HANDBOOK OF
ENDOCRINOLOGY
Second Edition
VOLUME I

EDITED BY
George H. Gass
Harold M. Kaplan


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PREFACE

This *Handbook of Endocrinology, Volumes I and II,* presents a review of selected topics by 36 authors. Each topic is broad in scope and intensive in approach. The endocrine literature is now so extensive that it would take several volumes to encompass it.

The present book is a general reference source for the academic endocrinologist, teacher, and researcher, for graduate students working in current areas of the field, and for biologists interested in the chemical control of bodily systems, adjunctive to neural regulation. Physicians with special interests in endocrinology will find chapters that have considerable relevance to their work. The references provided herein are numerous and updated. The descriptions of the endocrine processes provide data in the fields of anatomy, histology, physiology, and pathophysiology.

Overall, the reader will have access to a comprehensive survey of the chemical nature of hormones, their synthesis, secretion and transport, their actions and mechanisms of action, and their degradation and excretion, in mammals and man.

The editors fully appreciate the expertise and the large amount of time spent by the contributors. This book is their work.

George H. Gass
Harold M. Kaplan

THE EDITORS

George H. Gass, Ph.D., is the retired Chairman of the Department of Basic Medical Sciences of the Oklahoma State University College of Osteopathic Medicine (formerly the Oklahoma College of Osteopathic Medicine and Surgery). Previously he held the position of Director, Endocrinologic Pharmacology Research Laboratory at Southern Illinois University, during which time he also held the positions of Professor of Physiology and Professor of Medicine. He has had a very diverse career, including industry (Lederle Laboratories) and government (Food and Drug Administration).

Dr. Gass was awarded his doctorate at The Ohio State University. Following graduation Dr. Gass served in the Endocrine Branch of the Food and Drug Administration in Washington, D.C., where he performed biological assay procedures, biostatistics, and endocrine research for four years before leaving to enter higher education. Dr. Gass' best known work in the Food and Drug Administration was in the co-development of the uterine weight method for estrogen assay and detection. Dr. Gass assumed his duties at Southern Illinois University, Department of Physiology, in the fall of 1959 and immediately upon arrival set up the Endocrinologic Pharmacology Research Laboratory. A number of students obtained their research experience under Dr. Gass in that laboratory, where it was first discovered that a quantitative measure of a chemical carcinogen (diethylstilbestrol)-dose response of mammary tumors existed. This research has become a classic and, although published in 1964, has more recently been repeated by the Center for Toxicological Research with Dr. Gass consulting.

Dr. Gass, as a member of the staff of Southern Illinois University, received a number of honors and served on numerous occasions as a consultant for government and industry. Dr. Gass is a fellow of the American Association of Science, an Alexander von Humboldt fellow, and a Fullbright alumnus.

He was requested to serve as a consultant for the National Center for Toxicology, Food Administration, to help determine the carcinogenicity and estrogenicity of female sex hormones, both naturally occurring and synthetic. During his 18 years at Southern Illinois University he taught physiology and pharmacology. His last position as Chairman of the Department of Basic Medical Sciences allowed him intimate contact with the basic scientists in the college, including those in human anatomy, histology, pharmacology, physiology, behavior, and biochemistry.

Harold M. Kaplan, Ph.D., is Visiting Professor in the Medical Preparatory Program in the School of Medicine at Southern Illinois University (SIU) at Carbondale. Dr. Kaplan received the A.B. degree at Dartmouth College in 1930, the A.M. degree at Harvard University in 1931, and the Ph.D. degree at Harvard in 1933. He was an Assistant Instructor at Harvard, 1933–1934, and Instructor to Professor of Physiology at Middlesex University Medical School in Massachusetts, 1934–1945, as well as Department Chairman for many years. He was Professor of Veterinary Physiology and Department Chairman at Brandeis University from 1945 to 1947. He was Associate Professor of Physiology at the University of Massachusetts at Fort Devens from 1947 to 1949, serving as Department Chairman in 1948–1949. Dr. Kaplan was Associate Professor at SIU in 1949 and became Professor of Physiology and Department Chairman in 1971. He was simultaneously a professor in the SIU School of Medicine from 1974 to the present. He was Director of the SIU Animal Quarters (Vivarium) intermittently from 1950 to 1982.

