Metabolism Basics

■ Antidiuretic Hormone

Overview

The pituitary gland consists of two parts, an anterior and a posterior lobe. The anterior lobe releases trophic hormones that activate hormone production in their target organs. The hypothalamus secretes releasing hormones that control the secretion of these trophic hormones. The posterior lobe secretes two peptide hormones, oxytocin and antidiuretic hormone. The neurons that synthesize these hormones reside in the hypothalamus. The oxytocin- and antidiuretic hormone-producing neurons are in the large neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus. These hormones travel down the axons of these neurons, which are bundled in the stalk of the pituitary gland. They enter the bloodstream when the axon termini, housed in the posterior pituitary, release them. Neural impulses regulate the secretion of these two hormones. Oxytocin regulates uterine smooth muscle contraction during delivery, milk letdown during nursing, and helps establish maternal behavior. In males, it aids in sperm transport, and in both sexes, it contributes to pair bonding. Antidiuretic hormone (ADH), also known as vasopressin, regulates water reabsorption in the kidneys and at high concentrations, causes constriction of blood vessels.

Background

Approximately 60 percent of our body mass is water. Despite the stark differences in water intake and loss each day, the water content of our bodies stays about the same. The precise regulation of water content relies upon the kidneys, the vascular system, and ADH.

The kidneys consist of approximately 1 million microscopic units called nephrons. Nephrons are minifiltration units that filter the blood, returning necessary things back to the blood and excreting waste products in the urine. Nephrons have five main parts: (a) the glomerular capsule; (b) proximal convoluted tubule; (c) loop of Henle; (d) distal convoluted tubule; and (e) collecting duct.

The glomerular capsule is an interface between the bloodstream and the nephron. The renal artery branches from the descending aorta, and after entering the kidney, it branches into several segmental arteries. The segmental arteries move between the renal pyramids (triangular clusters of nephrons) as interlobar arteries. The interlobar arteries turn and line the border between the inner (medulla) and outer (cortex) layers of the kidney. This branch of the interlobar artery is called the arcuate artery, since it arcs over each renal pyramid. The arcuate arteries have several small branches called interlobular arteries whose further branches feed blood to the various nephrons. The arterial branch that enters the glomerular capsule of each nephron, the afferent capillary, deeply branches into several fine, tiny capillaries that form a knot-like cluster of capillaries called the glomerulus. The walls of the glomerulus have tiny pores in them. Covering the glomerulus are extensions of cells from the glomerular capsule called podocytes. Podocytes look like tiny octopi with lots of tentacles that spread over the surfaces of the glomeruli. Between the glomerulus and the podocytes is a layer of complex molecules called a basement membrane. This glomerulus-basement membrane-podocyte complex is the filtration unit of the nephron. Proteins cannot move through it because they are too charged. Cells cannot move through it because they are too big.

Fluid from the blood moves through the glomerulus-basement membrane-podocyte complex, and into the glomerular capsule. This material is known as the kidney "filtrate." From the glomerular capsule, the filtrate moves to the proximal convoluted tubule (PCT). The PCT uses energy-demanding active transport mechanisms to reabsorb sodium, glucose, amino acids, chloride, and potassium. Water passively moves with these other molecules. From the PCT, the filtrate moves to the loop of Henle, which has a thin, descending limb and a thick ascending limb. The descending loop of Henle is permeable to water but

impermeable to salts. The thick, ascending loop of Henle is impermeable to water but highly permeable to salts. As the filtrate traverses the descending loop of Henle into the medulla, it releases large quantities of water. As the filtrate travels to the ascending loop of Henle, active transport mechanisms reabsorb large quantities of sodium, potassium, and chloride. From the loop of Henle, the filtrate passages to the distal convoluted tubule (DCT). The DCT reabsorbs bicarbonate, an integral buffer for the body, and sodium. The hormone aldosterone regulates the reabsorption and secretion of sodium, potassium, and hydrogen ions into the urine by the DCT. The DCT empties into the collecting duct, which sends the urine into the renal calyces, which then merge into the renal pelvis. The ureters drain the renal pelvis and take the urine to the urinary bladder.

ADH works in the kidneys. Specifically, ADH regulates water reabsorption in the later part of the DCT and the collecting duct. Principal cells in these parts of nephrons have V receptors that bind ADH. Principal cells have, beneath their membranes, vesicles loaded with aquaporin 2 channel proteins. When ADH binds V receptors, these vesicles fuse with the membrane, inserting the aquaporin channels into the principal cell membrane. Aquaporin channels allow water to rush through the membrane, leading to extensive water resorption from the filtrate. This creates a concentrated urine and causes water conservations during times of dehydration.

Vascular smooth muscle also has V receptors. When ADH binds these receptors, they induce calcium release from internal stores, which causes smooth muscle contraction. Since smooth muscles surround blood vessels, ADH, at high concentrations, causes blood vessel constriction and increased blood pressure.

The solute concentration of the blood controls ADH secretion. When blood contains more water, it is less dense or has low plasma osmolality. Dehydration causes the blood to have less water, and the concentration of dissolved materials (solutes) is higher. In such cases, the blood has high plasma osmolality. The hypothalamus contains neurons called osmoreceptors that constantly measure the plasma osmolality. When the blood plasma osmolality is too high, the osmoreceptors stimulate the secretion of ADH. The regulation of ADH secretion rises linearly and steeply as the plasma osmolality increases. The hypothalamic osmoreceptors also control thirst, but ADH secretion ensues long before the thirst sensations begin.

ADH secretion is also stimulated by decreases in blood volume and blood pressure. Massive bleeding, for example, that causes a loss of 15 to 20 percent blood volume stimulates substantial ADH release, as do nausea and vomiting.

Applications

Excessive ADH production causes syndrome of inappropriate ADH secretion or SIADH. Increased ADH causes higher water retention and decreased plasma osmolality. The increased water content of the blood increases blood volume and blood pressure and dilutes the sodium concentration of the blood. These conditions induce the adrenal cortex to cease the production of the hormone aldosterone. Low aldosterone levels cause the kidney to dump sodium and lots of water into the urine to normalize the fluid volume. Unfortunately, this drops the sodium osmolality even lower.

