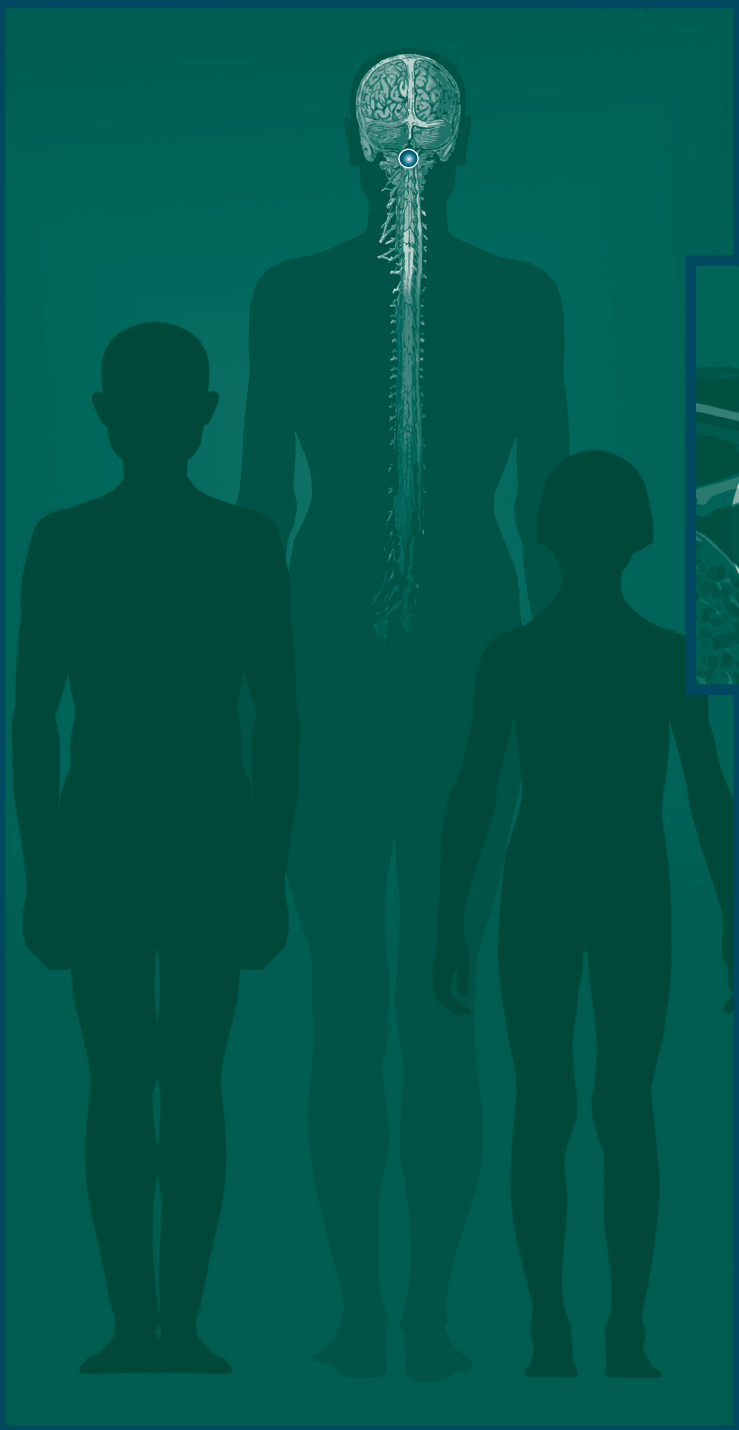
Office of Research on Women's Health Symposium on

Family Hormonal Health

Understanding Pituitary Disorders and Planning for Future Research



U.S. Department of Health
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An integrative report and recommendations from the symposium cosponsored by the National Institutes of Health (NIH) Office of Research on Women's Health, the Pediatric and Reproductive Endocrinology Branch, the NIH National Institute of Child Health and Human Development of the Department of Health and Human Services (DHHS), the National Naval Medical Center and the Pituitary Network Association.

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Foreword from the Director of ORWH

The Office of Research on Women's Health (ORWH) has been in existence since September 1990, and one of its mandates is to set a research agenda for women's health for the National Institutes of Health (NIH) and the scientific community that NIH funds. In setting that agenda, we not only focus on conditions that affect women, but also consider projects that address conditions that affect both men and women. This focus is a means of learning about sex and gender differences and similarities so that diagnoses and treatments can be appropriately applied to various populations.

In planning a research agenda, observations and anecdotes may spur our thinking and help us formulate scientific hypotheses, but it is the evidence generated by biomedical and behavioral research that will change how medicine and health care are practiced, how our healthcare professionals are educated, and what individuals will do to improve and protect their health. In approaching research on women's health and sex and gender factors, we have begun to focus on innovative interdisciplinary research, in which there is collaboration between medical and scientific disciplines, and in which the public is involved. The interdisciplinary approach to understanding how conditions affect both men and women leads us into the realm of pituitary hormonal disorders, which are an important consideration in the scientific research agenda.

The goals of the scientific symposium on family hormonal health were, first, to increase our awareness and scientific understanding of the all-encompassing nature of pituitary disorders so that the biomedical community can diagnose these conditions in their earliest stages. To that end, the symposium included presentations from several individuals about their own conditions and the effect the lack of early detection has had on their health and well-being. A second goal was to disseminate knowledge of state-of-the-art treatments for these conditions; this publication is one of several avenues for doing so. And third, the symposium was conducted to stimulate the thinking of the scientists who attended to identify research directions for funding that hold the greatest promise for addressing pituitary disorders.

