The Value of Endocrine Research

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The Endocrine Society®

Introduction.

Endocrinology is the study of hormones and how they regulate critical bodily functions such as metabolism, reproduction, blood pressure, bone growth, and weight. Endocrinologists study endocrine diseases and work toward developing treatments for a wide range of conditions, including diabetes, obesity, thyroid disorders, reproductive disorders, osteoporosis, breast cancer and prostate cancer. Endocrine research is vital to public health, as endocrine diseases result in substantial morbidity and mortality. Endocrinologists are continually working to understand the origins of endocrine-related diseases, including the effects of environmental exposures to chemicals that disrupt endocrine systems. As our comprehension of this important issue continues to develop, it will garner significant additional insight into the conditions discussed here. Ultimately, increased understanding of these complex issues will unveil new methods for prevention and therapeutics, providing improvements in health and significant future cost-savings in healthcare.

The Value of Endocrine Research

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Endocrinology—the study of **hormones** (chemicals released by cells that send messages to other parts of the body)—is critical for understanding many diseases and biological processes. Here are just a few examples of how endocrine research has led to the development of new treatments and a better understanding of diseases affecting millions of Americans today.

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Benefits of Past Endocrine Research

Diabetes

- New discoveries have led to treatments that help the body combat insulin resistance and reduce the chances of developing diabetes.
- A diverse array of medications allows doctors and patients to choose from a variety of treatment plans to find one best suited to the patient.

Obesity

- Obesity research has led to important discoveries regarding the consequences of excess fat tissue.

Thyroid Disease

- Better tools have been developed for the diagnosis, treatment, and monitoring of thyroid disease.
- An improved understanding of thyroid hormone therapy has made it easier to achieve stable dosing.

Osteoporosis

- The development of new drug treatments has increased the number of options available to osteoporosis patients.

Breast Cancer

- Detection has improved, resulting in earlier diagnosis.
- Thanks to improved treatments, breast cancer patients' lives have been prolonged and the number of deaths caused by breast cancer has decreased.

Assisted Reproduction

- Advancements in *In Vitro* Fertilization technology have made pregnancy possible for many couples otherwise unable to bear children.

Prostate Cancer

- Significant gains have been made in the understanding of how hormones promote prostate cancer growth.

Potential Future Benefits with Continued Support

Diabetes

- Continued advances will allow doctors to better manage diabetes symptoms.
- Scientists are continually working to discover genetic risk factors for diabetes, which will enable earlier intervention or prevention of disease.

Obesity

- Additional research will reveal the effects of excess body fat and the role of fat as an endocrine organ.
- Advances in obesity research will increase knowledge of the developmental effects of exposure to high and low fat diets.

Thyroid disease

- Better treatment options will be developed for patients based on an improved understanding of genetic susceptibility.
- Early detection efforts will greatly benefit populations with undiagnosed thyroid dysfunction.

Osteoporosis

- Further research will facilitate the development of new treatment options and help identify ways to optimize currently available therapies.

Breast Cancer

- Researchers will work to develop treatments for tumors that fail to respond to current therapies.
- Economic savings will be realized as tumors are identified at earlier stages and patients are able to be treated sooner.

Assisted Reproduction

- Further advancements will allow for increased success rates for all women seeking reproductive therapy, including women undergoing chemo-therapy or other fertility-disrupting treatments.

Prostate Cancer

- Further research will facilitate the development of new therapeutic strategies to block the development of prostate cancer.

Diabetes Treatments

Hormones & Blood Sugar Control

Diabetes Facts

Diabetes, now recognized as a major public health crisis, comes in two forms: type 1 and type 2.

- Type 1
  - The cells in the pancreas that make insulin are destroyed by the immune system.
  - Insulin is life-sustaining.
- Type 2
  - The body becomes insensitive to the normal effects of insulin.
  - Associated with obesity and much more common than type 1.
- 25.8 million Americans (nearly 8.3% of the population) have diabetes.
  - Of that number, 7 million Americans are estimated to have diabetes but are undiagnosed.
- Among U.S. residents aged 65 and older, 10.9 million or 26.9% had diabetes in 2010.
- An estimated 79 million Americans have pre-diabetes.
- Diabetes is the leading cause of blindness, kidney failure, and non-traumatic limb amputations, and is the seventh leading cause of death in the United States.
- The primary cause of premature death in diabetes patients is cardiovascular disease.
- In 2007, total costs attributable to diabetes for Americans was estimated at $174 billion—an increase of 32% since 2002.
- The NIH spent more than $1.1 billion on diabetes research in fiscal year 2009.

Efforts to identify compounds that help to maintain appropriate blood glucose levels are critical in the development of tools to treat both type 1 and type 2 diabetes. As the incidence of type 2 is rapidly increasing in the U.S., particularly among children, it is imperative that methods are developed for managing the disease over the course of the patient's lifetime.

The Discovery

Insulin and Beyond

The discovery of insulin by endocrine researchers in 1921 was one of the most important advances in medicine. This discovery was translated rapidly into clinical practice to treat diabetes. The clinical use of insulin transformed type I diabetes from a rapidly fatal disease in children and young adults to a chronic disease that must be managed over the course of the patient's lifetime. The rapid translation of basic science discoveries into clinical therapies such as this is the goal of all biomedical research.

More recent research has led to increased understanding of the mechanisms underlying the body's loss of sensitivity to insulin (commonly called insulin resistance) in type 2 diabetes and the development of new treatments for these individuals. For example, there is evidence to suggest that exercise and weight reduction both decrease insulin resistance. In fact, numerous studies including a landmark study funded by the NIH (the Diabetes Prevention Program),

have shown that these two interventions increase sensitivity to insulin and reduce the development of diabetes in people with pre-diabetes. The prevention of diabetes improves the quality and length of life, but while reducing healthcare costs substantially. In addition, researchers have discovered new medications that improve blood sugar control and reduce the incidence of diabetes and its complications.

In 1993, the landmark Diabetes Control and Complications Trial, funded by the NIH, proved that intensive control of blood sugar levels, or glycemic control, in people with type 1 diabetes decreases diabetes complications. Similar results have since been reported in type 2 diabetes. Unfortunately, at the time of these studies, the tools to achieve glycemic control were quite limited. U.S. physicians could only prescribe medications that made the pancreas work harder, or give insulin by injection to replace what was lost in the diseased pancreas. The number of tools available to combat diabetes has increased considerably in the last two decades due directly to advances in biomedical research.

The first of these new tools was metformin, approved by the Food and Drug Administration in 1994. Since that time, many more medications have been developed and approved for use in diabetes treatment. Recently, research has revealed that the hormones produced by the gut improve glucose control. NIH-sponsored research identified this new class of "incretin" hormones, known as glucagon-like peptide-1 (GLP-1) and glucagon inhibitory peptide. When an investigator funded by the Department of Veterans Affairs identified a form of GLP-1 in Gila monsters, a type of lizard, investigators conducted clinical trials to bring this new medication to market for people with diabetes. Research that led to the discovery of this treatment has also resulted in another new class of diabetes medications called dipeptidyl peptidase Type IV (DPP-IV) inhibitors.

