the brain, conservation would pronounce the word inaccessible. This warning, however, is quite unneeded by the genes audax omnia perpeti; for example, by such as announce that they think operations for the removal of tumors from the base *of* the brain are feasible; such daring characterized a specialist in cerebral surgery, whom the writer heard say that he believed it possible to so open the skull and lift up the brain as to catch a view of the foramen magnum. The reader may ask, Did he mean this of the living subject?" [29]. The first intracranial operation on the pituitary was performed only in 1889 by the British general surgeon Victor Horsley, who had an interest in the endocrine system and organotherapy and had already performed hypophysectomies and thyroidectomies in animals, but technical advancements occurred over the next two decades. Cushing's first approach to the pituitary via the extracranial (i.e., transsphenoidal) route took place in 1909, and an excellent surgical result was achieved. However, he remarked: "Surgeons, however, cannot afford to enter into this new field too precipitously, not simply by reason of the peculiar inaccessibility of the gland-for operative resources will overcome these difficulties – but principally on account of the present uncertainties in regard to its physiological properties" [14]. By 1912, Cushing had already achieved some excellent surgical outcomes, but he looked toward a different future: "It is conceivable that the day is not far distant when our present methods of dealing with hypophyseal enlargements, with scalpel, rongeur, and curette – new as these measures actually are and brilliant as the results may often be-will seem utterly crude and antiquated, for it is quite probable that surgery will, in the end, come to play a less, rather than a more important, role in ductless gland maladies. This Utopia, however, will be reached only when a sufficient understanding of the underlying aetiological agencies enables us to make more precocious diagnoses" [26].

Using his neurosurgical skills, Cushing was able to show in dogs that complete pituitary removal was lethal and concluded that the pituitary was essential to life. Although he was less successful in dissecting out the anterior and posterior lobes of the pituitary individually, he was able to show that partial destruction of the anterior pituitary was associated with the development of a Frohlich's syndrome. Although unable to prove it, Cushing, based on a clinical response to partial tumor resection in a patient with acromegaly, speculated that the acidophilic cells of the pituitary made a growth promoting factor that could account for the disordered growth. Though a researcher, Cushing was also a consummate clinician and sought to apply his knowledge in the clinic. Here is where he met Minnie G, one of his first patients with what Cushing called a polyglandular syndrome, but who in retrospect, clearly suffered from hypercortisolism (Fig. 1.3). Her case is described in his 1912 book, along with a group of cases exhibiting a polyglandular syndrome: "In brief, the term 'polyglandular syndrome' indicates merely that secondary functional alterations in members of the ductless gland series occur whenever the activity of one of the glands becomes primarily deranged. Further, the term as here employed is restricted to those cases in which it is difficult to tell which of the structures is primarily at

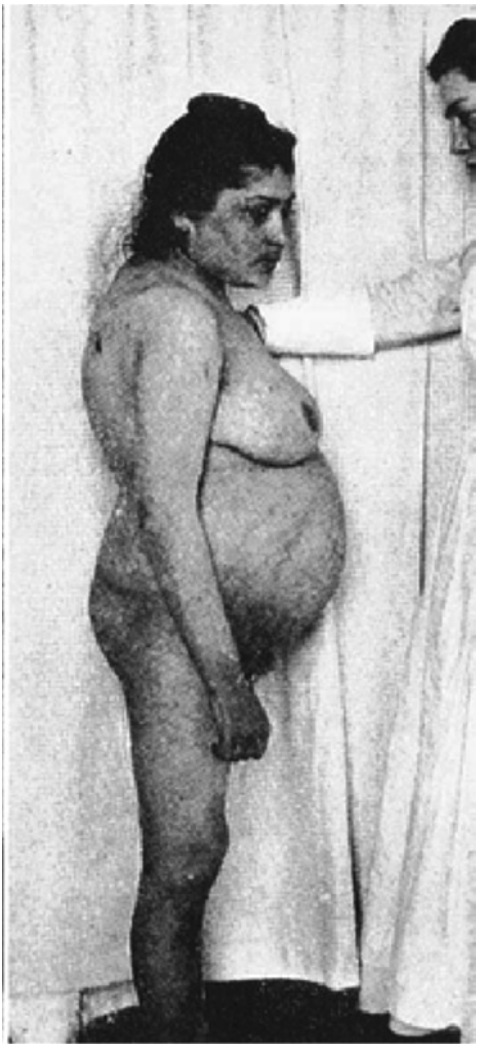

Fig. 1.3 Minnie G. Patient with Cushing's syndrome. From Cushing H. The pituitary body and its disorders. Philadelphia: J.B. Lippincott, 1912

fault" [26]. Furthermore, her case description ends with the tantalizing statement: "An exploration of the adrenals is under consideration". However, this was never undertaken.