We recognize that the symptoms of pituitary conditions are of many kinds and can be mistaken for symptoms of many other disorders or can be considered insignificant. We also recognize that pituitary health and pituitary conditions affect the entire family and the community in which individuals live because of the ramifications of those conditions. We know that pituitary tumors, as well as other conditions of the pituitary, are probably more common than many realize, and that some of these conditions may affect women differently than they affect men. Thus, we want to encourage interdisciplinary collaboration because of its potential to create optimum opportunities for translating research from bench to bedside to obtain the best clinical outcomes for pituitary conditions. Also, through collaboration among Government agencies, public institutions, the private sector, and organizations such as the Pituitary Network Association, we can optimize service resources and delivery to individuals, families, and communities.

I wish to thank some special individuals whose efforts were instrumental from the vantage point of ORWH for making this symposium a success. In particular, Dr. Eleanor Hanna took the lead at ORWH for the symposium and this publication. Dr. George Chrousos of the National Institute of Child Health and Human Development (NICHD), a researcher in this area of focus, was crucial to designing the scientific program and serving as a very effective liaison to the advocacy and scientific communities. Dr. Yvonne Maddox, deputy director of NICHD, and Dr. Mohamed Shakir of the National Naval Medical Center, have been our liaisons and strong supporters in this collaborative effort. And, of course, Robert Knutzen and the Pituitary Network Association have been central to this project in bringing the issues of pituitary disorders and hormonal disorders to our attention and for their persistence in ensuring that we grant these disorders the public attention that they deserve.

Vivian W. Pinn, M.D.

Family Hormonal Health:
Understanding Pituitary Disorders and Planning for Future Research

Introduction

The Office of Research on Women's Health (ORWH), in collaboration with the National Institute of Child Health and Human Development (NICHD), the National Naval Medical Center, and the Pituitary Network Association, convened a National Institutes of Health (NIH) Symposium on Family Hormonal Health to discuss the impact of pituitary disorders, both from the scientific perspective of an internationally recognized group of experts and from the personal viewpoint of three patients.

Overall, the goals of the meeting were to increase awareness and scientific understanding of the nature of pituitary disorders: to improve early diagnosis, to disseminate knowledge of state-of-the-art treatments, and to encourage collaboration among scientists and funders of research to determine the best way to proceed in order to improve treatment options and the quality and length of life for both men and women.

The following sections summarize and integrate the scientific discussions on pituitary disorders and the insights from three patients who discussed their experiences from detection of their pituitary disorders to their treatments.

The Pituitary Gland

The pituitary is a bean-shaped gland attached to the base of the brain by a thin stalk. Essential for growth, the pituitary functions as the "Master Gland" (see Figure 1). It receives input from the brain and the rest of the body, integrates that information, and then responds by producing hormones that regulate other glands and bodily functions. The pituitary sends signals to the thyroid gland, adrenal glands, and ovaries or testes, directing them to produce thyroid hormone, cortisol, estrogen, testosterone, and many other hormones. These hormones have dramatic effects on metabolism, blood pressure, sexuality, reproduction, and other vital bodily functions. In addition, the pituitary gland produces growth hormone (GH) for normal development of height and prolactin for milk production. This all occurs interactively via a system of negative feedback loops. The charts on the following page (see Figure 2 and Figure 3) detail the hormones produced by the pituitary gland and the organs it stimulates to produce other hormones.

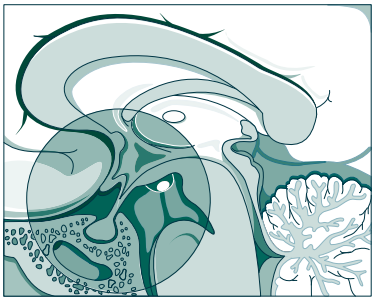


Figure 1. As the "Master Gland," the pituitary is essential for growth and overall hormonal regulation.

Causes and Consequences of Pituitary Gland Malfunction

Tumors (primarily benign), inflammation, infections, and injury can cause the pituitary gland to malfunction; in rare instances, spread of other tumors to the pituitary also can cause malfunction. In some cases, radiation therapy to the brain can cause normal pituitary cells to malfunction. Pituitary malfunctions result in headaches, compression of the optic nerve with loss of peripheral vision, and a variety of hormonal effects on the heart, gut, muscle, bone, and other parts of the body.

Pituitary disorders stunt growth in children and shorten the lives of all affected individuals by causing health complications such as mood disorders, sexual dysfunction or infertility, diabetes, osteoporosis, arthritis, and accelerated heart disease. Although pituitary tumors are present in nearly 20 percent of adults worldwide, many go undiagnosed for years because of the diffuse array of symptoms.

Pituitary disorders frequently go undiagnosed because they often signal unrelated conditions; therefore, pituitary disorders should be considered as a potential diagnosis by health professionals when working with a patient who presents a puzzling and diverse constellation of complaints and clinical findings. Medical, surgical, and radiotherapeutic options do exist for individuals with pituitary disorders; however, these therapies cannot be used until a patient is diagnosed appropriately.

Figure 2. Pituitary Hormones, Targets, and Functions

This chart details the hormones the pituitary gland produces, outlining the targets in the body and the functions of the hormones.