Dr. Kaplan was President of the Illinois State Academy of Science, 1969–1970, and is both a life member and honorary member. He was President of the American Association for Laboratory Animal Science, 1966–1967, and is a life member and honorary member. He was on the Board of Directors of the Institute of Laboratory Animal Resources, 1965–1969, and the Illinois Society for Medical Research, 1962–1986. He was on the Science Advisory Committee at Illinois Wesleyan University, 1970–1976. He was President of Sigma Xi (National Honor Society) SIU chapter, 1989–1990, as well as Phi Kappa Phi (National Honor Society), SIU chapter, 1976–1977 and 1983–1984. He was an editorial advisor for the National Forum, 1986–1989. He was President of the Emeritus Faculty Organization at SIU, 1993–1995. Dr. Kaplan has served as Science Consultant for the Applied Research and Development Laboratory in Mt. Vernon, IL, since 1983. He is a fellow of the AAAS. He was Chairman of the Editorial Board, Laboratory Animal Science, 1963–1974.

Dr. Kaplan is the co-author of about 200 research papers and has written 10 books. He is a contributor to five chapters in an accepted biological laboratory text.

CONTRIBUTORS

Nancy A. M. Alexiuk
Department of Anatomy
University of Manitoba
Winnipeg, Manitoba, Canada

Rebecca S. Bahn
Mayo Clinic
Rochester, Minnesota

Andrzej Bartke
Department of Physiology
Southern Illinois University
School of Medicine
Carbondale, Illinois

John B. Buse
Diabetes Care Center
Chapel Hill, North Carolina

Monica E. Doerr
Division of Endocrinology
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

Warren E. Finn
Department of Physiology & Pharmacology
College of Osteopathic Medicine
Oklahoma State University
Tulsa, Oklahoma

Milton D. Gross
Department of Internal Medicine
University of Michigan Medical Center
Ann Arbor, Michigan

Charles A. Hodson
Department of Obstetrics & Gynecology
East Carolina University
Greenville, North Carolina

Abby Solomon Hollander
Pediatric Endocrinology
St. Louis Children's Hospital
St. Louis, Missouri

Kathleen A. Jones
School of Medicine—MEDPREP
Southern Illinois University
Carbondale, Illinois

Bess Adkins Marshall
Pediatric Endocrinology
St. Louis Children's Hospital
St. Louis, Missouri

Brahm Shapiro
Department of Internal & Nuclear Medicine
University of Michigan Medical Center
Ann Arbor, Michigan

William E. Sonntag
Department of Physiology & Pharmacology
Gray School of Medicine at Wake Forest
Winston-Salem, North Carolina

Richard W. Steger
Southern Illinois University
School of Medicine
Carbondale, Illinois

Jerry Vriend
Department of Anatomy
University of Manitoba
Winnipeg, Manitoba, Canada

Hing-Sing Yu
Institute of Environmental Science
& Technology
San Antonio, Texas

TABLE OF CONTENTS

Chapter 1

SUMMATION OF BASIC ENDOCRINE DATA

Kathleen A. Jones

CONTENTS

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THYROID GLAND

TRIIODOTHYRONINE AND THYROXINE

Structure, Development, and Aging

The thyroid is present in all vertebrates. In humans, it has two lobes, connected by an isthmus, on either side of the trachea. It is enervated by parasympathetic and sympathetic fibers, which control only the diameter of the blood vessels they are in. Histologically it is composed mostly of follicles, containing colloid, which is thyroglobulin. There are also parafollicular cells, which produce calcitonin.

The gland begins to develop in the third embryonic week as an evagination of the pharynx and is clearly differentiated in the 15th week, producing thyroxine. The ultimobranchial body from endoderm cells of the sixth pharyngeal pouch is incorporated into the thyroid and produces the parafollicular or C cells. Thyroid tissue is present in all vertebrates.

Marked changes occur in the thyroid with age. Its structure then resembles the gland when it is in a state of hypothyroidism. Connective tissue increases and many follicles are obliterated. The gland is not essential to life, but its functions are.