The symptoms of SIADH can resemble dehydration, which is a manifestation of low blood sodium levels. The symptoms begin with headaches, nausea, and vomiting, followed by muscle cramps and tremors. As sodium levels continue to fall, the neurons in the brain begin to swell (cerebral edema). Cerebral edema causes mood swings and hallucinations. If the condition remains untreated, it will lead to seizures, coma, and death.

Several different conditions can cause SIADH. Trauma to the brain, brain infections, strokes, hemorrhages, or brain surgery can cause SIADH. Surgery, in general, increases ADH secretion for unknown reasons. Certain infections can cause SIADH, such as tuberculosis or certain lung infections. Some drugs can cause SIADH. The five drug classes most commonly associated with SIADH are:

1. pain relievers (analgesics) such as opioids or nonsteroidal anti-inflammatory drugs;
2. antiseizure drugs, in particular, carbamazepine;
3. antidepressants, particularly selective serotonin reuptake inhibitors or venlafaxine;
4. antipsychotic drugs; and
5. and cytotoxic drugs, particularly cyclophosphamide and vincristine.

Some tumors can produce ADH. Small cell carcinomas of the lung most commonly produce ectopic

ADH, but some cancers of the duodenum, pancreas, central nervous system, or lymphomas can also cause SIADH. Treatment of SIADH is with drugs called "vaptans," which antagonize the V receptor, and include conivaptan and tolvaptan.

Diabetes insipidus results from insufficient ADH. In this condition, low or absent ADH causes excessive water loss (0.8 to 7.9 gallons, or 3 to 30 liters per day) because of poor water reabsorption from the late DCT and collecting duct. Such dramatic water loss greatly increases the sodium concentration in the blood (hypernatremia). Diabetes insipidus can be complete or partial and may be primary or secondary (caused by some other condition). Also, diabetes insipidus may result from deficient ADH secretion (central diabetes insipidus) or renal resistance to ADH (nephrogenic diabetes insipidus). Some drugs, most famously lithium, can induce nephrogenic diabetes insipidus. Overconsumption of water can also lead to a form of diabetes insipidus called psychogenic polydipsia.

Treatment of central diabetes insipidus is with nasal ADH (desmopressin). Nephrogenic diabetes insipidus is treated with a low-salt diet, diuretics and nonsteroidal anti-inflammatory drugs.

Desmopressin is also used to treat two bleeding disorders, hemophilia A and von Willebrand disease. Hemophilia A results from a deficiency of clotting factor VIII. Mutations that perturb the synthesis of von Willebrand factor (VWF) cause von Willebrand disease. VWF glues activated platelets to the inner lining of blood vessels. Desmopressin increases the production of clotting factor VIII and von Willebrand factor and helps treat both bleeding diseases.

—Michael A. Buratovich

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Autoimmune Disorders

Causes and Symptoms

Autoimmunity refers to a group of widely varying diseases or disorders. These include familiar examples (type 1 diabetes mellitus, myasthenia gravis, multiple sclerosis, rheumatoid arthritis) and many that are not as familiar (idiopathic thrombocytopenic purpura, Graves' disease, Felty syndrome, Hashimoto's thyroiditis). The list is long and growing as researchers continue to ferret out the root causes of many disorders known for one hundred years or more. In many cases, environmental triggers or environmentally controlled flare-ups are common. All autoimmune disorders have one thing in common: the failure of the human immune system to distinguish between self (own) and nonself antigens, thus leading the body to attack itself and destroy tissues or organs.

Autoimmunity is not a rare event; it occurs in all people, and it does not necessarily give rise to disease. For instance, autoantibodies (antibodies directed against the self) destroy aged or damaged cells of the body. However, other autoantibodies arise by chance combinations of genes usually suppressed during development in the thymus gland; a phenomenon known as selection. If the thymus fails to do its job, the release of autoantibodies into the lymph nodes and the bloodstream, allows them to seek out, attack, and destroy antigens.

There are several ways to classify autoimmune disorders. Some diseases affect only one organ system, and some affect multiple systems. Examples of organ-specific disorders are Addison's disease and Graves' disease; nonorgan-specific disorders include systemic lupus erythematosus and scleroderma. Alternatively, one can classify autoimmune disorders by the type of immune system cells involved in their onset. Antibody-secreting B cells cause some autoimmune diseases, including myasthenia gravis, multiple sclerosis, rheumatic fever, systemic lupus erythematosus, and Graves' disease.

Other disorders are the result of the action of the systemic T cells; they include Addison's disease, type 1 diabetes mellitus, and Hashimoto's thyroiditis.

The onset of an autoimmune disorder hinges on many factors, some of which are still unknown. However, autoimmunity is multifactorial and multigenic. In other words, many environmental factors and many genes are involved in determining susceptibility to autoimmune disorders. Also, many environmental factors are involved in controlling the remission and flare-ups of autoimmune diseases. Most autoimmune disorders are probably the result of the release of T or B cells that, because they did not properly distinguish between self and nonself, should have been suppressed by the body's immune system but were not. Some autoimmune responses are a result of damage to, or tumors of, the immune system tissues (lymphatic system).

A variety of studies have established genetic links in autoimmune diseases, but because most are multigenic, there is no simple Mendelian inheritance pattern seen. Nonetheless, there seems to be a clear correlation between specific human leukocyte antigen (HLA) genes and certain autoimmune disorders. For instance, those who have HLA allele B27 have a ninetyfold greater risk than the normal population of developing ankylosing spondylitis. Those with allele DR3 have a twelvefold greater risk of celiac disease and a tenfold higher risk of Sjögren syndrome. In the case of insulin-dependent diabetes, the relative risk factor is fivefold if one has the DR3 allele or the DR4 allele, but if both are present, then the risk jumps to twentyfold. If the DR3 and DQw8 alleles are present, then the risk factor is one hundredfold. Yet, these alleles themselves do not automatically cause autoimmune disease, as evidenced by several studies on identical twins in which the rate of disease in the twin of an affected person ranged from 25 to 50 percent. Clearly, environmental factors can change susceptibility to autoimmune disease into actual manifestation.