Hormone	Target(s)	Function
Adrenocorticotropic Hormone (ACTH)	Adrenals	Stimulates the adrenal gland to produce a hormone called cortisol. ACTH is also known as corticotropin.
Thyroid-Stimulating Hormone (TSH)	Thyroid	Stimulates the thyroid gland to secrete its own hormone, which is called thyroxine. TSH is also known as thyrotrophin.
Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH)	Ovaries (Women) Testes (Men)	Control reproductive functioning and sexual characteristics. Stimulate the ovaries to produce estrogen and progesterone and the testes to produce testosterone and sperm. LH and FSH are known collectively as gonadotrophins. LH is also referred to as interstitial cell-stimulating hormone in males.
Prolactin (PRL)	Breasts	Stimulates the breasts to produce milk. This hormone is secreted in large amounts during pregnancy and breastfeeding but is present at all times in both men and women.
Growth Hormone (GH)	All cells in the body	Stimulates growth and repair. Research is being carried out to identify the functions of GH in adult life.
Melanocyte-Stimulating Hormone (MSH)		Exact role in humans unknown but increases skin pigmentation in amphibians.
Antidiuretic hormone (ADH)	Kidneys	Controls the blood fluid and mineral levels in the body by affecting water retention by the kidneys. This hormone is also known as vasopressin or arginine vasopressin (AVP).
Oxytocin	Uterus Breasts	Affects uterine contractions in pregnancy and birth, and subsequent release of breast milk.

Figure 3. Hormones Under the Control of the Pituitary Gland

This chart illustrates the organs that have been stimulated by the pituitary gland to produce other hormones.

Hormone	Organ	Function
Cortisol	Adrenals	Promotes normal metabolism, maintains blood sugar levels and blood pressure, provides resistance to stress, and acts as an anti-inflammatory agent. Cortisol also plays a part in regulating fluid balance in the body.
Thyroxine	Thyroid	Controls many bodily functions, including heart rate, temperature, and metabolism. Thyroxine also plays a role in metabolizing calcium in the body.
Estrogen	Ovaries	Facilitates growth of the tissues of the sex organs and other tissues related to reproduction. Estrogen also acts to strengthen bones and has a protective effect on the heart.
Progesterone	Ovaries	Promotes changes in the uterus that occur in preparation for the implantation of a fertilized ovum and prepares the breasts for milk production.
Testosterone	Testes	Responsible for the masculine characteristics of the body, including hair growth on the face and body, and muscle development. Testosterone is essential for producing sperm and also strengthens bones.

Certain pituitary tumors can cause Cushing's syndrome, a disease in which too many hormones, called glucocorticoids, are released into the bloodstream. This causes fat to build up in the face, back, and chest, and the arms and legs to become thin. Other symptoms include too much sugar in the blood, weak muscles and bones, a flushed face, and high blood pressure. Other pituitary tumors can cause a condition called acromegaly, in which the hands, feet, and face are larger than normal; in very young people, the whole body may grow much

larger than normal. Another type of pituitary tumor can cause the breasts to make milk, even though a woman may not be pregnant or may be beyond her reproductive years. It can also occur in men. Empty sella syndrome (ESS) is a disorder that involves the sella turcica, a bony structure at the base of the brain that surrounds and protects the pituitary gland. Flattening or regression of the pituitary gland within the sella turcica cavity may result in symptoms such as the ceasing of menstrual periods, infertility, fatigue, and intolerance to stress and infection. In children, ESS may be associated with early onset of puberty, GH deficiency, pituitary tumors, or pituitary gland dysfunction.

If symptoms indicate a possible pituitary disorder, a doctor may order laboratory tests to see what the hormone levels are in the blood. The doctor may also order an MRI (magnetic resonance imaging) scan, which uses magnetic waves to make a picture of the inside of the brain. Other special x rays also may be done. The chance of recovery and choice of treatment depend on the type of tumor, and the patient's age and general state of health.

Pituitary Tumors

Every year thousands of new patients are diagnosed with pituitary tumors in the United States; most pituitary tumors are adenomas, and few pituitary tumors are fatal. However, the number of pituitary tumors diagnosed is much lower than their actual number. Most of these pituitary tumors are benign and, therefore, are not included in statistics collected by cancer registries. By examining people who have died or who have had routine imaging studies of their brain, doctors have found that 15 percent to 20 percent of people have pituitary adenomas. Almost all individuals with these tumors will not experience any symptoms or impairment of their health.

Although pituitary tumors are the most common, not everything that grows within the pituitary is a pituitary adenoma. Inflammation can occur from pregnancy, infections in a compromised host, injury following a head trauma, and a variety of cancers that affect the pituitary. Although pituitary tumors are supposed to be benign, the recent World Health Organization classification failed to classify pituitary tumors as neoplasms and described them as simply adenomas. For individuals who have been devastated by a variety of complications of pituitary adenomas, a cancer is defined only when there is evidence of metastasis from the original tumor site. This means that a pituitary adenoma would have to spread to other parts of the body, typically within the central nervous system, in order to be classified as a cancer; however, spread of this nature is rare.

Extremely small and often hormonally inactive pituitary tumors are called incidentalomas. Only investigation can determine that such tumors can be classified as small and not producing hormonal excess. Some incidentalomas may grow rapidly in size and function.

Every year thousands of new patients are diagnosed with pituitary tumors in the United States; most pituitary tumors are adenomas, and few pituitary tumors are fatal.

The patient whose macroadenoma is shown in Figure 4 died of a pulmonary embolism, as a complication of Cushing's syndrome that was not recognized early enough. The major challenge is to identify these adenomas at an early stage.