In fact, the investment in basic and clinical research has led to 12 different classes of medications that can be used to treat diabetes. Because of basic science research, clinical researchers are now able to answer more sophisticated and vital questions regarding the best regimens to treat diabetes and the optimal treatment targets. In the past few years, landmark clinical trials funded by the NIH, ACCORD and BARI-2D, have focused on the best ways to treat diabetes and reduce associated death and complications. These trials would not have been possible without the research of endocrinologists, who helped develop many of the medications used in the trials and now used in the clinic.

The New Treatments

Why do we need new treatments when we have more options than ever before to treat diabetes? It is clear that diabetes is a very heterogeneous condition, so new treatment alternatives that treat the underlying cause of diabetes in individuals are needed. All medications have side effects and may not work equally in every patient who uses them. A diverse array of medications allows physicians and patients to work together to pick the best option for the individual. If the medication does not work as well as expected or has unacceptable side effects, a different medication can be used. Safety is another concern when producing new medications for patients with diabetes. As some of the results of prior landmark trials become available, it is clear that continued research is needed to produce medications that work effectively, but also safely in patients.

Well Worth the Investment

New diabetes medications would not have been developed without federally-supported basic and clinical research. The collaborative research effort of basic and clinical scientists eventually led to the approval of new classes of medications for diabetes, the first new treatments for diabetes in the past 80 years.

Basic science research

- Frequently guided by the observations of clinical research scientists
- Identified biological pathways of insulin resistance and impaired metabolism
- Developed medications to target key pathways
- Working to discover common genetic risk factors for disease

Clinical research

- Provided information and feedback to basic scientists
- Tested rationally-developed medications in humans

Without the continued support of both basic and clinical research in diabetes, these medications would have never been developed. Now, with this broadened portfolio of treatments, it is possible to help most people with diabetes achieve optimal blood sugar control.

These advances have taken diabetes from a rapidly fatal disease to a chronic disease. Eventually diabetes will be a chronic disease that does not rob Americans of their length or quality of life. We are closer to this goal than ever before.

Work Left to Do

The primary goals of medical research are to provide the tools and guidance to prevent and treat disease, and to reduce patient suffering. Continued federal support for research in diabetes is essential to attain these goals.

Obesity Research

Obesity Facts

Fat tissue stores excess energy in the form of triglycerides. If energy intake exceeds energy expenditure, we store surplus calories as fat. We define obesity as an excessive amount of fat tissue, known as adipose tissue. Genetic, environmental and behavioral factors determine whether or not someone becomes obese due to long periods of excessive caloric intake. Body Mass Index (BMI), a measure of weight compared to height, can be used to indicate whether a person is overweight or obese.

- Over two-thirds of U.S. adults are overweight or obese, defined as a BMI greater than 25.
- Over one-third of U.S. adults are obese, defined as a BMI greater than 30.
- One in twenty U.S. adults is morbidly obese, defined as a BMI greater than 40.
- The prevalence of overweight and obesity has steadily increased for both genders, all ages, and all racial/ethnic groups, and has almost tripled over the past 50 years.
- Individuals who are obese have a significantly increased risk of death from all causes, as well as cardiovascular disease, diabetes and cancer. The increased prevalence of obesity drives a widespread increase in the complications associated with obesity and is a major reason for the increasing occurrence of both type 2 diabetes and cardiovascular disease in the general population.
- Obesity in the United States causes direct medical costs of $147 billion per year, just over nine percent of all medical spending.

Research during the past 20 years has greatly improved our understanding of the role of adipose tissue beyond a mere storage compartment for fat. It fulfills an important role as an endocrine gland, and strongly contributes to the production of protein and lipid factors that lead to complications associated with obesity.

The Discovery

Adipose Tissue as an Endocrine Organ

The fat cell, or adipocyte, is a unique cell type in many respects. It stores excess energy in the form of lipids (fats). As a result, it can dramatically change its size as a function of the body's energy needs. The ability to dramatically grow (and shrink, if need be) makes adipose tissue unique, as it is one of the only tissues in the body with this capacity other than cancer cells.

The adipocyte is also able to secrete a number of hormones. These hormones, termed "adipokines," have been shown to have a variety of effects on the brain. The discovery of two adipokines, leptin and adiponectin, in the mid-1990s set the groundwork for a better understanding of how adipose tissue communicates with other organs throughout the body, including the brain, the heart, skeletal muscle, the liver, and the insulin-producing cells of the pancreas.

Leptin, which is produced in proportion to the amount of fat tissue in the body, suppresses food intake and increases energy expenditure. In a lean state, leptin suppresses appetite and signals to the brain that the body has had enough to eat. However, as we progress from a lean to an obese state, the increased adipose tissue produces more leptin, which causes inflammatory blood cells to move into adipose tissue. This, in turn, further alters the pattern of adipokine secretion from adipocytes. Once in excess, leptin would be expected to reduce further food intake and increase energy expenditure. However, systems that control feeding in lean individuals do not work normally in obese individuals, and there is strong evidence that the leptin control system breaks down in the obese state and fails to induce appetite suppression and energy expenditure.

Interest is re-emerging in the role of brown fat in energy expenditure in humans. Brown adipocytes are packed full with energy-producing mitochondria, and the major role of brown adipocytes is the generation of heat. While the prevailing view for many years was that these cells are only found in newborns, it is now clear that even as adults, we use brown adipocytes when exposed to cold, thereby effectively burning excess calories and dissipating the energy through heat. As we gain weight, this process becomes increasingly impaired. The potential to induce brown adipocyte formation with drugs bears great promise from a therapeutic perspective, since this would allow us to expend more energy and, as a result, reduce our fat mass and lose weight.

The Treatments

Still a Long Way to Go

Despite many efforts in the field, there is no drug treatment directed against obesity that is deemed safe and effective. The most efficient approach remains lifestyle changes that include a reduction in caloric intake and an increase in physical exercise. The standards for drug therapy for obesity have been set very high by health authorities, mostly due to the fact that patients will have to be exposed to these treatments for prolonged periods of time.

Treatments targeted towards an improvement of adipose tissue health will reduce inflammation and the associated health risks (insulin resistance, type 2 diabetes, and cardiovascular disease), but also carry the inherent danger that they may promote the growth of tumors as they alter the body's natural defenses against tumor growth. Interventions targeted at signals from the brain that control either food intake or energy expenditure have also proven problematic. Central circuits controlling food intake are closely linked with other circuits in the brain, and interference can cause depression in some individuals.

To date, the most effective interventional approach to combat extreme obesity has proven to be bariatric surgery. The Roux-en-Y gastric bypass procedure causes drastic weight loss. Independent of the weight loss, striking improvements in insulin sensitivity—the body's ability to use insulin properly—have been observed. This may relate to changes induced by altered food absorption, altered secretion of gut hormones involved in digestion and nutrient absorption, or other causes that remain to be defined.

Well Worth the Investment

Recent research advances have led to great progress in our understanding of the molecular changes associated with obesity.