Cushing commented that in addition to skeletal undergrowth, adiposity and sexual dystrophy on the one hand, painful and tender adiposis with asthenia and psychic disturbances on the other, the case is an instance of the combination of intracranial pressure symptoms with amenorrhea, adiposity, and low physical stature. "A syndrome which might well be due to hypophyseal deficiency. But here, however, the similarity to the cases of hypopituitarism, which hasn't been heretofore discussed, ends … A symptom-complex of this type has been described in association with certified *adrenal lesions,* which makes it appear that the adiposo-genital

syndrome may occur with derangements of other of the ductless glands than the hypophysis itself … It will thus be seen that we may perchance be on the way toward the recognition of the consequences of *hyperadrenalism*" [26]. He continued his clinical practice and laboratory investigation, accumulating a total of 12 cases that formed the basis of his classic 1932 paper [30]. Shortly thereafter, the syndrome was given the eponym Cushing's disease by Bishop and Close [31]. Although aware of the occurrence of adrenal hyperplasia in some cases, Cushing nevertheless held to the view that the pituitary was the primary problem, with the main factor being basophil adenomas of the pituitary gland which were found in two of the patients. He wrote: "While there is every reason to concede, therefore, that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal, or with adrenal tumors, the fact that the peculiar polyglandular syndrome which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the adrenal cortex other than a possible secondary hyperplasia, will give pathologists reason in the future more carefully to scrutinize the anterior-pituitary for lesions of similar composition" [30]. He thought that hypersecretion of gonadotropin, along with growth hormone one of the two pituitary factors known, might be the factor responsible, but he was not able to produce this experimentally. Collip's discovery of adrenocorticotropic hormone (ACTH) would open the way to another path for investigation. Cushing's success owed to his keen powers of observation, skills as an experimentalist, as well as serendipity in his ability to relate disease syndromes to an overproduction or to an absence of secretory products of the pituitary; he set a very high standard for other clinician–investigators to follow [27]. Among those who met and probably exceeded this standard was Fuller Albright.

Fuller Albright and Hyperadrenocorticism

Fuller Albright (1900–1969) was considered to be the preeminent clinical and investigative endocrinologist of his day by many of his contemporaries and his 1944 address to the American Society for Clinical Investigation is considered a classic [32]. Schwartz noted that in a brief introductory note to his bibliography, Albright wrote, "In my opinion, my contributions divide themselves into two groups: (a) clinical descriptions and (b) elucidations of pathological physiology." In category (a), he, along with his students and associates, described de novo or made definitive contributions to the delineation of an astonishing 14 major syndromes over a 20-year-period [32]. In category (b), not only did he excel in the area of calcium metabolism for which he is best known, but also in the area of adrenal function (and others). I have elected to single out and describe in some detail his exploration of the workings of the adrenal cortex because his efforts in this area serve to illuminate the synergistic interactions between bedside medicine and basic science. At the same time, these studies provide elegant and instructive examples of how an astute clinical observer can unravel complex hormonal and metabolic interactions [32].

Interestingly, in Albright's diagram of the do's and don'ts of clinical investigation, a picture of a patient with Cushing's disease is prominently displayed [16]. This diagram was annotated by Felix Kolb, a member of the Metabolic Research Unit at University of California, San Francisco, which was led by Dr. Peter Forsham. This unit played an important role in describing a number of aspects of Cushing's disease and its management. In addition, among the most heavily cited life sciences papers between 1945 and 1954 was Albright's Harvey 1942–1943 Lectures on Cushing's syndrome [32, 33]. Here, Albright described the logical progression of his hypotheses and his moving from bench to bedside and back. His investigations stemmed from clinical observation. He wrote: "To be absolutely accurate, one should probably confine the term 'Cushing's Syndrome' to those individuals who present a certain striking clinical picture (vide infra) associated with a basophile tumor of the pituitary. However, the author will use the term to refer to patients with the clinical picture regardless of the etiology. From a clinical point of view, the syndrome is so striking that it seems almost certain that all individuals with it have some common denominator as regards the etiology" [32, 33].