Most medical schools teach that pituitary tumors are unusual lesions that give rise to specific symptoms that are clearly either acromegaly or Cushing's syndrome. That characterization is no longer accurate. Results of a meta-analysis (Ezzat et al., 2004) showed that, across seven autopsy studies and five radiological studies with variable incidences of pituitary tumors, the overall estimated prevalence of pituitary tumors in the general population is almost 17 percent. Most of these patients have nonfunctional tumors. Prolactin-produc-

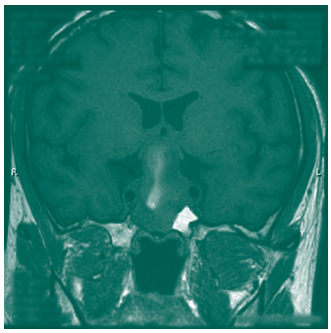


Figure 4. The patient whose macroadenoma is pictured died of a pulmonary embolism, as a complication of Cushing's syndrome that was not recognized early enough.

ing cells found in about one-fourth of the individuals in these studies suggest that functional tumors give rise to hormonal excess that may have subtle emotional, reproductive, and sexual impact. Most of these tumors are microadenomas, but a small percentage are macroadenomas; corroborated blood hormone values were available in one study, proving that hormones are being secreted and are creating a clinical effect. Even when these tumors are clinically nonfunctioning and do not secrete excess hormone, they give rise to pressure effects such as headache; they can press on the optic nerve giving rise to loss of peripheral vision, and they can compromise normal function of the gland with patients developing hypopituitarism.

Etiology of Pituitary Tumors

Scientists do not know exactly what causes most pituitary tumors. During the past few years, great progress has been made in understanding how certain changes in a person's DNA can cause cells in the pituitary to produce a tumor. About 3 percent of all pituitary tumors are caused by a condition that is inherited; these pituitary tumors usually occur in adults, and genetic testing of family members is available.

... pituitary disorders can progress for 10 or 15 years without diagnosis or appropriate treatment. It is critical that endocrinologists instruct other healthcare providers to make the clinical diagnosis of a pituitary disorder at an earlier stage.

Much less is known about the causes of nonhereditary pituitary tumors; although, recent studies indicate about 40 percent of growth hormone-secreting adenomas have an acquired mutation in a specific protein called Gs-alpha. Several other genetic abnormalities have been found in other types of pituitary adenomas, but it is not clear whether abnormal genes are essential for pituitary tumor formation. What is known is that there is a loss of the normal regulatory mechanism that keeps the glandular cells from overproducing their hormone and growing; this is likely the result of gene alterations.

Diagnosis of Pituitary Tumors

The first step in diagnosing a pituitary tumor is for the doctor to take a complete medical history to check for risk factors and symptoms. The doctor should know if anyone in the patient's family has had a pituitary gland tumor, hyperparathyroidism (overactive parathyroid gland), multiple kidney stones, multiple stomach ulcers, hypoglycemia (low blood sugar), or adrenal gland tumors, because these conditions raise the possibility that the patient may have inherited the gene for multiple endocrine neoplasia, type 1. A general physical exam and visual exam provide other information about signs of pituitary tumors and other health problems. Other diagnostic tools include biochemical testing, venous blood sampling, imaging tests, MRI scans, and examination of pituitary tissue specimens.

Central Importance of the Pituitary Gland in Normal Functioning and Disease

If untreated, pituitary complications can lead to reduced survival. Pituitary patients can suffer from tumors as well as other diseases. Functional abnormalities, such as nonneoplastic mass lesions, hypoplasia, cysts, and inflammatory lesions, can affect the pituitary and its function. A pituitary disorder can be merely an incidental finding, and some pathologists identify pituitary lesions on autopsy in the absence of any evidence that those lesions affected the living patient. More often, health complications arise from these disorders, affecting everything from mood and sexual function to metabolic disorders such as diabetes mellitus, osteoporosis and arthritis, and accelerated heart disease.

Metabolic disorders in adults can be subtle. Patients suffer from lethargy, cardiovascular dysfunction, water and electrolyte imbalance, emotional dysfunction, and reproductive and sexual dysfunctions. These complex and nonspecific findings may be difficult to associate with pituitary disease, and a definitive diagnosis may take many years during which time the patient does not receive appropriate treatment.

Detection of Pituitary Diseases

Advancements in Detection. Tremendous advancements have occurred in detecting pituitary tumors clinically, biochemically, and radiologically. The advent of MRI scans allowed radiological detection of even smaller tumors than computed tomography (CT) scans could

observe. During the last several decades, the ability to refine biochemical testing has improved, for detecting both decreased levels of circulating pituitary hormones and elevated levels of pituitary hormones in their targets, such as insulin-like growth factor 1 (IGF-1) and gonadal hormones. Despite these advances, pituitary disorders can progress for 10 or 15 years without diagnosis or appropriate treatment. It is critical that endocrinologists instruct other healthcare providers to make the clinical diagnosis of a pituitary disorder at an earlier stage.

Patient Presentation. The relatively asymptomatic state of pituitary disease and the constellation of nonspecific complaints are a major barrier to early diagnosis; often the diagnosis is delayed and the pituitary tumor remains asymptomatic for a prolonged period of time. Patients with pituitary disorders present to various medical specialties a wide variety of often nonspecific complaints. Some patients can even be asymptomatic, but once an endocrine disorder is suspected, patients are referred to endocrinologists.

Increased awareness is the most important first step in diagnosing pituitary tumors. Medical professionals who are knowledgeable about the pituitary are more likely to be able to put together the pieces of this puzzle when confronted with a constellation of clinical complaints.