Basic science research

- Increased the understanding of the specific brain cells that play an important role in governing the effects of leptin on food intake and energy expenditure.
- Elucidated how adipocyte-derived hormones exert protective effects against high fat diets by controlling appetite and energy expenditure.
- Defined the initial steps that lead to adipose tissue dysfunction, including a lack of oxygen in the cells' microenvironment and other factors that lead to inflammation.
- Increased the understanding of how local adipose tissue inflammation leads to a reduction in insulin sensitivity.

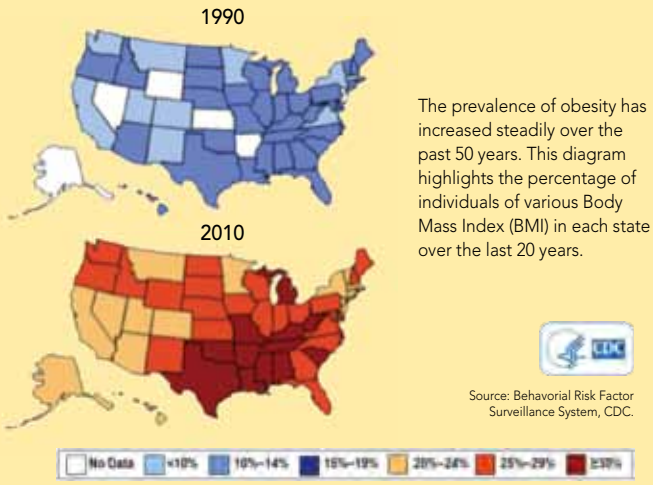
Clinical research studies

- Highlighted the relevance of brown adipose tissue to overall energy balance in humans.
- Have taught us about the longevity of our fat cells and the limited ability to expand our fat cell numbers at later stages of life.
- Have generated insights into how bariatric surgery causes changes at multiple levels resulting in improved insulin sensitivity.
- Identified genetic mutations as a cause of obesity in humans.

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 2010

(*BMI ≥ 30, or about 30 lbs. overweight for 5'4" person)



The prevalence of obesity has increased steadily over the past 50 years. This diagram highlights the percentage of individuals of various Body Mass Index (BMI) in each state over the last 20 years.

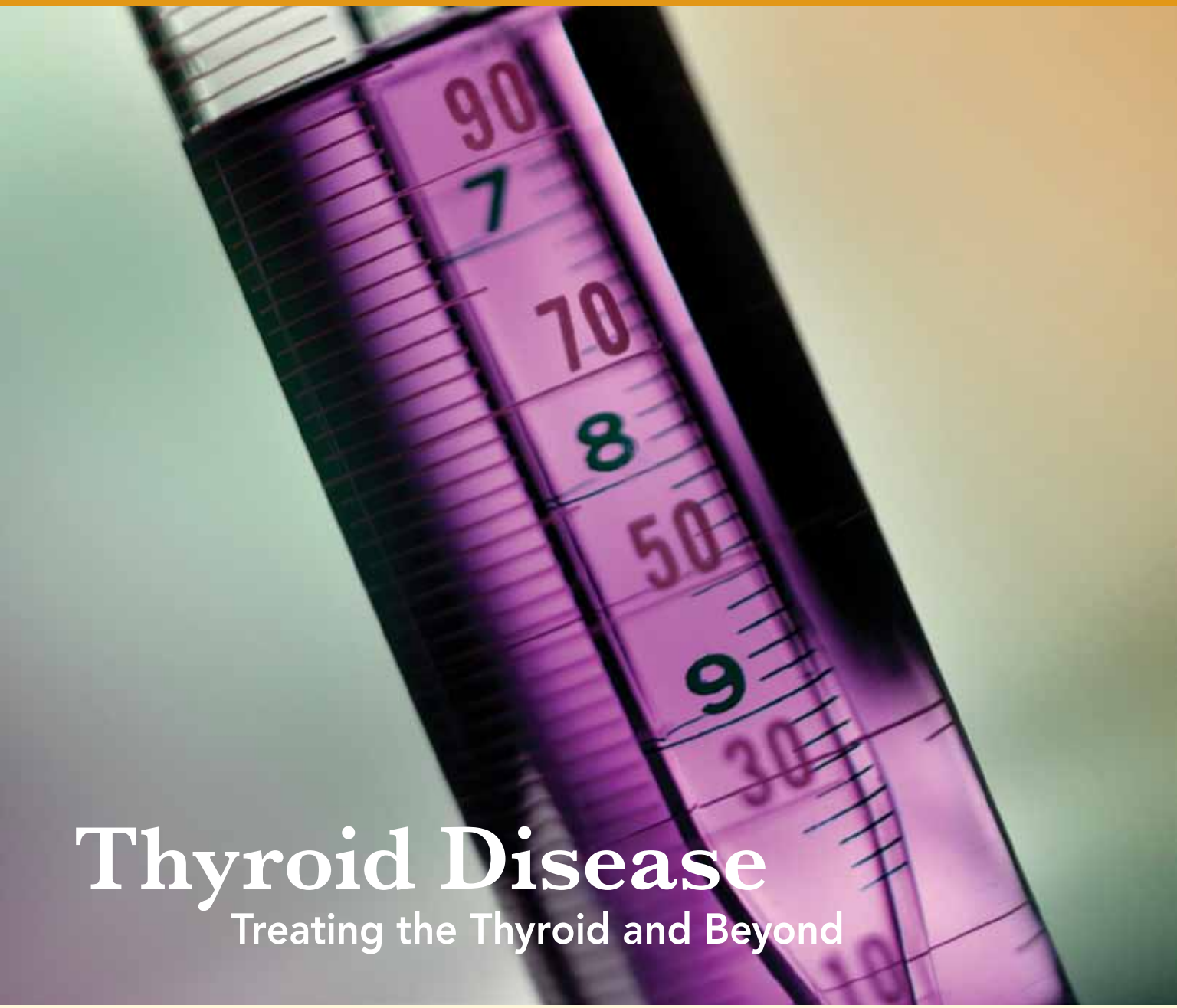
Source: Behavorial Risk Factor Surveillance System, CDC.

Work Left to Do

Given our limited potential to effectively counteract the increased accumulation of lipids in an obese state, we clearly still have a long way to go to learn how to effectively manage the negative consequences of excess caloric intake. It is clear that we need a "healthy" amount of adipose tissue, since patients who lack adipose tissue can become severely resistant to insulin. Some questions that need to be answered are:

- How can we improve the performance of our fat cells so they continue to work properly even as they expand?
- What can we do to avoid the lack of proper oxygen supply to adipose tissue, the root of many secondary consequences, such as inflammation?
- Which factors play a critical role in the communication between adipocytes and the immune system?
- What other, as yet unidentified genes might predispose us to obesity?
- The developing fetus is very susceptible to nutritional extremes. What are the developmental effects of either too little or too much nutrient availability in the womb, and how do these early prenatal exposures translate into an increased susceptibility to obesity and type 2 diabetes later in life?
- What are the critical changes associated with obesity that are responsible for the associated susceptibility to cancer?