His first attempt was to see whether this symptom complex could not be entirely explained on the basis of hypergluconeogenesis coupled with a resistance to glucose oxidation resulting from a hyperadrenocorticism. Since this hypothesis should lead not only to too much sugar, but also to too little protein, it might likewise explain the deficiency in tissues, notably the weakness of the muscles, osteoporosis, thin skin, and the easy bruisability. It might also explain the obesity. If the disorder does not involve a change in the total energy output but merely a change in the proportions of carbohydrates, fats, and proteins in the "metabolic mixture," one would expect the increased burning of protein to result in decreased burning and hence in storage of fats. However, Albright quickly saw problems with this hypothesis. He found it somewhat disconcerting that the patients with Cushing's disease studied in the clinic were never found to be in markedly negative nitrogen balance before therapy was instituted; indeed, most of them have been in slightly positive nitrogen balance. Moreover, patients with hypoinsulinemic diabetes, in whom the diabetes is not under control, do not develop a clinical picture like Cushing's disease in spite of the markedly increased conversion of proteins into sugars which occurs in that condition. This argument was stressed by Dr. Robert Loeb in a personal communication, who argued that the diabetes in Cushing's disease is the result of overproduction rather than the underconsumption of sugar. Finally, his hypothesis predicted that patients with Cushing's disease be resistant to ketosis. Abandoning that hypothesis, he tested another one, positing a fundamental disturbance in the ability to burn fat. However, a study in a single patient showed that not to be the case. Albright wrote: "When it came to looking around for a new hypothesis, the one certain fact from a clinical point of view was that the patients with Cushing's disease were suffering from deficiency of tissues. Since the evidence already presented made it quite clear that the disorder was not an excessive breakdown of tissue, the alternative thesis suggested itself, namely that there was a difficulty in synthesis of tissue. It seemed possible that the fundamental disorder was still a hyperadrenocorticism with respect to the 'S' hormone, but that this hormone, instead of converting proteins and hence

tissues into sugar, inhibits the production of tissue" [32, 33]. In other words, as aptly put by Dr. E. C. Reifenstein, Jr., the hormone is anti-anabolic rather than catabolic. This hypothesis explained all the experimental results. He (Albright) wrote: "The author is aware of no data which do not harmonize with this new theory. However, he feels that such data will undoubtedly be forthcoming and that a new hypothesis or a further modification of the present one will be necessary" [32, 33]. The issue was not settled in the literature for several years, made more complicated by the different pathologic findings in different patients – basophilic adenomas of the pituitary, adrenal tumors, and adrenal hyperplasia. Ectopic ACTH syndrome was still to be recognized, although a case consistent with this diagnosis had been reported in 1928 [34]. For both Harvey Cushing and Fuller Albright, success was in large part a result of the combination of clinical and experimental expertise and the synergy of rigorous logic and knowledge-based intuition [32].

Further Elucidation of the Pathophysiology and Clinical Features of Cushing's Disease as the Discipline of Endocrinology Evolved

Following the periods of clinical description and identification of hypercortisolism as the underlying feature, in the third period, various causes of hypercortisolism were delineated: (1) autonomous secretion of cortisol by an adrenocortical neoplasm, (2) hypersecretion of cortisol in response to excessive secretion of ACTH by the pituitary gland and (3) hypersecretion of cortisol in response to "ectopic" ACTH. Other related conditions were described, e.g., Nelson's syndrome and the accelerated growth of an ACTH-secreting pituitary tumor following adrenalectomy for Cushing's disease [35]. However, when Grant Liddle described these three periods, the number of etiologies of Cushing's disease was relatively limited. In part, this reflected limitations in the technology of diagnosis [1]. However, during this time, advances in laboratory techniques and imaging facilitated more accurate diagnosis; tests were developed to distinguish among these types of hypercortisolism, e.g., dexamethasone suppression testing and ACTH measurements [36]. Developments in diagnosis and corresponding advances in imaging techniques and therapy continue to this day, e.g., inferior petrosal sinus sampling, salivary cortisol levels, CRH testing [37]. The identification of subclinical autonomous glucocorticoid hypersecretion which is a frequent finding in incidentally discovered adrenal masses reflects technological advances in radiologic imaging [38, 39].