Autoimmune disorders are much more common in women than in men and are usually more severe in women. This is likely due to the effects of estrogen, which has a role in enhancing the expression of HLA genes and activating macrophages, thus leading to higher tissue destruction. Some autoimmune responses are noted to flare and subside throughout the menstrual cycle, in conjunction with the rise and fall of estrogen levels. Stress is also a contributing factor that can cause an autoimmune disorder to flare. Stress induces the hypothalamus and pituitary glands, which release hormones that directly stimulate the immune system.

Some kind of infection typically precedes the manifestation of some autoimmune diseases. Infections may contribute to autoimmunity in several ways. Some microbes produce antigens that are very close in structure to human antigens. The antibodies produced against the invading organism in such cases also attack self-antigens because of their chemical similarity; this is called "molecular mimicry. Examples of this response are poststreptococcal glomerulonephritis and rheumatic fever. Other invaders may damage human cells and release molecules not usually seen by the immune system (sequestered proteins). The immune system regards these self-proteins as foreign and initiates an immune response against them (a similar response may occur when trauma or injury releases normally sequestered proteins). An example is sympathetic ophthalmia. In it, eye lens proteins that not typically seen in the circulation are released, triggering antibodies that may attack the opposite (uninjured) eye.

The symptoms of autoimmune disorders are as varied as the disorders themselves. No one set of symptoms fits all disorders. Symptoms may be systemic or localized, progressive, or stable. Symptoms may also be life-threatening or merely annoying.

Multiple sclerosis (MS) is an autoimmune disorder involving the central nervous system. Nerve axons of the white matter of the brain are usually surrounded by myelin protein sheaths that protect the nerves and speed the transmission process. In individuals with MS, these myelin sheath proteins are gradually attacked and destroyed, slowing transmission so that patients develop a loss of control of motor function and vision. This disease often progresses irregularly and unpredictably and is irreversible. It appears to be the result of both B cells (producing antibodies against oligodendroglia, the cells that make myelin protein) and T cells (acting against a peptide product from the myelin protein). Although what triggers the initial response is unclear, but it may follow infection with either Epstein-Barr or hepatitis B virus. More than 2.1 million people worldwide are affected by MS, mostly women diagnosed between ages twenty and fifty.

Systemic lupus erythematosus (SLE), known simply as lupus, is a generalized disorder that occurs predominantly in women. It is linked to B cells and

the production of antibodies against parts of the deoxyribonucleic acid (DNA) molecule. These DNA antibodies cause tissue damage by combining with free and protein-bound DNA (from cells damaged by disease or the normal aging process). They form immune complexes that deposit in the kidneys and arterioles, leading to tissue destruction, fibrosis, and joints, leading to arthritis. Autoantibodies against red blood cells or platelets may also occur in SLE. Antibodies against muscles may be present and contribute to muscle inflammation, while the presence of antibodies to heart muscle may lead to myocarditis and endocarditis. Antibodies against skin components lead to a characteristic "butterfly rash" on the bridge of the nose and the area around the eyes seen in many patients with SLE; this rash worsens in sunlight's presence.

Rheumatoid arthritis is a common, crippling disease. It is controlled by B cells in the joints that are activated to produce several antibodies, including rheumatoid factor. The result is the formation and deposition of immune complexes in the joint cartilage. B cells also make antibodies against cartilage in some cases. The resulting destruction activates chemicals that stimulate T cells to come to the area, and they release destructive enzymes, just as they would if bacteria invaded the joints. All these responses lead to joint damage, inflammation, and pain. As the disease progresses, the synovia swell and extend into the joints, causing further pain and discomfort along with disfigurement of the joints. The cause of antibody activation is unknown and may be quite variable.

Both Hashimoto's thyroiditis and Graves' disease are forms of autoimmune thyroiditis. In Hashimoto's disease, antibodies are formed against a protein within the thyroid cells, leading to attack of the cells and destruction of much of the thyroid tissue. In Graves' disease, B cells make antibodies against the receptors for thyroid-stimulating hormone (TSH), the pituitary hormone that stimulates the thyroid gland to produce thyroid hormone. These autoantibodies stimulate the TSH receptors, hyperstimulating the thyroid. The thyroid gland produces excess thyroid hormone, a condition known as thyrotoxicosis.

An individual with myasthenia gravis experiences muscle fatigue and extreme weakness with only mild exercise, such as walking short distances. B cells make autoantibodies against the nicotinic acetylcholine (ACh) receptor found in skeletal muscle. Motor neurons that control large muscles release ACh, which binds to nicotinic ACh receptors at the junction between the motor neuron terminus and the muscle cell, a specialized structure called the motor end plate. Inhibition of the nicotinic ACh receptor by autoantibodies prevents ACh from binding, and the muscle cannot contract. If a few receptors are blocked, then the muscle may still respond weakly. If enough antibodies are present to block a large number of receptors, then the threshold limit for muscle response will not be achieved. The muscle will not respond even in the presence of repeated stimulation from the neuron.

Scleroderma, also known as progressive systemic sclerosis, predominantly affects middle-aged women and is caused by collagen deposition in various tissues of the body. B cells make autoantibodies against the centromere portion of the DNA. Symptoms include calcium deposition in the skin, sensitivity to cold, and decreased esophageal motility. The lungs often experience fibrosis, as do the kidneys.

Finally, type 1 diabetes mellitus results from immune-mediated destruction of the pancreatic islets. People with type 1 diabetes mellitus (T1D) have a strong genetic predisposition to develop this disease. However, a host of observations strongly implicate viral infections as one of the primary triggers of T1D. Many types of viruses, including mumps, rubella, enteroviruses, cytomegalovirus, and DNA rotavirus, have all been implicated as contributors to T1D pathogenesis. Viral infections of the pancreatic cells bring cytotoxic T cells to the pancreas. These cells destroy viral-infected cells but also become sensitized against pancreatic beta cells. The gradual and progressive destruction of the beta cells deprives the, typically, young patient of the ability to make insulin, and diabetic ketoacidosis ensues. Without injections of exogenous insulin, the prognosis of the patient remains grim.