Given the tremendous suffering and costs associated with clinical complications related to obesity, any insights that can be gained regarding the prevention of excess weight gain or improvements that lead to better metabolic health once an individual reaches an obese state, will have a significant effect on the quality of life, life expectancy and the health care system as a whole. There is a profound need for cost-effective prevention policies to be implemented in schools and for effective drug interventions based on the ongoing advances in research.



Thyroid Disease

Treating the Thyroid and Beyond

Thyroid Facts

Thyroid disease affects the health and productivity of millions of Americans, particularly women and the elderly.

- Thyroid hormones are key regulators of metabolism and affect the rate of nutrient consumption of every cell, tissue, and organ in the body.
- Over 13 million Americans are currently under treatment for thyroid dysfunction.
- An additional 12 million are estimated to have unrecognized thyroid dysfunction.
- Conditions of both thyroid over-activity (also known as hyperthyroidism) and under-activity (hypothyroidism) are five times more common in women than in men.
- Undetected hypothyroidism in pregnant women increases the risk of miscarriage, pregnancy complications, and childhood learning disabilities.
- Six percent of U.S. women develop a thyroid problem in the year following pregnancy.
- Thyroid dysfunction is both more common and harder to recognize in the elderly.

The implications of thyroid disease are far-reaching as the thyroid gland produces hormones that influence cells throughout the body. Numerous aspects of a patient's health are affected by thyroid disease, so being able to effectively treat and care for the thyroid is critical.

The Discoveries

Our understanding of thyroid function continues to be challenged as new technologies allow researchers to probe the mechanisms behind thyroid disorders. Studies on the genetic underpinnings of thyroid function have led to the discovery that not all people respond the same way to thyroid hormone medication, which may explain why some people with hypothyroidism have lingering symptoms when given conventional treatments. The current medications to treat hyperthyroidism have life-threatening toxicities that constrain their use. They also cross the placenta and therefore raise concerns for use in pregnancy. New compounds developed by researchers at the National Institutes of Health are showing therapeutic effects in blocking the overproduction of thyroid hormones that occurs in hyperthyroidism, representing the first breakthrough in treating this condition in more than 50 years. Additional research suggests that the compound L-carnitine may be the first to be used as supplemental treatment to boost the effect of existing treatments for hyperthyroidism. Population-based research is examining the most cost-effective way to detect and treat unrecognized thyroid dysfunction, particularly in pregnant women and the elderly.

Beyond the direct impact on people suffering from thyroid disease, research into mechanisms of thyroid action has led to the development of new thyroid hormone-like molecules that have broad potential to treat a variety of non-thyroid conditions. These analogs mimic beneficial effects of thyroid hormone in specific tissues with underlying problems, while avoiding detrimental effects in others. These "thyromimetic" drugs are currently under testing as treatments for obesity, high cholesterol, heart failure, thyroid cancer, cognitive decline, and mood disorders. In addition, a recently-discovered pathway for thyroid hormone action holds promise for a new way to treat a wide range of cancers and some other conditions, such as acne rosacea, that involve overproduction of blood vessels. These discoveries are examples of how unanticipated findings from researching fundamental mechanisms can translate into whole new therapeutic areas.

The Treatments

Although there have been no new FDA-approved therapies for hyperthyroidism or hypothyroidism in more than 50 years, several promising therapies are on the horizon. These treatments are undergoing clinical trials to test their long-term safety and efficacy in humans. Currently, levothyroxine (a synthetic thyroid hormone), is easily administered and utilized to treat hypothyroidism and meets the thyroid replacement needs of millions of Americans.

Work Left to Do

The work ahead encompasses the entire spectrum of research types, including targeted basic and translational (lab bench to bedside) research studies, along with multicenter clinical trials. There are several areas that show particular promise over the next few years. For example, the use of genetic testing to identify the subgroup of hypothyroid patients who could benefit from combined supplementation with two types of thyroid hormones, rather than the standard type (levothyroxine) alone is under investigation. Novel formulations of levothyroxine are in testing that make it easier to take with other medications, and this would particularly facilitate the regimen for elderly patients prescribed multiple medications. In addition, studies are underway to improve identification of women at risk for postpartum thyroiditis and its associated postpartum depression. Clinical trials of new drugs to treat hyperthyroidism that are safer than those currently in use and drugs that selectively target specific pathways of thyroid effects to treat chronic non-thyroidal conditions will be developed, and trials will be conducted to efficiently and cost-effectively find and treat thyroid dysfunction in the populations who would benefit most from early detection.

Well Worth the Investment

Advancements in the understanding of thyroid diseases have been made possible by federally-supported basic and clinical research and lead to new developments in treatment options.

- State-of-the art tests have dramatically improved the ease of diagnosing thyroid dysfunction and monitoring its management.
- A better understanding of the medical conditions and medications that affect the absorption and metabolism of thyroid hormone therapy makes it easier to achieve stable dosing.
- Identification of thyroid autoimmunity and mild thyroid dysfunction early in pregnancy can decrease pregnancy complications.

These advances have resulted directly from the investment of research funding both in the discovery and understanding of basic mechanisms, and in the application of these findings to improving human health.

Osteoporosis
New and Emerging Therapies

Osteoporosis Facts

Osteoporosis and its precursor, low bone mass, are major public health threats in the United States, especially to those ages 50 years and older.

- More than 10 million Americans suffer from osteoporosis.
- Osteoporosis or low bone mass affects greater than 50% of people ages 50 years and older in the United States (over 40 million individuals).
  - Both men and women are affected.
  - Women are four times more likely to be diagnosed.
- Osteoporosis (meaning "porous bone") is characterized by low bone mass and structural deterioration of bone tissue, significantly increasing the risk of fractures (>1.5 million fractures annually).
  - Treatment costs for osteoporotic fractures remain high, though associated mortality has decreased during the past decade.
  - Fractures to major bones such as hip or vertebrae result in large cost burden.
- Costs can be significantly decreased by further advancements in treatment and fracture prevention.

The decrease in mortality associated with osteoporosis is largely due to improved diagnostic tools (increased bone density testing) and better treatments. Advances in both areas have been and continue to be aided by federally funded basic and clinical research.

The Discoveries

Though we typically think of bones as rigid, they are in reality highly dynamic structures. In fact, the skeleton is estimated to turn over (i.e., be replaced by new bone) at a rate of about 10% per year. Through daily wear and tear, microfractures form in both the cortical (outer shell) and trabecular (inner network) bones. Specialized cells in the body work non-stop to repair these minor as well as more major fractures through a process called bone remodeling. Though there are many steps in this process, we can generally compartmentalize them into two phases: resorption and formation. During the resorptive phase, specialized cells called osteoclasts break down bone, creating cavities where new bone is formed. New bone is produced by a second class of cells called osteoblasts, which lay down the bone matrix in the form of proteins such as collagen. Collagen and other proteins then become mineralized with calcium, phosphate, and magnesium, adding stiffness to the bone.