Pituitary diseases may present differently to different specialists. A dermatologist might see a patient with oily diaphoretic skin, which, for an endocrinologist, would serve as proof of acromegaly, but may not be so recognized by a dermatologist. Similarly, many other medical specialists will see pituitary patients because of specific complaints related to their disease, complaints that hint at the full medical picture. Infertility, menstrual irregularities, and galactorrhea are the presenting symptoms to a gynecologist or an obstetrics specialist. Urologists may see hypogonadism, impotence, or low testosterone levels. Carpel tunnel syndrome or headaches may be the presenting symptoms in patients with as-yet-undiagnosed acromegaly who seek out a neurologist. Proximal muscle weakness may be the presentation of Cushing's syndrome. The pituitary tumor may put pressure on the optic chiasm, resulting in visual field defects, diplopia, and blurred vision, all of which would be presented to an ophthalmologist. Enlarging feet size and bone abnormalities may be the complaints presented to a podiatrist. The primary care physician sees patients with all of these complaints and might also see patients with pituitary disease who suffer from depression, fatigue, and polyuria. In most cases, all of the above-mentioned medical professionals do not initially consider a diagnosis of a pituitary tumor, but after some time and for a variety of reasons, these patients eventually receive a workup from a healthcare professional who makes the diagnosis of a pituitary tumor.

Diagnosis. Increased awareness is the most important first step in diagnosing pituitary tumors. Medical professionals who are knowledgeable about the pituitary are more likely to be able to put together the pieces of this puzzle when confronted with a constellation of clinical complaints. Once patients become or are made aware of the possibility of pituitary disease, and therefore seek the advice of an endocrinologist, the endocrinologist examines blood and urinary hormone levels and conducts MRI scans to document the presence of an abnormality in the brain.

Tumor Classification. Pathologists classify tumors based on their clinical function or clinical silence, and then, based on the type of cell in the pathology specimen, different tumor types are identified based on transcription factors, hormone production, and the architecture that holds the cells together. Pathologists can measure hormones from the target organ in order to accurately diagnose the abnormality, and they can localize transcription factors in hormones to prove that the patient's pituitary tumor is the reason for the clinical presentation. Tests such as electromicroscopy, immunohistochemistry, and molecular analyses can show specific parts of tumors that are responsible for hormone production.

Current Treatment Options

Treating pituitary tumors depends on the type of tumor and how far it has invaded into the brain, as well as the patient's age and overall health. Three kinds of treatment

are used: surgery to remove the tumor, radiation therapy using high-dose x rays or proton beams to kill tumor cells, and drug therapy to shrink and sometimes eradicate the tumor. Drugs can also block the pituitary gland from making too much hormone.

Surgery remains the mainstay of treating pituitary tumors, and new methods are continually being identified. In the past, surgical procedures for patients with pituitary tumors were limited to invasive brain surgery. Today, many patients are being treated using advances in surgical therapy that have improved patient outcome. Two different approaches to tumor removal are a transsphenadal operation, in which the tumor is removed through a cut in the nasal passage or upper lip, leaving no external scar, and a craniotomy, in which the tumor is removed through a cut in the skull.

Dopamine agonists are widely used for medical management of prolactinomas. Octreotide has become a mainstay of medical therapy after surgical failure for acromegaly; for patients with unique tumors that fail to respond to octreotide, new drugs are in development. For pituitary-related depression, new treatments being explored include corticotropin-releasing hormone (CRH) and other peptide antagonists, anticonvulsants, neurotropic agents, serotonin transporter agents, and nerve growth factors.

To summarize, normalizing measurable symptoms will restore most people with pituitary disorders to a normal quality and length of life.

Neuroendocrine Effects of Pituitary Disorders on Psychological State and Psychosocial Interactions

Growth factors are made in the pituitary gland by pituitary cells and also from sources around and outside of the pituitary. Multiple mechanisms give rise to a tumor: Mutations can result in abnormal cell clones that will be stimulated to grow; a pathway can exist where growth factors and hormonal stimulation are the primary problem; and other events can occur within hyperplastic cells to give rise to expansion and tumor formation.

Children and Adolescents. Growth and development are affected in children with pituitary disorders. The effects of hormones on growth include the following:

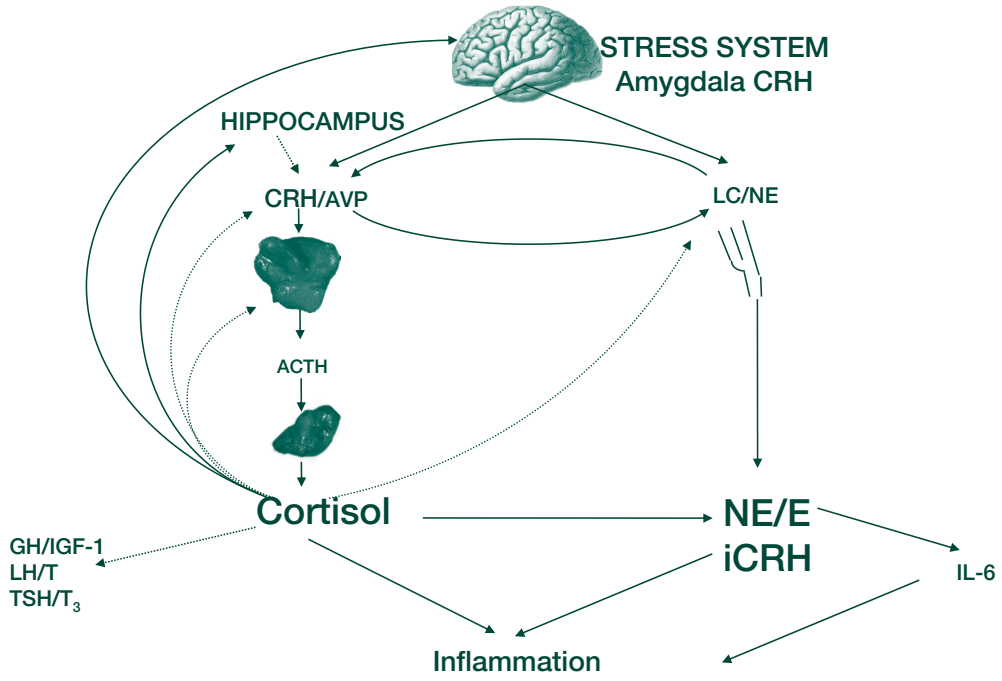
- **Stature:** children may stop growing or may overgrow.
- **Body composition:** children may lose muscle and may gain abnormal fat that could affect the rest of their lives.
- **Puberty:** children could experience puberty too early or too late.
- **Attentional problems and psychopathology:** children and adolescents may suffer the concurrent effects of attentional problems or psychopathology, both of which may be associated with later adult pathology.