Treatment and Therapy

Most autoimmune disorders are not curable; they develop into chronic conditions that require a lifetime of care and monitoring. Treatment is quite varied and depends on the underlying cause and etiology of the disease. Overall, the goals of treatment are to reduce the symptoms and to control the disease or disorder while at the same time, allowing the immune system to continue fighting the viruses and bacteria affecting the body daily. The most generalized treatment is the administration of immunosuppressive drugs.

The most commonly used drugs are azathioprine, cyclophosphamide and corticosteroids to reduce the inflammatory responses seen in many autoimmune disorders. Drugs such as methotrexate have gained wide acceptance in the treatment of rheumatoid arthritis and other autoimmune disorders. Still, they have systemic side effects that, in some cases, may be worse than the autoimmune disorder itself, such as suppression of the basic immune responses involved in fighting off common viruses and bacteria. While the doses used to fight autoimmunity are much lower than those used to suppress organ graft rejection, these general effects may still be seen, especially in older individuals whose immune systems are declining as a result of age. Thus, pharmaceutical companies have poured significant resources into discovering drugs that can suppress only the self-reactive antibodies and not the entire immune system.

Hormones, proteins, or other substances usually produced or secreted by the cells or organs damaged in autoimmune disease (such as thyroid hormone or insulin) can generally be supplemented to the point that they are within the proper physiologic range. Sometimes this works well. For instance, Graves' disease can be effectively controlled by removing the overactive thyroid gland and then supplementing thyroid hormone in the patient. Treating type 1 diabetes in children with insulin injections, however, is a much trickier proposition. A single injection cannot duplicate the finely controlled release of insulin from the beta cells of the pancreas.

Many investigators have worked on vaccinations for autoimmune disorders, using animal models of varying types. Some results have been promising, even if the mechanism of action is still mostly unexplained. Vaccinations against autoimmune thyroiditis, encephalitis, and arthritis have been successful in some animal models.

Another approach is the use of oral tolerance therapy. The doctor gives the patient large quantities of the offending autoantigen in the hope that tolerance to the particular protein will develop. This approach is similar to the process of desensitization in allergy sufferers. Oral doses of myelin, for instance, have shown some success as a treatment for patients with multiple sclerosis.

Perspective and Prospects

The history of human understanding of autoimmune disorders is quite short. Early in the twentieth century, Paul Ehrlich described a condition of "horror autotoxicus," the attack of the human immune system against the body's tissues. His studies set the stage for fairly rapid advancement in the understanding of the human immune system. Knowledge of the genetic and molecular basis for autoimmunity, however, along with the realization that autoimmunity is a normal part of immune system development, began in the 1980s mainly due to the development of genetic and biochemical tools allowed new insights into the cause of thee diseases. Even where the cause was well established (such as with insulin-dependent diabetes, established in the 1920s), no significant changes in treatment became available until new genetic tools became available. The entire field of immunology, which until the 1970s was in its infancy as a medical field, has grown exponentially as new molecular tools have enabled researchers to elucidate the pathways by which autoimmunity exacts its toll.

There is still plenty to do, both in terms of determining pathways and in developing new therapies aimed at specific targeting of these pathways. With the Human Genome Project's completion, an incredible amount of new knowledge is available that will help researchers produce treatments that are much more targeted and specific than those used in the past. An increased understanding of the immune system and pathways of inflammation provides multiple new targets for novel and innovative therapeutic strategies not only to treat autoimmune diseases but to prevent them.

—Kerry L. Cheesman,
updated by Michael A. Buratovich

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■ Banting and Best Isolate the Hormone Insulin

Summary of Event

Historical documents demonstrate that ancient people knew about diabetes mellitus. A deficiency in the "islets of Langerhans" part of the pancreas induces the disease in its juvenile form. These islets fail to produce the hormone insulin, which is essential for the utilization of glucose by cells. When deprived of their primary fuel (glucose), the muscle cells produce energy from fat, which results in high blood levels of toxic ketone bodies (acetone).

The person with diabetes has very high glucose levels in the blood (hyperglycemia) and urine (glycosuria). The patient consumes much fluid, produces much urine, and is always hungry and weak; yet, despite constantly eating, the patient loses weight. Once ketone bodies begin to accumulate in the blood, the brain ceases to function, and the patient slips into a coma and dies.

The German histologist Paul Langerhans discovered, in 1869, specific cells in the pancreas that were later named "islets of Langerhans." The Swiss anatomist Johann Conrad Brunner, in 1682, showed that if he removed the pancreas, the experimental animals began to drink and urinate continuously. These findings, and others, demonstrated a connection between the onset of diabetes and pancreatic lesions, inaugurating a new era: the study of the pancreas as the causative factor of diabetes.

Later, researchers produced diabetes in experimental animals by surgically removing the pancreas. Eventually, scientists discovered that the pancreatic islets of Langerhans are the source of the insulin. Unfortunately, from 1910 to 1920, attempts to extract insulin from the islets of Langerhans failed.

In 1920, a young Canadian surgeon received an inspiration that would become the turning point for the elusive pancreatic hormone. On October 31, Sir Frederick G. Banting was preparing a lecture on the pancreas for his medical class. He had an idea after reading an article in the journal *Surgery, Gynecology and Obstetrics* that reported that the blockage of the pancreatic duct caused the pancreas to shrivel, leaving the islets of Langerhans untouched. He realized that when one tried to extract the insulin from the islets of Langerhans, the pancreatic digestive juice destroyed the hormone before it could be isolated. By letting the pancreas shrivel first, there would be no digestive juice left, and the hormone could be isolated intact.

Banting presented his idea to John J. R. Macleod, head of the physiology department of the University of Toronto, and requested permission to conduct the necessary experimental work in his laboratory. Although Macleod did not believe in the existence of an islet hormone or that Banting would be able to prove otherwise, after lengthy deliberations, he permitted Banting to use the facilities and provided him with a graduate student assistant, Charles Herbert Best.

Banting and Best began their experiments on dogs on May 17, 1921. On August 3, the two researchers had the first conclusive result showing that their pancreas extract lowered the blood sugar of dogs who became diabetic after surgical removal of their pancreases. At first, Macleod was skeptical about Banting's report on the successful isolation of the antidiabetic hormone, and he made the two researchers repeat their experiments several times. After he was satisfied that the results were valid, he invited James Bertram Collip to join the group.