Classification

The two chief hormones are L-thyroxine (T_4) and 3,5,3′-1-triiodothyronine (T_3). Another is reverse T_3 (rT_3). Thyroglobulin is the storage form and has no hormonal properties per se. Very little thyroglobulin enters the circulation. Calcitonin, secreted by the C cells, will be considered separately. The hormones T_3 and T_4 are glycoproteins.

Biosynthesis

The synthesis starts with iodide, which the thyroid follicles actively take up. The iodide is oxidized to active iodine, which is incorporated into tyrosine. This is followed by peptide linkages, which are glycoproteins called thyroglobulin. Monoiodotyrosine (MIT) and diiodotyrosine then develop. These couple to form T_3 and T_4, although very little rT_3. An enzyme called thyroid peroxidase catalyzes the whole sequence of reactions.

Release

To obtain the release of T_3 and T_4, there is proteolysis of thyroglobulin followed by endocytosis. Thyrotropin-releasing hormone (TRH), which is hypothalamic in origin, stimulates the pituitary to synthesize and release the thyroid-stimulating hormone (TSH). This promotes the uptake of iodide by the thyroid.

Normal Bodily Effects

The effects vary with the specific hormone that is circulating to the cells of the body. The material stored in colloid as thyroglobulin is translocated to the lumen of each thyroid follicle. T_4, which is necessary for life, is the dominant circulatory form and gives rise to most of T_3 and just about all of rT_3. The hormones circulate almost totally bound to proteins. Thyroxine-binding globulin is the major binding protein; it is a glycoprotein-α-globulin. Other binding proteins are albumin and a thyroid-binding albumin.

A major effect is to increase protein synthesis in all bodily tissues. T_3 is about four times as active metabolically as T_4; T_3 has about two-thirds of the biologic activity of the thyroid hormones. There are effects on thermoregulation, food metabolism, growth and development, reproduction, water and electrolyte activities, and neural behavior.

Basis of Bodily Effects

Thyroid-stimulating hormone is involved, from the anterior pituitary. It binds to the membranes of the follicles and stimulates adenylate cyclase. cAMP is produced, but its control over T_3 and T_4 release needs further study. T_3 and T_4 can enter virtually all body cells when unbound.

CALCITONIN (THYROCALCITONIN)

Structure, Development, Aging

Since calcitonin is produced in the thyroid gland, refer to relevant data for the thyroid. The parafollicular cells of the thyroid are the secretory elements for calcitonin. These originate in the neural crest in the fetus. In vertebrate animals there is an origin in the ultimobranchial body. Calcitonin concentration in the plasma reduces with age and is generally lower in women than in men.

Classification

Calcitonin is a single-chain polypeptide, containing 32 amino acids, with a molecular weight of about 3500. There are species differences in the amino acid sequence. This suggests that the specific sequence order determines the characteristic action. Human calcitonin has been synthesized.

Biosynthesis

Calcitonin is produced in the human thyroid gland in parafollicular cells that lie in the interstitial tissue among the thyroid follicles. The precursor of calcitonin is preprocalcitonin, which hydrolyzes to calcitonin and other polypeptides. The gene for calcitonin is transcribed and changed to a different mRNA in the brain, a peptide called calcitonin-gene-related peptide, whose function other than vasodilation is unknown.

Release

Calcitonin secretion and release increase when the thyroid gland is normally perfused with high plasma concentrations of calcium. Potent natural stimulants include gastrin, dopamine, estrogen, β-adrenergic agonists, and other substances. In man, the thymus and parathyroid may secrete some calcitonin. Hypercalcemia may be the major stimulus for calcitonin secretion.

Normal Bodily Effects

Calcitonin decreases circulating calcium and phosphate levels by inhibiting release of these substances from bone to plasma. This is opposite to the action of the parathyroid hormone (PTH; parathormone). Calcitonin is a short-term regulator of calcium ion concentration, whereas PTH is a long-term regulator that more than offsets the calcitonin effects. Thus, overall, the calcitonin control in the human adult is weak. The hormone has a half-life less than one hour and is excreted by the kidneys. Its peak effect is less than one hour. Calcitonin may be effective against hypercalcemia caused by excessive calcium intake. Whether it is essential for development and maintenance of the skeleton is not clear.