Pituitary disorders in adolescents are particularly difficult to diagnose properly. All the psychological and emotional problems of being a "normal" adolescent appear—growth and development, societal pressure, drug-related issues, and peer pressures all impinge on the pituitary system. For adolescents, it is critical to sort out those issues that are endocrine-based and for which medical intervention can be successful, while also attending to all the other "normal" adolescent issues.

Depression. Depression is a systemic disorder. Pituitary dysregulation helps to sustain and perpetuate major depression and the hormonal abnormalities that are part of its overall pathophysiology. Stress precipitates depression and influences its incidence, course, and severity. The stress response and some forms of depression share phenomena, mediators, and circuitries. Each can be associated with fear, mood, and cognition, as well as alterations in arousal, autonomic function, and neuroendocrine regulation.

The stress response increases the anticipation of harm and fear-related behaviors and the shift to well-rehearsed automatic programs. The stress response leads to breakdown of muscle, bone, and other tissues for fuel; long-term effects related to loss of muscle and increased fat tissue (no change in weight but change in body composition); loss of bone and long-term osteoporosis; priming of the immune system to anticipate possible injury, which is an inflammatory state; priming of the coagulation system as a defense against blood loss; and increased heart rate and blood pressure, resulting in hypertension and cardiac disease.

Figure 5. HPA Axis Stress Response



As seen in Figure 5, the pituitary plays a central role in the regulation of the stress response. The hypothalamic pituitary-adrenal (HPA) axis, shown on the left, together with the autonomic system, shown on the right, are activated during stress to protect against the cause of stress. Thus, when an individual is stressed, the pituitary is stimulated by the releasing factors CRH and AVP to produce ACTH, which in turn stimulates the adrenals to produce cortisol. In parallel, the autonomic system is activated to produce the catecholamines, Norepinephrine (NE) and Epinephrine (E), two other key stress hormones. Figure 5 shows how the HPA axis and autonomic system interact with each other; how the growth and thyroid axes are suppressed by the HPA axis; and how cortisol, the catecholamines, and CRH influence inflammation. The amygdala is the fear-generating system in the brain and locus coeruleus (LC) is the arousal system. IL-6 is the inflammatory cytokine interleukin-6.

Reproduction, growth, thyroid function, and immune function are all distressed in the presence of major depression. Emerging data indicate that young children with obsessive-compulsive disorder and depression are shorter, starting relatively early in life; although this result needs to be replicated, it points to the possibility of alterations in pituitary function as a consequence of depression.

Melancholic depression is a state of pathological hyperarousal. The pituitary is involved in all of the characteristics of melancholic depression. Patients with melancholia are very anxious, especially about themselves, and they feel worthless and dread the future. There is a loss of cognitive flexibility in patients with major depression—they have difficulty concentrating and formulating complex plans—and they exhibit decreased sleeping, decreased food intake, decreased sexual activity, and diversion of energy away from growth and reproduction. Thirty percent of the major depressions are melancholic and are characterized by this pathological hyperarousal, but 20 percent to 25 percent of the major depressions are atypical. Patients with atypical depression are characterized by profound lethargy and fatigue; they feel much less alive than usual; they have increased appetite; and they sleep more. Emotional memory is influenced by pituitary adrenal activity, and serious, life-altering disorders are often associated with pituitary dysregulation.

Stress hormones profoundly increase the strength of the negatively charged emotional memory trace. This represents a mechanism by which the unconscious memory of a previous life-threatening situation can provide reflexive responses to promote survival. Mel-

ancholic depression seems like a continuous state of negative emotional memory recall without access to the contextual content. Atypical depression may be a loss of contact with emotional memory and, hence, a loss of connection to one's self and one's past, which at times, can feel like a terrible state of emptiness. Both forms of depression are characterized by a loss of the capacity to experience pleasure.

Another message common to all three was the need for health practitioners to recognize and help them and their families cope with the psychosocial aspects of pituitary disorders.

Major depression doubles the risk of mortality in patients of any age, independent of smoking and other risk factors for poor health; doubles in the incidence of premature coronary artery disease, also independent of smoking; and more than doubles the risk for premature osteoporosis. These phenomena are reasons for diagnosing and treating depression or any hormonal disorder at the earliest possible stage.