Charles H. Best (photo courtesy of the University of Toronto)

On December 12, Collip began working on the purification of the extract to make it injectable into humans. On January 23, 1922, Collip and others tested their extract on a fourteen-year-old boy dying of diabetes. The injection of the extract lowered his blood sugar and cleared his urine of ketone bodies and sugar.

The first official paper on the discovery, "Internal Secretion of the Pancreas," was published in February 1922, in the *Journal of Laboratory and Clinical Medicine* by Banting and Best. On October 26, 1923, the Swedish Nobel Committee awarded the Nobel Prize in Physiology or Medicine to Banting and Macleod for the discovery of insulin. The two winners, accompanied by Best and Collip, traveled to Stockholm two years later. On September 15, 1925, at the ceremony's presentation, Banting shared his half of the prize with Best and Macleod, followed suit by sharing his award with Collip.

Significance

To appreciate the importance of this discovery, one need only consider the plight of the millions of diabetics before this discovery. The fate of diabetic children was particularly tragic, as, shortly after the onset of the disease, they changed from being healthy and active to weak and tired; soon after, they became comatose and died. The parents of such children knew quite well that a diabetes diagnosis was equivalent to a death sentence.

The discovery of insulin at the University of Toronto was one of the most revolutionary events in the history of medicine. Its impact was so significant because of the miraculous effect insulin had on diabetic patients. The most dramatic example of its spectacular power was its ability to conquer the diabetic coma. At the start of the twentieth century, more than 15 million diabetics were living without insulin and probably died at an early age. One of these was the American physician George Richards Minot, a juvenile diabetic, saved by using insulin. As an adult, he discovered a treatment for pernicious anemia, another disease that had always been lethal.

—René R. Roth

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■ Herbert Wayne Boyer: Production of Human Insulin

When financier Robert Swanson heard about genetic engineering technology, he had, what was then, a radical, potentially crazy idea. "What if," he surmised, we could use genetic engineering technology to produce human insulin on an industrial scale for diabetic patients?" This stunning proposal

could potentially solve a dire problem facing twentieth-century medicine—the number of diabetics in the United States was increasing while the supply of bovine and porcine pancreases from which people with diabetes received their insulin was decreasing. To address this upcoming shortage, Swanson, in collaboration with molecular biologist Herbert Boyer, founded the biotechnology company, Genentech. Their initial mandate was to use molecular cloning and genetic engineering techniques to produce human insulin on an industrial scale. The Swanson-Boyer Genentech team elicited the assistance of Arthur Riggs and his colleagues at the City of Hope clinical research hospital in Duarte, California, in this project.

At this time, the National Institutes of Health (NIH) guidelines regulating recombinant DNA research prohibited the use of human deoxyribonucleic acid (DNA) in recombinant DNA experimentation. Therefore, the Genentech-City of Hope team thought that the best approach was to synthesize the human insulin gene rather than isolate it. Under a loophole in the guidelines, recombinant DNA molecules made from synthesized genes would not fall under the prohibitions. The strategy was to synthesize, clone, and express in *Escherichia coli* (*E. coli*) bacteria cells a human gene that would code for human insulin. Riggs suggested that he and his colleagues Keiichi Itakura, Herb Heyneker, and John Shine first synthesize, clone, and express a smaller gene, to test the feasibility of this technology. Riggs and others used the human growth hormone (somatostatin) gene, which encodes a fourteen-amino acid protein, and is significantly smaller than insulin (fifty-one amino acids). This project was completed in August 1977 and published in December 1977.

Soon after completion of the somatostatin project, the Genentech-City of Hope team, with the assistance of Itakura, David Goeddel, Dennis Kleid, and Roberto Crea, began the human insulin project. Since insulin is composed of two polypeptide chains, the strategy was to synthesize, clone, and express separately in *E. coli*, a gene coding for each polypeptide. These polypeptides were synthesized, isolated, mixed, joined, and folded into a functioning insulin molecule. On September 6, 1978, Genentech and City of Hope announced that they had successfully cloned and expressed the human insulin gene in *E. coli*. Twelve days earlier, on August 25, Genentech licensed the production of human insulin to Eli Lilly.

Herbert Wayne Boyer (photo courtesy of Science History Institute)

In 1980, a small-scale clinical trial involving fourteen patients was begun in England, followed by a much larger clinical trial in the United States in 1982. Human insulin became the first human protein of medicinal value to be produced by genetic-engineering techniques and approved for use by the US Food and Drug Administration (FDA). The FDA approved the use of human insulin, marketed as Humulin, on October 29, 1982.

—*Charles L. Vigue*

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■ Carbohydrates

Digestion and Absorption

Dietary carbohydrates are macronutrients. Carbohydrates may be simple or complex, depending on their chemical structure and how quickly they are broken down and absorbed. Carbohydrates include monosaccharides, such as glucose, fructose, and galactose; disaccharides (two monosaccharides

linked together), such as sucrose, maltose, and lactose; and polysaccharides (many monosaccharides linked together in polymers), such as starches and fiber. Simple carbohydrates include monosaccharides and disaccharides, while complex carbohydrates include polysaccharides.

Carbohydrates are broken down into glucose by the enzyme amylase. Starches are first broken down in the mouth by salivary alpha-amylase and then in the small intestine by alpha-amylases of both salivary and pancreatic origin. Enzymes linked to the small intestine's inner lining: maltase, sucrase, and trehalase, further digest the resulting simpler sugars, yielding absorbable monosaccharides. These sugars cross the cells lining the small intestine via specialized molecular transport mechanisms and then diffuse into the intestinal capillaries and reach the bloodstream.

Metabolism

In the body, the primary role of carbohydrates is energy production and storage. Carbohydrates can also be joined to proteins (glycoproteins, for cell-cell interactions) or fatty acids (glycolipids, which provide energy and can be markers for cellular recognition).

The body converts most digestible carbohydrates into glucose, which is a universal energy source for cells. Cells store excess glucose as glycogen (glycogenesis), which is degraded (glycogenolysis) when energy is needed. Glucose is maintained at a constant level in the blood by the interplay of insulin, glucagon, and other hormones.

Carbohydrate-related diseases are often genetic, linked to inborn errors in enzymes or cellular transporters. Examples are galactosemia, glycogen storage diseases, and lactose intolerance.