Basis of Bodily Effects

The mechanism underlying the effects involves calcitonin receptors in bones and kidneys. The action permitting the decreasing of calcium in plasma is the inhibition of bone resorption induced by cAMP. There is an increase in osteoblastic activity, but this lasts only a few days. The prolonged effect is in preventing the formation of osteoclasts. In the long run, the parathyroids regulate the level of extracellular calcium.

PARATHYROID GLAND

PARATHYROID HORMONE

Structure, Development, and Aging

There are two pairs of parathyroid glands in man. Each is close to the posterior wall of the thyroid glands. The parathyroids are present only in vertebrates. They secrete PTH.

In the fetus at the fifth week the endoderm of the third pharyngeal pouch differentiates into the inferior aspect of the parathyroids. The endoderm of the fourth pharyngeal pouch is the superior aspect.

The parathyroid glands in the adult human are composed mainly of chief and oxyphil cells. The chief cells secrete PTH and persist throughout life.

Classification

The hormone, PTH, is a single-chain polypeptide containing 84 amino acids.

Biosynthesis

PTH is synthesized as a large precursor molecule on the ribosomes. The precursor is transported to the endoplasmic reticulum in which preproparathyroid hormone is enzymatically changed to proparathyroid hormone and the latter is sent to the Golgi apparatus. The resulting definitive hormone is encapsulated into granules, which are released as the ionized calcium in the extracellular fluids is decreased.

Release

It is the level of ionic calcium in the blood that controls hormonal secretion by way of a negative feedback system. The volume of secretion varies inversely with the calcium level.

Normal Bodily Effects

The major effect is to increase the plasma calcium level. About 90% of the calcium in the body is sent to bone, as a calcium phosphate compound. The hormone degrades the bone matrix. Many other hormones are also involved in bone activity, mostly for growth (e.g., growth hormone and sex hormones) and bone catabolism (e.g., thyroid and glucocorticoids).

PTH promotes calcium resorption by the renal tubules as well as by the renal excretion of phosphates. Still another area of activity is absorption of calcium from the small intestine to the blood, but this involves the adjunctive action of vitamin D.

Basis of Biological Effects

PTH activates adenylate cyclase in bone and kidney, resulting in cAMP production. Since all varieties of bone cells have PTH receptors, the cAMP levels are responsive to PTH. The first effects of PTH occur in minutes, but the subsequent events take days to weeks and involve proliferation and resorption of bone.

PTH increases plasma calcium by decreasing its absorption through the kidney. It augments calcium absorption from the alimentary canal and brings calcium from bone to plasma.

VITAMIN D

RELATIONSHIP TO PARATHYROID HORMONE

Structure

Vitamin D is a general term for a variety of related compounds which are determined by the chemical pathway of their formation. The one of interest herein is vitamin D_3 (cholecalciferol). Other forms will not be discussed. Vitamin D_3 is synthesized in the skin by the action of sunlight.

Classification

Vitamin D is a sterol.

Biosynthesis

The most important member of the group of related sterols comprising vitamin D is D_3. The ultraviolet light of the sun produces it in the skin of mammals. The light activates certain provitamins, e.g., 7-dehydrocholesterol.

Vitamin D is not per se the active chemical that causes the effects once ascribed to the compound. It has to be changed in the liver to cholecalciferol, which is then converted in the liver to 25-hydroxycholecalciferol. The latter conserves D_3 by allowing it to be stored in the liver for several months.

The final conversion is from 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, which is the most potent form of vitamin D. This conversion occurs in the kidneys and cannot proceed in the absence of the kidneys or the parathyroid hormone. The hormone secretion is itself controlled greatly by plasma calcium ion concentration and the same is the case for 1,25-dihydroxycholecalciferol.

Release

The vitamin D_3 is transported in the plasma bound to a globulin which is called vitamin-D-binding protein (DBP). It is this form that transports vitamin D_3 from the skin to the blood. Some vitamin D_3, which travels in the blood, is exogenous.

Normal Bodily Effects

Vitamin D, generally considered to be a hormone, acts with PTH as the chief regulators of calcium and phosphorus activities. It is antirachitic and is an essential cofactor for PTH. The PTH promotes formation of the active metabolite of vitamin D.