Patient Perspectives on Pituitary Disorders

The previous sections summarize the scientific discussions at the symposium; however, an important part of the story comes from the patients themselves. A woman with Cushing's syndrome, a man with a pituitary tumor, and a man with acromegaly provided examples of the devastating consequences they faced during the process of detecting, diagnosing, and ultimately finding treatment for their pituitary disorders. With early diagnosis, expert care, and the support of multiple medical specialists, these three individuals give hope to the millions of people who suffer from pituitary disorders that they can regain control of their lives.

All three patients experienced a significant delay in diagnosis, an average of 9 years. Consequently, they urge all health practitioners to check symptoms that could indicate an endocrine disorder in order to make a timely diagnosis. All three also emphasized the need for health practitioners to recognize and help them and their families cope with the complex psychosocial aspects of pituitary disorders.

The following are excerpts from testimonials from patients who provided personal insights into their struggles with pituitary disorders.

Sharmyn McGraw

Cushing's Syndrome

My story about Cushing's is not much different than that of most people trying to get a diagnosis for this horribly misunderstood disease.

I sought help from more than 15 highly recommended physicians, and, with each new doctor, I showed photographs of myself, hoping that the drastic physical changes would convince them that there was something medically wrong with me. Some were very sympathetic, but most of them just offered prescription drugs and were convinced I was a compulsive overeater with a mental disorder. Some labeled me a hypochondriac and others labeled me prediabetic or premenopausal. They told me I had fibromyalgia, a spastic colon, acid reflux, and a sleep disorder. I had many painful and expensive medical tests, including two upper endoscopies, a horrible colonoscopy, a bone marrow biopsy, multiple CT scans and ultrasounds, and the removal of my thyroid.

I borrowed a friend's computer and looked up "cortisol," and there on the computer screen was Cushing's syndrome, a hormone disorder caused by prolonged exposure of the body's tissue to high levels of the hormone cortisol. I carefully read the rest of the article, and that is when I realized I had actually diagnosed myself with Cushing's.

In most cases, pituitary disease can be treated either medically or surgically if a timely diagnosis is made. Oftentimes, quality of life is much improved once proper medical treatment has been started. Unfortunately, most people affected by this debilitating disease go far too long before finding the source of the problem, becoming permanently disabled. The psychological aspects of Cushing's, or any pituitary disorder, is devastating. Many patients are treated medically for many years as having a mental disorder, whereas, in reality, they have a hormonal imbalance caused by a treatable pituitary tumor.

Diagnosing Cushing's requires more than looking at the patient; running appropriate tests is the only way to get a correct diagnosis. High levels of cortisol cause a horrible psychological imbalance and significantly impact the quality of life. Healthcare providers should remember that a patient's laundry list of symptoms could very well be caused by a treatable pituitary tumor.

Bram Levy

Prolactinoma

I was very fortunate at the age of 19 to have a doctor who said, "Let's look at the pieces, and we'll start to put things together. You were growth-hormone deficient as a child, and you have headaches. We need to take a CT scan to rule out the possibility of a pituitary tumor." Had it not been for that doctor, I would be somewhere else today, with more severe headaches and facing the possibility of long-term infertility and all the other side effects that come with having a pituitary tumor. It took one doctor who happened to know that certain pieces of a puzzle fit together, and who knew to give me a CT scan. He found that I have a very large—about 2½ to 3 centimeter—prolactinoma. My prolactin level was around 2,000; normal is less than 20.

That was the scariest day of my life. I was told I had a tumor in my brain. I would not say I was happy, but there was a sense of relief. I now knew that I looked young for a reason, and I knew there was some reason for having those headaches. I was glad that I was going to begin some form of treatment. That is how I was diagnosed.

The most important part that my family and I played was that we were our own advocates. If we had listened to what each doctor told us to do, we would have gone straight ahead with one doctor or two doctors and done exactly what they told us. But we took the time to find out exactly what our treatment options were, and we got as many opinions as we possibly could and found out what the best course of action was for my case; not what was best for a prolactin case or for a child who has prolactinoma, but what was best for me, Bram Levy.

I do not consider myself cured, as I do not think it is possible to have a pituitary tumor and ever be cured. I do consider myself managed, and that is about the best I can hope for. I will continue to be monitored for the rest of my life, and I will continue to take most of the medications for the rest of my life. I take adult growth hormone now, which helps with body composition, and I am happy with the results so far.

Robert Knutzen

Acromegaly

Acromegalics have an insidious and often well-hidden series of severe complications that are still far beyond most physicians' abilities to diagnose, predict, or understand—and therefore beyond their ability to fully treat.

I was born with large hands, which my mother unsuccessfully tried to hide under the blanket so that her first born would not be thought of as being deformed. I had constant migraine headaches, but no one looked for an underlying cause. I had a series of remarkable, at least to me, sexual problems: I almost lost a testicle in my late 30s and premature ejaculation was the norm.

An ugly, hot temper followed me most of my life. I was aggressive and verbally abusive, and often terrified my own family for reasons that were rational to me but in retrospect clearly unacceptable to others. Today, we know this as acromegalic rage.

Neurosurgeons and endocrinologists distanced themselves from me because they did not understand that who and what I had become was as a result of my illness, not a result of willful misbehavior. My prostate grew, my cholesterol level increased, and my blood pressure shot up, but all of these problems have been controlled with medications. I now have a support system of family, friends, physicians, and surgeons who guide me and advise me along the way.