Diabetes mellitus is a metabolic disorder characterized by excessive blood glucose. Insulin deficiency causes type 1 diabetes; type 2 results from insulin resistance, impaired insulin secretion, and increased glucose production.

According to the 2015–2020 Dietary Guidelines for Americans, carbohydrates, preferably starches and natural sugars, should represent 45 to 65 percent of total calorie intake. Refined simple sugars provide calories but very little nutrition, so their intake should be limited. Too much dietary sugar can lead to health problems such as tooth decay, malnutrition, and weight gain. Fiber-rich fruits and vegetables, whole grains, and legumes are healthy and nutritious sources of carbohydrates.

Perspective and Prospects

Food availability in developed countries has reached unprecedented levels. The per capita consumption of carbohydrates, particularly refined sugars, increased dramatically in the late twentieth and early twenty-first centuries. Since the 1990s, obesity rates have been climbing steadily, and so has the incidence of diabetes and related health problems. Current research in nutrition and carbohydrate metabolism is addressing the issue, which has reached epidemic proportions. Dietetic and pharmaceutical researchers have made significant progress in dietary manipulation and drug development.

Diets low in carbohydrates have gained popularity as a way to lose weight or to manage health problems such as diabetes, cardiovascular disease, and high blood pressure. Low-carb diets emphasize proteins such as meat, poultry, fish, and eggs and nonstarchy vegetables such as asparagus, brussels sprouts, cauliflower, celery, cucumbers, salad greens, peppers, and tomatoes. Low-carb diets exclude most grains, legumes, fruits, bread, sweets, pasta, and processed foods. Most low-carb diets recommend 2.2 to 4.6 ounces (60 to 130 grams) of carbohydrates per day, compared to the 7.9 to 11.4 oz (225 and 325 gm) of carbohydrates per day recommended by the Dietary Guidelines for Americans for individuals eating 2,000 calories a day. The American Heart Association reports that there is insufficient evidence for the heart-healthy benefits of low-carb diets in the long term. Still, the group recommends that individuals favor complex carbohydrates, such as legumes and whole grains, over simple sugars and processed foods.

—Donatella M. Casirola

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Carl F. Cori: The Metabolic Relationship between Glucose and Glycogen

During their research into carbohydrate chemistry in Buffalo, New York, Carl and Gerty Cori developed a procedure for measuring glucose phosphate in muscle tissue. Exposure of the muscle to the hormone epinephrine produced a significant increase in the concentration of this carbohydrate. Concurrently, there was a decrease in the level of free phosphate in that tissue. However, an unaddressed question remained, namely, if a relationship between the two events existed. Around the same time, a colleague of Carl Cori's, Polish biochemist Jakub Parnas, discovered that a decrease in glycogen concentration in tissue accompanied the reaction observed by the Coris. They named this process phosphorolysis, reflecting the reduction in phosphate levels. The Coris and Parnas decided to establish a collaborative relationship to investigate the discovery.

The nature of the results observed by the Coris suggested several metabolic steps were occurring during these reactions. They found that the reaction mixture's reaction rate significantly increased if they added adenosine monophosphate (AMP). The significance was initially unclear. The calculations addressing the changes in concentrations of the reactants and products of the reactions also produced discrepancies, explainable only if they assumed the production an unknown intermediate.

Carl F. Cori (photo courtesy of the Nobel Foundation)

Using a variety of purification steps, the Coris were able to crystallize this metabolic intermediate and determined it was an unusual form of modified glucose: glucose-1-phosphate. The molecule was eventually synthesized in the laboratory and was named the Cori ester.

The isolation of the intermediate was critical in explaining the results observed in previous experiments, and it provided a pathway for the conversion of glycogen into glucose. The degradation of glycogen yields its constituent glucose, but phosphate is added to glucose by an enzyme; the Coris named this enzyme glycogen phosphorylase. Phosphate consumption by this reaction explained the reduction in phosphate levels that the Coris had observed in the muscle tissue. The phosphorylase activity, in turn, is boosted in the presence of the AMP, which also explained the earlier results. The reactions that the Coris discovered were critical in understanding the interconversion of glucose and glycogen in the liver and muscles.

—Richard Adler

Fluids and Electrolytes

Structure and Functions

Humans live in a wide variety of environmental conditions. Some days are hot and wet, others are cold and dry, and most are somewhere between. At the same time, as foods and liquid are taken in, the body is exposed to a variety of chemical substances over a wide range of concentrations. Amid these widely changing circumstances, the internal environment, to which the body's cells are exposed, remains essentially unchanged. This regulation of the internal environment, which is called homeostasis, is necessary for the correct functioning of the body. Essentially, all the organs and tissues of the body play roles in the homeostatic processes, and the main control mechanism operates through the movement of body fluids.

There are several different body fluids, but they are all solutions of solutes in water. The identity of the solutes and their concentrations differentiates one body fluid from another. Among the solutes, two categories exist. Some solutes dissociate into electrically charged particles when they dissolve and are thus called electrolytes. Others remain as neutral particles dissolved in the water and are nonelectrolytes. Both types of solutes play important roles in the correct physiological functioning of the body, but it is the electrolytes that draw the most attention. This is the case because the fluids and the electrolytes are interdependent and because imbalances of these factors are associated with a vast array of illnesses.

Although subject to some variation with age, gender, and physical condition, the body is composed of about 60 percent water by weight. For purposes of classification, this water is considered to be present in compartments. It is important to recognize that this terminology is conceptual only and does not refer to the existence of any real, separate, water-containing compartments in the body. Approximately 25 cubic decimeters of water are contained within the body's cells; this is the intracellular fluid. Most of the remaining fluid, about 12 cubic decimeters, is termed extracellular and exists in the regions exterior to cells. The extracellular fluid is further subdivided into the categories of interstitial fluid, which surrounds the cells; intravascular fluid, which is located within the blood vessels; and transcellular fluid, which includes the fluid found in the spinal column, the region of the lungs, the area surrounding the heart, the sinuses, and the eyes, along with sweat and digestive secretions. These subcategories are listed in order of the amount of fluid present. Of all these types, only the intravascular fluid is directly affected when a person drinks or eliminates fluid. Alterations in the other regions occur in response to that change, however, and there is a continual dynamic exchange of fluid among all compartments. The balance of conditions created by this exchange determines the state of health of the individual.