As endocrinology narrowed its focus toward the inner workings of the cell, i.e., glucocorticoid receptors and genetic abnormalities, additional types of Cushing's disease were identified. Some cortisol-producing adrenal tumors or, more frequently, bilateral macronodular hyperplasias, are under the control of aberrant membrane hormone receptors, or altered activity of eutopic receptors. Food-dependent Cushing's disease was shown to be associated with ACTH-independent macronodular adrenal hyperplasia [40]. In this condition, cortisol secretion appears to be

regulated by the aberrant expression of several G-protein-coupled receptors, specifically glucose-dependent insulinotropic polypeptide (GIP). In the adrenal tissue of affected individuals (both the adrenal nodules and the adjacent cortex), GIP and LH-receptor overexpression were found. Primary pigmented nodular adrenocortical disease (PPNAD) is a rare form of ACTH-independent Cushing's disease that may occur alone, but is found to be associated with the Carney complex (CNC) in 90% of the cases [41]. A form of multiple neoplasia syndrome, it is characterized by pigmented lesions on the skin; cardiac and cutaneous myxomas; multiple endocrinal tumors (adrenal, testicular or ovarian, thyroid, and hypophysis); and, less frequently psammomatous melanotic schwannoma, ductal adenoma of the breast, and rare bone tumors. It is an autosomally dominant inherited syndrome and somewhat fewer than half of the affected families have mutations in the gene *PRKAR1A*, which acts as a classical tumor suppressor. Additional developments in therapy have been based on molecular approaches, e.g., glucocorticoid receptor blockers [42]. However, notwithstanding the advances that have occurred in molecular biology and genetics, the endocrinologist practices in a context and developments outside the traditional discipline of endocrinology have also played a role in the way Cushing's disease is viewed, e.g., the elucidation of psychiatric manifestations of hypercortisolism [43]. Of note, Harvey Cushing himself was a pioneer in the psychosomatic approach to endocrine disease. This is reflected in his insistence on assessing every patient's mental status, in his insights into possible pathogenetic roles for stressful life events, in recognizing the occurrence of organic affective disorders ("the effects on the psyche and nervous system of chronic states of glandular overactivity or underactivity"), and in understanding the ailment of residual symptoms ("it is even more common for a physician or surgeon to eradicate or otherwise treat the obvious focus of disease, with more or less success, and to leave the mushroom of psychic deviation to vex and confuse the patient for long afterwards, if not actually imbalance him") [44]. The fact of residual symptoms implies long-term changes at the cellular/molecular level as a consequence of hypercortisolism.

Clinical Epidemiology and Healthcare Delivery (Health Services as They Apply)

As commonalities were found at the molecular level, there were developments in other areas, especially in health care delivery. The Institute of Medicine in 1995 offered the following definition of health services research: "Health services research is a multidisciplinary field of inquiry, both basic and applied, that examines the use, costs, quality, accessibility, delivery, organization, financing, and outcomes of health care services to increase knowledge and understanding of the structure, processes, and effects of health services for individuals and populations" [45]. This broad definition is explicitly concerned with several characteristics of health care and with the health of both individuals and populations. These concerns are especially relevant to the increasing interest in determining the value of health care and in managing the

health of populations. Much of recent health services research has focused on medical outcomes defined as the health status of persons, groups, or communities that can be attributed to health care. Thus, outcomes research has been defined as the evaluation of medical practices integrating the best available information on safety, effectiveness, and outcomes as experienced by patients. Although outcomes research has a long history, its landmark application in the USA can be traced to a rivalry between two Harvard Medical School students: Ernest Codman and Harvey Cushing [46]. From 1894 to 1895, students were responsible for the administration of anesthesia at the Massachusetts General Hospital. After the death of Cushing's first patient, Cushing and Codman began a contest to obtain the lowest mortality rate. Although it is not clear who won, one result of the competition was the creation of anesthetic records. Codman became a surgeon in Boston and expanded upon his idea that the end results of treatment should be monitored and reported. In addition to keeping records of the patients' condition at discharge, he performed 1-year follow-up examinations and reported the results. His application of these ideas and their rejection by the medical establishment offers lessons for today. The development of measures of health care outcomes is critical to health services research. A wide variety of outcome measures have been developed and each has its problems. For example, mortality is easily defined but is usually such a rare event that the applicability of statistical analysis is limited. Although it is easier to establish criteria for an outcome measure in which data are collected prospectively, health services research frequently is performed retrospectively. Because outcomes may not be measurable for an extended period of time after the episode of care, conclusions about cause and effect are less certain. Measurement of health-related quality of life (HRQoL) is increasingly important in health services research, especially in evaluating the impact of chronic disease and the effectiveness of its treatment. Valid instruments are available to measure both comprehensive (generic) and disease-specific domains of function and well-being, and both are important in chronic illness. Chronic exposure to hypercortisolism has significant impact on patient's health and HRQoL, as demonstrated with generic questionnaires. Webb et al. developed a disease-specific questionnaire to evaluate HRQoL in patients with Cushing's disease (CushingQoL) [47]. Sonino et al. also developed a clinical index for rating severity in Cushing's disease to facilitate assessment of response to therapy [43].