Far too few patients are diagnosed in a timely fashion. Far too few are treated by experts for the myriad medical problems that often befall a pituitary patient. Far too few understand that pituitary disorders, acromegaly among them, first attack our mental and emotional well-being, then our sexual well-being, then our internal organs—long before we are recognizable as patients. Medical schools must teach that only by listening to a patient's stories can an accurate and thorough workup be ordered that will diagnose that patient. A Cushing's patient or an acromegalic patient cannot be diagnosed merely by looking at them, except in the late stages of their disease.

Moving Forward

Increased awareness of pituitary disease should result in early diagnosis and treatment before its multiple complications are beyond repair. Unfortunately, this is not always the case. Although it is critical that advances continue to be made in identifying the causes of pituitary tumors and devising improved and specific targeted treatments with fewer complications, the experts at the meeting pointed to the need to facilitate research that focuses on the psychosocial consequences of pituitary disorders for the patient and his or her family in order to educate and involve more medical specialties in understanding pituitary disorders and treating the whole patient. This knowledge will be helpful in managing the psychological complications of patients with endocrine disorders, as well as in identifying endocrine manifestations among patients with diagnosed psychological disorders.

Although advances are encouraged and will continue to be made in identifying the etiology of and perfecting treatments for pituitary disorders, the experts at the workshop identified the following as significant research needs for the future:

- To develop and teach screening methods for earlier diagnosis of pituitary disorders before their multiple complications are beyond repair.
- To explore the psychosocial consequences of pituitary disorders in the patient and his or her family.
- To determine the nature of pituitary dysfunctions associated with psychiatric disorders.

Additional Information

More information about pituitary disorders can be found on the following Web sites:

- The Office of Research on Women's Health (ORWH) stimulates and coordinates trans-NIH research efforts that focus on sex and gender differences in disorders that primarily affect or have implications for women's health. Visit http://orwh.od.nih.gov.
- The National Institute of Neurological Disorders and Stroke (NINDS) is the primary NIH Institute for research on pituitary disorders. Visit www.ninds.nih.gov.
- Other NIH Institutes conducting research on or related to pituitary disorders include the National Institute of Child Health and Human Development (NICHD) at www.nichd.nih.gov, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at www.niddk.nih.gov and the National Institute of Mental Health (NIMH) at www.nimh.nih.gov.
- The Pituitary Network Association is an international nonprofit organization for patients with pituitary tumors and disorders, their families, and the physicians and healthcare providers who treat them. Visit www.pituitary.org.

Reference

Ezzat, S., Asa, S. L., Couldwell, W. T., Barr, C. E., Dodge, W. E., Vance, M. L., et al. (2004, August 1). The prevalence of pituitary adenomas: A systematic review. *Cancer, 101*(3):613–619.

Presentations

This document is not a typical meeting summary, but is based on what happened at the meeting. All content was derived from the following presentations:

Introduction and Opening Remarks
Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health, National Institutes of Health

Family Hormonal Health: The Broader Picture
Yvonne T. Maddox, Ph.D.
Deputy Director, National Institute of Child Health and Human Development, National Institutes of Health

Hormonal Disease Is No Apparent Impediment to Good Health
Captain Mohamed K. Shakir, M.D., FACP, FRCP
Director, Department of Endocrinology, National Naval Medical Center, Professor of Medicine, Uniformed Services University of the Health Sciences

Session I
Session Chair: Ian McCutcheon, M.D.
Professor of Neurosurgery, University of Texas, M.D. Anderson Cancer Center

The Pituitary Gland in Health and Disease
Sylvia Asa, M.D., Ph.D.
Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto
Pathologist-in-Chief, University Health Network and Toronto Medical Laboratories

Impact of Hormonal Disorders in Childhood
George P. Chrousos, M.D.
Chief, Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health

The Transition Years: Neither Child Nor Adult
Alan Rogol, M.D., Ph.D.
Professor of Pediatrics, University of Virginia

The Endocrinology of the Stress Response and Its Relevance to Depression, Anxiety, and Other States
Philip W. Gold, M.D.
Chief, Clinical Neuroendocrinology Branch, National Institute of Mental Health, National Institutes of Health

Three Personal Perspectives on Living with Hormonal Disorders
Sharmyn McGraw, Bram Levy, and Robert Knutzen

Session II
Session Chair: Edward Oldfield, M.D.
Chief, Surgical Neurology Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health

The Young Male: What Are His Options and Choices?
Marc R. Blackman, M.D.
Chief, Endocrinology, National Center for Complimentary and Alternative Medicine, National Institutes of Health

A Young Woman's Hormonal World
James Segars, M.D.
Staff Clinician, National Institute of Child Health and Human Development, National Institutes of Health

Hormonal Needs and Disorders in the Mature Female
Jennifer Larsen, M.D.
Professor and Section Chief of Diabetes, Endocrinology and Metabolism, University of Nebraska Medical Center

Surgical Treatment of Pituitary Disorders

Edward Laws, M.D., FACS
Professor of Neurosurgery and Medicine,
University of Virginia

Difficult Pituitary Problems: Options and Solution

Ian McCutcheon, M.D.
Professor of Neurosurgery, University of Texas,
M. D. Anderson Cancer Center

Panel Discussion: What Do We Know, Where Do We Go from Here, and What Is the Future Role of Research?

Drs. McCutcheon, Asa, Chrousos, Rogol, Laws, Oldfield, and Larsen
***Moderator*: Shereen Ezzat, M.D.**
Professor of Medicine and Oncology
Head, Endocrine Oncology, University of Toronto

A videocast of the symposium is available at:
http://orwh.od.nih.gov/news/pastmeetings.html.

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