The solutes that are electrolytes generate positively charged ions called cations and negatively charged ions called anions. The amount of positive charge present in a solution is always equal to the amount of negative charge. The major cations present are hydrogen, sodium, potassium, calcium, and magnesium. The most important anions are chloride, hydrogen carbonate, hydrogen phosphate, sulfate, and those derived from organic acids such as acetic acid. Several other ions of both types are present at very low levels. The nonelectrolytes present include urea, creatinine, bilirubin, and glucose. All these solutes are involved with particular biological changes in the body, so their presence at the correct concentration is vital.

The fluid and its solutes move within the body by means of several transport mechanisms, some of which move solutes through the fluid and some of which move either water or the solutes from one side of a cell membrane to the other. The mechanisms available are diffusion, active transport, filtration, and osmosis. Diffusion is the movement of particles through a solution from a region in which the concentration of the particles is high to a region in which it is lower. The energy that drives this motion is thermal energy, and the transport rate is increased by increasing the temperature, which increases the concentration difference from point to point and is faster for smaller particles. Cell walls are a barrier to this type of transport unless the solute particles are small enough to pass through pores in the wall or are soluble in the cell wall itself. Active transport provides another means of moving solutes across cell walls. The energy for such movement is provided by a series of chemical reactions involving adenosine triphosphate. The movement of sodium out of and potassium into cells, as well as

the transport of amino acids into cells, occurs in this manner. Filtration is a means by which both water and some solutes are transported through a porous membrane. The solutes transported are those that are small enough to pass through the pores in the membrane. The driving force for filtration is provided by a difference in pressure on the two sides of the membrane, and the motion occurs from the high-pressure side to the low-pressure side. The pressure in this case results from gravity and from the pumping action of the heart. Osmosis is a process by which water is moved across a semipermeable membrane as the result of the influence of a different type of pressure. When two solutions of different concentrations of solute particles are separated by a semipermeable membrane, an osmotic pressure develops that acts as the driving force to move water from the side of the membrane where the concentration of solute particles is lower to the side where the solute particle concentration is higher.

A solute's concentration in the body fluid has a great effect on the transport of materials and thus on the body's health. Concentrations in body fluids are expressed in several ways. Electrolyte concentration is often expressed in terms of milliequivalents of solute per cubic decimeter of solution. This is a measure of the amount of change, positive or negative, provided by that solute. A solution with twice the number of milliequivalents per cubic decimeter will have twice the concentration of change. This also measures the solute's combining power, because one milliequivalent of cations will chemically combine with one milliequivalent of anions. Osmolality, osmolarity, and tonicity refer to a solution's ability to provide an osmotic pressure. Osmolality and osmolarity are proportional to the number of particles of solute present in the solution. When solutions of different osmolalities or osmolarities are separated by a semipermeable membrane, there will be a flow of solvent across the membrane. Isotonic solutions have equal osmotic effects. Tonicity is a way of comparing the osmotic potential of solutions by referring to one as being hypotonic, isotonic, or hypertonic to the other.

Disorders and Diseases

There are two ways to approach thinking about the health role of body fluids and electrolytes. One is to consider one particular fluid component, such as sodium, that is out of balance and proceed to trace possible causes of the imbalance and appropriate treatment modes. It must be noted, however, that there are many possible illnesses that could cause any particular imbalance. The second approach is to consider a representative number of specific diseases and to look at their effect on the fluid and electrolyte balance and how such effects may be treated.

The first of these two approaches is adopted here because it highlights the fluids and electrolytes themselves rather than the diseases. Two imbalances will be considered as examples of the types of effects seen. First to be considered is the volume of fluid itself. Second, the balance of calcium will be given attention because of the connection of calcium deficiency with the bone brittleness that often occurs during aging.

Volume imbalance that is larger than the system's normal regulatory ability to control may occur in either the intracellular or extracellular fluid or both and may be in the direction of too little fluid (dehydration) or too much (overhydration). Both of these effects may result from a number of underlying illnesses, but each is, by itself, life-threatening and requires direct treatment. Often, this treatment precedes the diagnosis of the root cause.

The body apparently senses fluid volume imbalance with receptors near the heart, and several coping responses are triggered. Dehydration can be the result of vomiting, diarrhea, excessive perspiration, or blood loss. In such cases, the body's responses are in the direction of maintaining the flow of blood to vital organs. Vessels at the extremities are constricted, and those in the regions of the vital organs are dilated. Kidney function is greatly slowed, the reabsorption of sodium is increased, and the production of urine is markedly decreased, ensuring water retention. Centers in the hypothalamus respond and cause the individual to become thirsty. Thus, the body acts to protect its most important functions while at the same time stimulating actions from the individual that will bring additional fluid volume into the system. The manner in which the individual responds to being thirsty will determine other bodily changes. If plain water is used to quench the thirst, the extracellular fluid becomes less concentrated in electrolytes than is the intracellular fluid, causing an osmotic

pressure imbalance that the body regulates by transporting more water into the cells, producing overhydration there and aggravating the original dehydration in the extracellular fluid. Notice that this means that drinking large amounts of water can, strange though it may seem, cause dehydration. If saltwater is ingested, the reverse occurs, with a resulting dehydration of the cells that in turn triggers extreme thirst but few cardiovascular problems. Proper volume replacement thus requires that the water brought into the system be of the same electrolyte concentration as the cellular fluids—that is, that they be isotonic. In that case, the osmotic pressure remains balanced and the fluid volumes in both of the major compartments can be built up.

Diabetes insipidus results from inadequate production of antidiuretic hormone by the posterior pituitary. Antidiuretic hormone induces water resorption by the kidneys. Without proper secretion of this hormone, the kidney excretes large quantities of water, causing significant dehydration. The sizeable water loss also increases sodium concentrations in the blood (hypernatremia).

Diabetes mellitus results from insufficient insulin signaling. The liver responds to poor insulin signaling by releasing large amounts of glucose and ketone acids into the blood. These molecules are excreted by the kidneys into the urine with lots of water. This causes dehydration, electrolyte imbalances, and acid-base disruptions.