The activities of osteoclasts and osteoblasts are 'coupled' (the two cell types communicate with one other) such that the act of breaking down bone provides the signals required to stimulate new bone formation. In osteoporosis, bone resorption outpaces bone formation, leading to an overall net loss of bone density, architecture, and stability. Current treatments are aimed at slowing resorption and/or enhancing formation. However, the coupling between osteoclast and osteoblast activity creates a therapeutic challenge. That is, slowing bone resorption

ultimately leads to impairments in new bone formation. More research is needed to better understand bone physiology so that new treatments can be developed that maximize drug efficacy while at the same time reducing unwanted side effects.

Research over the past decade or so has led to significant advancements in our understanding of bone physiology. Many of these advances have been translated into new or developing therapeutics for osteoporosis. Here, we highlight three such discoveries that have been significantly advanced through federal funding.

Osteoprotegerin: In 1997, a factor made in the body called osteoprotegerin (or OPG) was discovered to inhibit bone resorption by blocking the development and activity of osteoclasts.

Cathepsin K: In 1996, NIH-funded investigators discovered that the cathepsin K gene was mutated in patients with a rare bone disorder known as pycnodysostosis. These individuals exhibit an elevation in their bone density known as osteosclerosis. This and subsequent investigations (many federally funded) confirmed a necessary role for cathepsin K in the degradation of bone proteins during bone resorption.

Sclerostin: Molecular genetic analyses of patients with two rare disorders, sclerosteosis and van Buchem's disease, led to the identification, in 2001 and 2005, of a novel player in bone remodeling called sclerostin. Patients with these disorders have increased bone mass and associated loss-of-function mutations in the sclerostin gene, suggesting that sclerostin normally functions as an inhibitor of bone formation.

The Treatments

Current osteoporosis treatments fall into two general classes: the anti-resorptives and the anabolics. The former function to inhibit osteoclast function, therefore slowing bone loss. The latter serve to stimulate or augment osteoblast (bone-building) activity. Current anti-resorptive therapies (such as bisphosphonates and selective estrogen receptor modulators or SERMs) and the one approved anabolic agent (parathyroid hormone 1–34 or teriparatide) all increase bone mineral density and decrease fracture rates. However, each has drawbacks that compromise their clinical utility as well as patient adherence to treatment. These include, but are not limited to, overall drug efficacy, the frequency and route of drug administration, gastrointestinal side effects, limits in duration of treatment, and uncertainties regarding the effects of long-term use. Indeed, recent evidence suggests that long-term bisphosphonate treatment may be associated with an increased incidence of fractures in the long bones of the leg. Therefore, new therapies are needed for prevention and treatment of osteoporosis and other bone diseases. The three discoveries described above have each, in relatively short order, led to the development of first-in-class treatments.

Denosumab: In 2010, denosumab, which mimics the actions of OPG, received FDA approval for the treatment of osteoporosis, bone metastases, and treatment-induced bone loss (for example, in women receiving aromatase inhibitors for breast cancer).

Odanacatib: Odanacatib, currently in phase III clinical trials, is the most advanced of the cathepsin K inhibitors currently in development for anti-resorptive treatment of postmenopausal osteoporosis.

Well Worth the Investment

Advances in osteoporosis treatments would not have been possible without federally-supported basic and clinical research.

- It is clear that federal funding of OPG, cathepsin K, and sclerostin actions in bone remodeling has been money well spent in our ongoing effort to prevent and treat osteoporosis and other debilitating bone disorders. Continued support will assuredly pay dividends.
- As described here, denosumab, odanacatib, and anti-sclerostin therapy represent recent examples of drugs either in the clinic or in trials within 10–15 years of their initial target identification.

Investigations of bone physiology and endocrinology serve as a model within the biomedical sciences of how basic science observations can be rapidly translated into novel therapeutics at the bedside.

Anti-sclerostin therapy: The vast majority of osteoporosis drug therapies are in the anti-resorptive class. At present, only one anabolic treatment, teriparatide, is FDA approved, but must be given by injection and for a maximum of 24 months. Therefore, new anabolic treatments are needed. A new drug that prevents sclerostin from inhibiting osteoclast function, leading to enhanced bone formation, is currently in early phase II clinical trials.

Work Left to Do

Though we have learned much to date and have been successful in translating basic research findings into novel therapeutics, more work is still needed. In addition to odanacatib and anti-sclerostin therapy, other drug candidates are making their way through clinical trials. These include anti-resorptive Src inhibitors (e.g., Saracatinib) and novel SERMs (e.g., lasofoxifene). In addition, the so-called calcilytics and dickkopf-1 inhibitors are being developed as novel anabolic (bone-building) agents. Continued federal funding will foster new discoveries and new advances. At the same time, funding of clinical trials will facilitate optimization of currently available therapies. Collectively, this work will lead to a day when osteoporosis, if not preventable, will become a manageable condition.

Breast Cancer

A Model for Hormone Actions in Cancer

Breast Cancer Facts

Breast cancer is a devastating illness, largely affecting women, but also affecting a small number of men in the United States.

- Breast cancer is the 2nd most common cancer affecting women in the United States.
- In 2010 there were over 207,000 new cases of breast cancer in women.
- Approximately 12% of women will be diagnosed with breast cancer in their lifetime.
- Nearly 2,000 cases of breast cancer are diagnosed in men each year.

The mortality rate has significantly decreased over the past decade. This is due largely to early detection and improvements in breast cancer treatments.

Improved early detection and treatments were made possible by investment in research.

- The federal government spent more than $500 million per year on breast cancer research from 2003 through 2009.

While significant progress has been made, more research is needed.

- It is estimated that nearly 40,000 women will die each year from breast cancer, a mortality rate of 24.5 per 100,000 women.
- The mortality rate in African American women is very high at 32 per 100,000 women.

The Discovery

Steroid Hormone Action and Breast Cancer

Several factors are associated with an increased risk of breast cancer, including age, family history, ethnicity, genetics, and hormonal factors. In particular, the steroid hormone estrogen (17 beta-estradiol, or E2) is linked to the risk of breast cancer. E2 was originally discovered and described by Edward Adelbert Doisy, an agricultural scientist, in 1935. Estrogen is found across all mammalian species and is required for the development of the breasts, for other secondary sex characteristics, and for normal fertility. Because normal breast cells and many breast tumors require estrogen to grow, controlling how estrogen is made and how it works is a critical part of the prevention and treatment of breast cancer.

The active hormone estrogen is made from cholesterol, which is obtained from food or made in the body, through the action of several enzymes (proteins that synthesize and modify compounds). The final step in estrogen synthesis is the modification of testosterone (another hormone) into active E2, which is mediated by an enzyme called aromatase. Both men and women synthesize E2. Women have higher levels during their reproductive years, and almost no E2 after menopause as their ovaries stop functioning, whereas men continuously produce moderate levels of E2 in their testes throughout their lifetime. The majority of E2 in women is produced in the ovaries, but the adrenal glands continue to produce compounds that can be converted to E2 either by the adrenals or by other tissues that contain the enzyme aromatase, such as breast tissue. Thus, E2 can be produced locally in the breast both before and after menopause.