Among the issues affecting the management of Cushing's is variation in practice. The Evidence-Based Medicine movement has reached endocrinology in general and Cushing's disease in particular. For example, systematic reviews of diagnostic tests have been conducted and evidence-based practice guidelines have been developed. An Endocrine Society Task Force developed a guideline for the diagnosis of Cushing's disease and Biller et al. reported on the development of a consensus approach to the treatment of patients with ACTH-dependent Cushing's disease [37, 48]. This process involved 32 leading endocrinologists, clinicians, and neurosurgeons with specific expertise in the management of ACTH-dependent Cushing's disease representing 9 countries. Another issue is that there is variation in outcomes across surgeons depending on experience, skill, and other factors. The consensus statement said: "The most important treatment recommendation that an endocrinologist makes to a

patient with Cushing's disease is referral to a neurosurgeon with extensive experience in operating on patients with corticotroph microadenomas" [48]. Even under the best circumstances, remission rates after transsphenoidal pituitary microsurgery range from 42 to 86% [49]. Because Cushing's disease is rare, experience varies. An early example of practice variation is found in a letter to the New England Journal of Medicine which tabulated the number of cases and remission rates for transsphenoidal surgery for Cushing's disease [50]. Among 25 sites, the number of cases ranged from 2 to 15 per year and the remission rates ranged from 10 to 100% [50]. However, in a study of 958 neurosurgeons, Ciric et al. concluded that complication incidence is significantly higher in less-experienced surgeons in his study [51]. Cushing's disease treated by adrenalectomy presents similar issues. Moreover, Kissane and Cendan reported outcomes from laparoscopic adrenalectomy (LA) comparing patients with Cushing's disease with those with other adrenal pathology. LA in patients with Cushing's disease is associated with longer hospitalizations, more frequent major complications, and higher advanced care requirements, especially for patients undergoing bilateral adrenalectomy [52]. Thus, the history of Cushing's disease and its treatment continue to evolve.

Conclusion

The history of Cushing's disease has played out amid the background of developments in medicine and endocrinology. This history illustrates linkages between science and practice at multiple levels. Both Harvey Cushing and Fuller Albright played active roles to solidify the links. Each studied in the laboratory questions that arose at the bedside and contributed to the rise of endocrinology. Both served as Presidents of the Association for the Study of Internal Secretions (Cushing 1921–1922 and Allbright 1945–1946).

These efforts took place against a background of issues surprisingly relevant to contemporary issues. In a letter to Harvard Medical School Dean David Esall (7 March 1925), Cushing wrote: "If the pre-clinical departments succeed in driving the clinician out of the school entirely, instead of encouraging him to work there, it will be one more source of estrangement between those departments which deal with patients and those which do not" [53, 54]. Addressing the dedication of the William H. Welch Medical Library of the Johns Hopkins University School of Medicine in 1929, he commented upon the progressive decentralization of medical schools and the increasing specialization of both preclinical and clinical departments. He said: "More and more the preclinical chairs at most of our schools have come to be occupied by men whose scientific interests may be quite unrelated to anything that obviously has to do with Medicine, some of whom I, indeed, confess to a feeling that by engaging in problems that have an evident bearing on the healing art they lose caste among their fellows. They have come to have their own societies, separate journals of publication, a scientific lingo foreign to other ears, and are rarely seen in meetings of medical practitioners, with whom they have wholly lost