Overhydration is a less common occurrence that is usually associated with cardiovascular disease, severe malnutrition and kidney disease, or surgical stress. When the heart is not able to act as an effective pump, a back pressure builds in the circulatory system that causes fluid to be filtered through the walls of the vessels and that results in the accumulation of fluid in the interstitial regions around the heart and lungs. A decrease in proteins in the bloodstream, resulting from either malnutrition or kidney malfunction, lowers the osmotic pressure in the blood and causes water retention in the interstitial spaces. Accumulation of excess fluid in the interstitial spaces is called edema. This same end condition also arises when the kidney excessively filters fluid from the bloodstream into the interstitial spaces. The treatment of overhydration takes the form of fluid intake restriction, restriction of dietary sodium, and the use of diuretic therapy to stimulate urine production.

Calcium, much of which comes from milk and milk products, is the fifth most abundant ion in the body and is involved with the formation of the mineral component of teeth and bones, the contraction of muscles, proper blood clotting, and the maintenance of cell wall permeability. Calcium is added to extracellular fluid as a result of the intestinal absorption of dietary calcium and bone resorption. It is lost from the extracellular fluid via secretion into the intestinal tract, urinary excretion, and deposition in bone. The maintenance of a proper calcium level mainly depends on processes occurring in the intestinal tract. Only a very small part of the body's total calcium is in fluids. Both hypocalcemia and hypercalcemia, the shortage and the overabundance of calcium in the fluids, may occur. Unlike the case of water shortage or excess, however, there are few direct visual consequences of a calcium imbalance; one must rely on laboratory testing of the fluid and on indirect physical assessment.

Hypocalcemia in the blood is associated with reduced intake, increased loss, or altered regulation, as in hypoparathyroidism. Bone, a living material, continually absorbs and desorbs calcium. The parathyroid gland secretes a hormone that regulates bone resorption and thus can raise the calcium level in the extracellular fluid at the expense of decreasing the amount of bone. Obviously, this cannot be a long-term mechanism to provide calcium. The same hormone also regulates the absorption of calcium from the intestines and the kidneys. Vitamin D is an essential, although indirect, factor in permitting the absorption of calcium from the intestine. A deficiency of this vitamin is a major cause of hypocalcemia. When the calcium level in the extracellular fluid falls below normal, the nervous system becomes increasingly excited. If the level continues to fall, the nerve fibers begin to discharge spontaneously, passing impulses to the peripheral skeletal muscles, where they cause a contractive spasm. Often, this is first seen in a contracting of the fingers. Generalized muscular spasming can be lethal if the calcium imbalance is not corrected quickly. Immediate calcium deficiency is treated with the administration of either oral or intravenous calcium compounds, with vitamin D therapy, and with the inclusion of foods of

high calcium content in the diet. In the longer term, treatment of the underlying illness is necessary.

The opposite imbalance, hypercalcemia, can occur as a result of an excessive intake of calcium supplements and vitamin D, in conjunction with a high-calcium diet. Calcium excess is also associated with some tumors and with kidney or glandular diseases. It has also been found to be caused by prolonged immobility, in which case the bones resorb because of the lack of bone stress. This latter effect has been of major concern in the space program. Too high a level of calcium in the intercellular fluid causes a depression of the nervous system and a slowing of reflexes. Lack of appetite and constipation are also common results. At very high levels, calcium salts may precipitate in the blood system, an effect that can be rapidly lethal. Again, in the long term, the underlying cause of the imbalance must be corrected, but treatments do exist for more immediate alleviation. As long as the kidneys are functioning correctly, intravenous treatment with saline serves as a means of flushing out excess calcium. Calcium also can be bound to phosphate that is delivered intravenously, but there is a risk of causing soft tissue precipitation of the calcium phosphate compound. Dietary control is used, at times in concert with steroid therapy, to counter high calcium levels. If resorption is the cause of the excess, there are therapies, both chemical and physical, that are effective in increasing bone deposition.

Perspective and Prospects

From the earliest times, those concerned with the treatment of illnesses have had their attention drawn to the fluids present in or exuded by the human body. The color, smell, and texture of fluids being given off by a sick or injured person provided clues to the nature of the illness or injury. Bleeding was commonly practiced as a means of venting the illness so that health could be restored. Lancing of ulcerative conditions was also practiced by early healers. These early attempts at understanding and of treatment have been greatly refined, and the search for better understanding and improved treatment modes continues.

This concern with fluids and electrolytes is easy to understand. The fluids and their components constitute both the external and the internal environment for all the body's tissues and cells. Any abnormality in the cells or tissues is reflected in a variation from normal conditions in the fluids. All major illnesses and many minor ones have associated with them a fluid and electrolyte disorder. Fluids are more readily accessible for study than are tissues from deep within the body; hence, a considerable effort has been directed at measuring fluid constituents and interpreting the findings. The testing of fluids has evolved from highly labor intensive measurements of a few components to highly automated testing procedures applied to dozens of components. The reliability and precision of the measurements continue to increase, and the scope of measurements continues to expand.

Not all that is to be known about fluids and electrolytes, however, depends on laboratory testing. Some knowledge can be collected from close observation of the patient. Although the resulting measurements are not precise, they are nevertheless important because they are much more immediately available. Physical symptoms that carry information about fluids and electrolytes include the following: sudden weight gain or loss; changes in abdominal girth; changes in either the intake or output of fluids; body temperature; depth of respiration; heart rate; blood pressure; skin moisture, color, and temperature; the skin's ability to relax to normal after being pinched; the swelling of tissue; the condition of the tongue; the appearance of visible veins; reflexive responses; apparent mental state; and thirst. Each of these observations, and more, is readily available to one who is monitoring the health of an individual.

As is the case with most testing and data-gathering situations, interpreting the test and observation results is the critical step. Any one measure, by itself, points to a vast array of possible illnesses. Only by considering the whole and recognizing the existence of patterns in the information can a health professional narrow the possibilities. It is this recognition of patterns that develops with education and experience, and it is this step that relies on judgment that makes medicine an art as well as a science.

—Kenneth H. Brown

Further Reading

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