E2, like all steroids, exerts its biological function by interacting with, and activating, cellular proteins called "receptors. Scientists have found that

the binding of E2 to estrogen receptors (ER) causes the receptor to change shape and to change its contacts with other proteins, called co-activators. These interactions regulate biological activity by changing patterns of gene activity in cells. Thus, E2 binding to ER begins a program of altered gene activity, which in some breast tumors is directly related to tumor growth. One of the first tests performed on breast tumor biopsies is for the detection of ER proteins. The classification of a tumor as ER-negative or ER-positive helps to determine if the tumor may be sensitive to ER-directed therapies.

The Treatments

Tamoxifen and Aromatase Inhibitors

Because estrogen directs growth in many breast tumors, researchers thought that drugs that interfere with the function of estrogen would be useful in the fight against breast cancer. Collaborations between chemists and biochemists resulted in the development of several compounds that could bind to the ER in place of E2. These compounds, called "anti-estrogens," prevent the binding of E2 to the ER, so that the ER is unable to change shape or recruit co-activators. Instead, the anti-estrogens cause the ER to bind "co-repressor" proteins, effectively shutting off ER activity and actively preventing changes in gene expression. Tamoxifen was identified as one such compound, and was used successfully in experiments to prevent the growth of breast cancer cells. Subsequent testing in humans demonstrated tamoxifen's usefulness in slowing tumor growth or preventing recurrence of tumors. Furthermore, tamoxifen and another similar drug, called raloxifene, are approved by the FDA as chemopreventive agents to reduce the risk of breast cancer in women who have a greater chance of developing the disease.

Though effective against breast cancer, long-term treatment with tamoxifen increases a woman's risk of uterine cancer. A more recent approach in breast cancer treatment has been to prevent the synthesis of E2 by treating patients with inhibitors of the aromatase enzyme. Biochemists developed small molecules that bind to the enzyme and destroy its E2-synthesizing activity. Clinical trials demonstrated that these compounds are at least as effective as tamoxifen in treating patients with breast cancer, and can even be used on tumors for which tamoxifen does not work. In addition, patients treated with aromatase inhibitors do not show increased risk of uterine cancer. As a result, aromatase inhibitors have now become a common clinical approach to treat breast cancer in post-menopausal women.

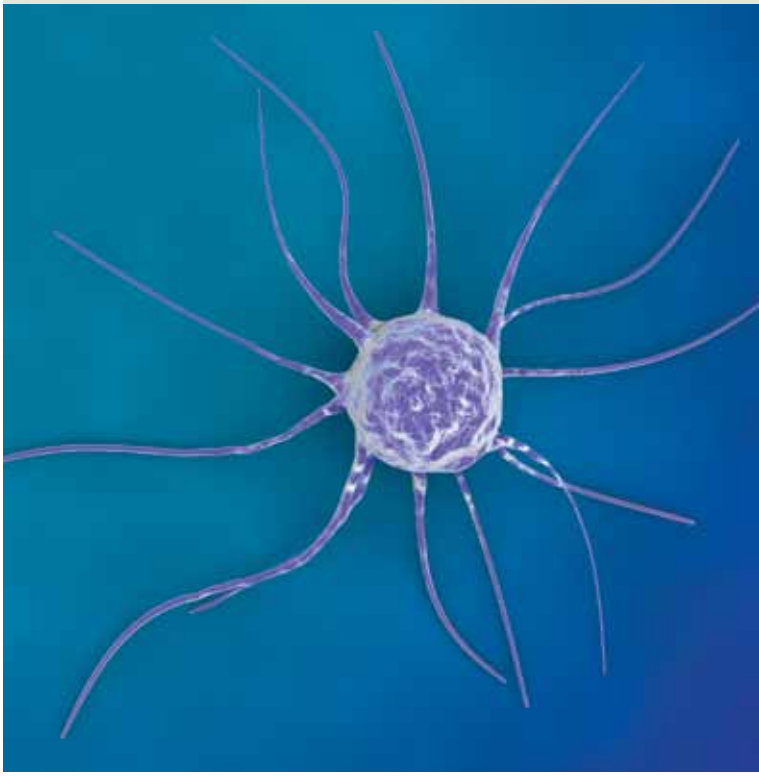
Because anti-estrogens and aromatase inhibitors are such effective drugs, all breast tumors are now tested for the absence or presence of ER. The ER is a model for how detection of specific molecules in tumors can lead to new cancer treatments, and this work has been credited with prolonging the lives of breast cancer patients and reducing the number of deaths caused by breast cancer (according a report from the National Cancer Institute).

Well Worth the Investment

Federal funding of breast cancer research and scientific discovery has resulted in an increasing arsenal of breast cancer treatments.

- Treatments offer hope to the more than 200,000 women diagnosed with this disease yearly in the U.S.
- The cost of treating breast cancer in this country is more than $8 billion per year.
- The government invests over $500 million in breast cancer research annually.

The continued federal funding of breast cancer research will save not only thousands of women's lives but billions in taxpayer dollars.



Work Left to Do

Although many estrogen receptor-positive tumors respond to tamoxifen or aromatase inhibitor therapy, not all do. Some tumors that do respond initially can develop resistance to these drugs over time. These tumors typically are more aggressive and may have higher levels of receptors for other proteins, called growth factors (such as epidermal growth factor, or EGF). Other tumors may express both ER and growth factor receptors, and ongoing research is directed at new therapies that might be effective in these types of tumors. Research is also needed to identify markers to discriminate which tumors will respond to ER-based drugs and which will not, saving women valuable time that may otherwise be wasted on ineffective drugs. Furthermore, more research is needed to understand why African American women, who have the same incidence of breast cancer as other populations, have more aggressive tumors and a much higher mortality rate.

Assisted Reproduction

Hormones and Fertility

Assisted Reproduction Facts

In Vitro Fertilization (IVF) technology has given hope to countless couples who are otherwise unable bear children.

- Over 4 million babies have been born to date worldwide using IVF technology.
- According to the Centers for Disease Control (CDC), in 2007:
  - Pregnancy through IVF was achieved in an average of 32% of attempts.
  - 25.6% of IVF procedures resulted in live births (ranging from 12.6% in women in the oldest age group of 41–42 years, to 41.4% for women under age 35).
- Success rates for women in all age groups are increasing as technology advances.

Further advancements in technology will allow for increased success rates for all women seeking reproductive therapy, improved outcomes for women undergoing chemotherapy or other fertility-disrupting treatments, and increased access to assisted reproduction.

The Discoveries

The earliest IVF treatment procedures required women to undergo hormonal stimulation (in order to mimic or accentuate normal hormone actions) and subsequent inpatient monitoring during the final stages of treatment. Surgical teams had to be at the ready to carry out egg harvesting procedures within hours of a sign of impending egg release (commonly referred to as ovulation). Timing had to be just right, and there was a high failure rate. The cost and inconvenience associated with these early procedures prevented the widespread use of IVF as a viable option. Improving the manipulation of hormones to control the growth of eggs over the past 30 years has afforded the option to many more individuals.

The discoveries that led to IVF becoming a mainstream medical treatment began with the isolation of gonadotropin releasing hormone (GnRH). GnRH is the hormone responsible for initiating a hormone cascade that leads to egg maturation and ovulation. The discovery of GnRH was so significant to the field of reproductive medicine that the researchers responsible for discovering that this type of hormone was produced in the brain, Roger Guillemin and Andrew Schally, were awarded a Nobel Prize in Medicine in 1977.

GnRH is released in pulses from the hypothalamus (a portion of the brain that controls many important biological functions). This pulsatile secretion precisely orchestrates a number of hormonal events, the combination of which drive egg maturation and ovulation.Prolonged administration of GnRH was found to disrupt the hormone cascade, thereby preventing egg maturation and ovulation.Scientists have taken advantage of this discovery to create drugs that act like GnRH (so called agonists) and others that inhibit GnRH action (antagonists) to manipulate the ovulatory cycle. Indeed, these drugs are used

both in the context of assisted reproduction and in the treatment of hormone-dependent diseases such as prostate cancer and endometriosis.

The Treatment

IVF can be used to treat infertility associated with endometriosis, structural problems with the uterus or fallopian tubes, ovulatory disorders, low sperm counts, and other unexplained fertility issues.

Since the discovery of GnRH and the development of GnRH agonists and antagonists, women who undergo IVF typically begin hormone stimulation and then receive either a long-acting GnRH agonist or a GnRH antagonist to block the patient's own cycle so that hormonal changes necessary for ovulation can be controlled carefully by the physician. This allows the physician to provide the trigger for ovulation rather than one occurring spontaneously, perhaps at the wrong time, in women undergoing treatment. Egg harvesting is performed 34 hours later through a hollow needle.

Once harvested, the eggs are mixed with sperm and fertilized in a laboratory. After fertilization, the embryo grows for several days in the laboratory before being transferred to the woman's uterus. The current practice is to grow, harvest, and fertilize as many mature eggs as possible because the harvesting procedure is somewhat invasive and the processes of fertilization and embryo growth outside the body are relatively inefficient and costly. Moreover, excess fertilized embryos that are not transferred to the recipient woman can be frozen and are then available if initial attempts are unsuccessful, preventing the need for repeated egg harvesting.

Well Worth the Investment

Coupled with other technical advances, the use of GnRH agonist and antagonist molecules has made IVF the most effective modality for infertility treatment.

- In 2008, approximately 38 out of every 100 couples who underwent an IVF procedure delivered a live baby.
- In the United States, among the 436 clinics that report to the Society for Assisted Reproductive Technology, 148,055 IVF cycles were performed and resulted in 46,326 live births (www.cdc.gov/art).

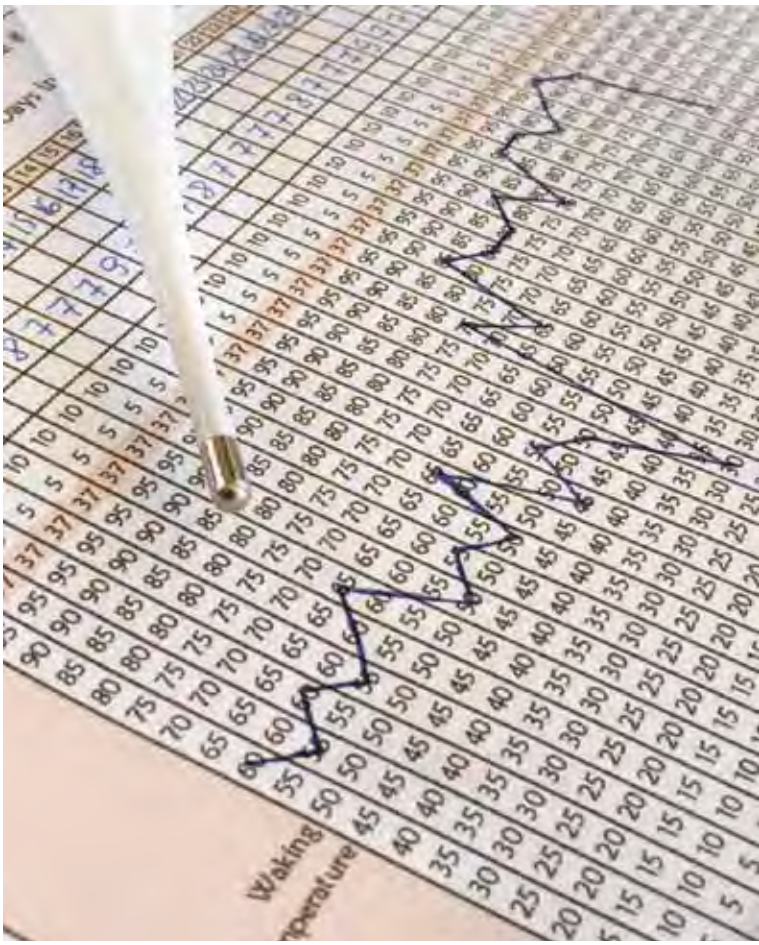
IVF continues to change the lives of infertile couples around the world who desire a family and is especially effective for parents who are more and more frequently choosing to delay the birth of their first child until after the natural peak in fertility.

Work Left to Do

Many aspects of IVF could be improved to increase efficiency, decrease costs, and increase the proportion of infertile couples with access to the procedure. Newer, more advanced techniques of ovarian stimulation may avoid the need for the creation of large numbers of mature eggs. Advances in stem cell research and the ability to turn stem cells into egg or sperm cells could circumvent the need for ovarian stimulation and egg harvesting altogether. With the availability of IVF, researchers are developing ways for young women and men who are facing sterility-causing cancer treatments to bank their eggs and sperm, and thus reproduce once their cancer treatments are completed and they are once again healthy. With additional breakthroughs, women of advanced reproductive age will be more likely to benefit from IVF. Later in life, women are often unable to produce enough eggs to harvest and fertilize under current IVF practices, likely due to age-related genetic abnormalities within their eggs. Methods to detect, prevent and even circumvent this process are currently underway.

Louise Brown Turns 32.

The first 'test tube baby' resulting from IVF was Louise Brown, born July 25, 1978. Robert G. Edwards, a scientist well-versed in the biology of fertilization, developed the hormones to stimulate the ovaries, and Patrick Steptoe, the gynecologist who treated the patients and obtained the eggs, developed the methods now widely used for human egg fertilization and in vitro embryo growth and development. Dr. Edwards was awarded the 2010 Nobel Prize in Physiology or Medicine for his work on IVF, the same year Louise Brown celebrated her 32nd birthday.



Prostate Cancer

A Hormone Dependent Cancer

Prostate Cancer Facts

Prostate cancer represents a major health challenge in the United States.

- Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer death amongst men in the United States.
- In 2011, it is predicted that over 217,000 men in the United States will be diagnosed with prostate cancer.
- Approximately 32,000 American men will die of this disease.
- Early stage tumors can be readily treated.
- Surgery or radiation therapy can cure early disease.
- A screening test for PSA, a protein that circulates in the blood can facilitate early detection of prostate cancer in some cases.
- Prostate cancers that have metastasized (spread outside the prostate) can be slowed but not cured.
- Prostate cancer is poorly responsive to chemotherapy.
- Metastatic prostate cancer is treated using drugs that reduce male hormones called androgens (e.g. testosterone)
- Drugs introduced in the last 2 years are yielding significant advances in treating the deadly stage of this disease.

Given the high prevalence of prostate cancer in the U.S. population and the lack of a sustainable cure for this disease, there has been an intensive focus during the last 20 years on understanding the means by which hormones promote prostate cancer growth, and on developing novel drugs that will block this process. Significant gains have been realized in recent years, and new agents to treat prostate cancer show early promise in clinical trials. These preliminary successes have further illuminated the importance and value of understanding hormone action in prostate cancer.

The Discoveries

Prostate cancer is unlike any other tumor type, in that it requires androgens, a type of steroid hormone, for survival and growth. Testosterone is the most abundant circulating androgen, of which approximately 95% is made by the testicles and 5% in the adrenal gland. The link between androgens and prostate cancer was first realized in the 1940s by Dr. Charles Huggins and his student, Dr. Clarence Hodges, who observed in animals that castration (thereby eliminating testosterone made in the testicles) resulted in prostate cancer regression. This notable finding earned Dr. Huggins the Nobel Prize in 1966 "for his discoveries concerning hormonal treatment of prostatic cancer."

Huggins' discovery fueled decades of research geared toward understanding how androgens stimulate prostate cancer growth, and how this pathway might be capitalized on to develop therapeutic agents. This era of discovery revealed staggering insights into the relationship between hormones and cancer. Functionally, it was discovered that in prostate cancer cells, testosterone is converted into an androgen that is approximately 10 times more potent than testosterone itself—dihydrotestosterone, or DHT for short, thus explaining in part why androgens have such a significant effect in the prostate. DHT binds to a molecule called the "androgen receptor" or AR, which is activated by this interaction. Activated AR allows prostate cancer cells to survive, divide and metastasize. These laboratory findings, combined with the knowledge that stopping production of androgens caused prostate cancers to shrink, led directly to development of more sophisticated medicines. Blocking androgen production and AR function remains the most effective means to treat prostate cancers that have spread beyond the prostate.

The Treatments

For reasons that are not well understood, metastatic prostate cancer does not respond to standard chemotherapy. Thus, the current standard of care for all patients with advanced disease is to use drugs that reduce the levels of androgen hormones and block the androgen receptor. An initial challenge for the research field was to generate drugs that block testosterone production, and therein mimic Huggins' discovery that castration leads to prostate cancer regression. Drugs called GnRH agonists reduce androgen production in the testicles and are widely used today for advanced prostate cancer. At the same time, scientists and clinicians working together to understand AR activity in prostate cancer realized the need for additional drugs that would bind directly to the AR and block AR function. As such, a battery of compounds was generated that are clinically effective at suppressing AR function, and are now used in combination with GnRH agonists. Importantly, the combination of GnRH agonists and drugs that block AR proved effective in the vast majority of patients—resulting in a period of disease remission. However, within 2–3 years, tumor growth recurs, and it is this phase of the disease for which there is no cure and that leads to patient morbidity.

In the last 10 years, the major impetus of the field has been to understand how prostate cancers become resistant to therapy. Strikingly, it is now quite clear that resistant prostate cancers resume growth as a result of restored AR function, despite the continuation of therapies designed to reduce androgen production and block AR function. Laboratory scientists have identified several different means by which AR becomes reactivated leading to tumor recurrence (relapse). For example, mutations of AR develop that permit tumors to resist therapy. Development of such mutations presents a significant clinical problem, as it is not yet clear how we will identify which patients have tumors harboring mutations, and how these patients can be treated. Alternatively, it is now realized that a subset of resistant prostate cancers develop the means to produce their own androgens. This existence of such a process indicated that it may be essential to block not only androgen production in the testicles but also androgen produced in the adrenal gland. Collaborations between laboratory scientists and clinicians allowed for the development of precisely such a drug (abiraterone acetate), which has shown significant effect in clinical trials as an agent capable of treating patients with advanced prostate cancer. While significant progress has been made in terms of translating basic science knowledge of androgen and AR function into clinical benefit for patients with this disease, much has yet to be learned with regard to treating the most lethal form of prostate cancer.

Well Worth the Investment

As described above, basic understanding of androgen function and integration of clinical findings have led to development of effective means for treating prostate cancer in the early stages:

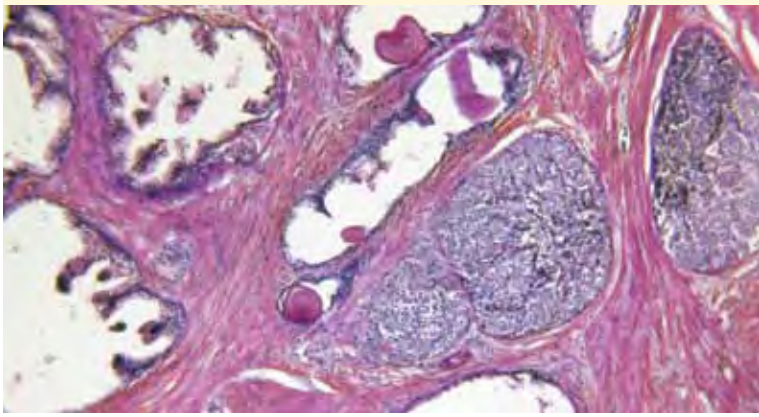
Basic science research

- Discovery that prostate cancers of all stages require androgen and AR function
- Identification of AR and the manner by which AR promotes tumor growth.
- Identification of the means to block androgen and AR function.
- Discovery of the means by which AR becomes reactivated after initial therapy leading to drug resistance.

Clinical research

- Development of the means to treat patients with metastatic disease.
- Development of screening tools to identify patients with cancer.
- Development of improved drugs to block AR function.

Treatment for metastatic prostate cancer is based on the tumor's requirement for androgens to survive and grow. Collaborative efforts between basic endocrine researchers and clinicians led directly to our current understanding of how the androgen and AR pathways function to promote disease progression, and to the recent development of more effective agents for treating this lethal disease.



Work Left to Do

In light of the recent findings that tumors find ways to restore androgen and AR function after treatment, it is clear that new therapeutic strategies must be developed that prevent this process. For the laboratory scientist, it is imperative to identify the means by which prostate tumors become resistant to therapy and develop drugs that are even more effective at blocking androgen and AR function. Oncologists will need tools for identifying the best therapeutic approaches for each individual with prostate cancer. Concerted efforts by scientists and clinicians will be critical for improving treatment and reducing death and suffering from this highly prevalent disease.

The Value of Endocrine Research

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