Vitamin D_3 causes resorption of bone much like PTH does. Small amounts of the vitamin can calcify bone, by increasing the absorption of calcium and phosphate from the intestine.

Vitamin D_3 is more important than PTH in maintaining skeletal structure and function. The targets of the vitamin's active metabolites are bone and intestine. D_3 is a potent stimulator of calcium absorption from the intestine and it facilitates the rate of formation of bone. Pharmacologic doses stimulate resorption of calcium from bone into the blood.

Biochemical Basis of Bodily Effects

The mode of action of vitamin D_3 may involve a metabolite of D called 1,25-dihydroxycholecalciferol; this metabolite increases the transport of calcium across cell membranes, acting as a hormone, and it also aids formation of calcium-binding protein in the intestinal cells, as well as causing formation of ATPase in the lining cells affected. The same metabolite also aids phosphate absorption, acting perhaps through a calcium-absorption mediator.

Bone contains exchangeable calcium that is in equilibrium with calcium in the extracellular fluids. This provides a quick buffering system which keeps extracellular calcium ions from rising or falling excessively.

THYMUS GLAND

Structure, Development, and Aging

The thymus is a lymphoepithelial endocrine gland located in the mediastinum, and it extends from the thyroid in the neck into the thoracic cavity. It is well developed before birth. It reaches maximum size at about two years of age and then gradually regresses, especially after puberty. Only about 15% of its structure remains at age 50. The gland is replaced by fatty tissue, which decreases its capacity to provide T cells in later life. The origin of the gland in the fetus is mainly the third but also the fourth pharyngeal pouches. The earliest origins of the thymus, thyroid, and parathyroids are virtually common. Thymic tissue is present in every vertebrate.

The thymus is involved in T-lymphocyte activity. The precursor cells of these lymphocytes start their development in the fetus, and the process continues from the neonate throughout life. The cell production eventually passes from the bone marrow to the thymus and thence to the peripheral lymph tissues. The thymus can produce T cells independently of the bone marrow. For B-lymphocytes, the bone marrow is the area of maturation, and the cells migrate to the lymphoid organs. Both B and T cells can undergo mitosis in the peripheral lymphoid structures. Among the lymphoid structures, the thymus has the highest rate of cell proliferation.

Classification

The earliest thymic factor, extracted from animals, was called thymosin (thymic hormone). This is the best characterized of the thymic humoral factors. Thymosin α-1 (molecular weight 3,100) and β-4 (molecular weight 5,250) are both peptides. Thymopoietin (molecular weight 5,500), thymic humoral factor (molecular weight 3,200), and protein human thymic factor (molecular weight 56,700) are polypeptides. Serum thymic factor (molecular weight 847) is a nonapeptide.

Biosynthesis

Because the thymic hormones are virtually all polypeptides, their synthesis is the same as that of proteic substances in general.

Release

The thymus is very sensitive to other hormonal influences. Nonhormonal agents also influence the rates of synthesis and secretion, and their identification and chemical changes require more information and definition.

Normal Bodily Effects

The thymus is involved in producing lymphoid cells that travel to organs such as the lymph nodes and the spleen. The T-lymphocytes are important in thymic function. They are active in cellular immunity. Some, called helper cells, secrete lymphokines, the most important being interleukin-1 (IL-1) and interleukin-2 (IL-2). IL-1 is a polypeptide whose chief origin

is the macrophage. This substance stimulates production of IL-2 as well as B-lymphocytes. IL-2 activates the hypothalamus in the production of fever. IL-2 also acts as a growth factor that stimulates proliferation of B and T cells, suppressor T cells, and also natural killer cells which are not thymic in origin.

T-lymphocytes secrete not only the lymphokines mentioned above, but also interferon (for antiviral and antitumor function), macrophage-activating factor (which promotes phagocytosis), chemotactic factors (which attract leukocytes to an infected region), and a macrophage-migration inhibiting factor (which prevents phagocytes from leaving an infected area). T-lymphocytes, unlike B-lymphocytes, do not form plasma cells or antibodies.

The thymus is involved as a site of origin in autoimmune disease. In myasthenia gravis, where there is great muscular weakness and fatigue, acetylcholine receptors at neuromuscular junctions are significantly decreased in number. The B-lymphocytes that function specifically for the production of acetylcholine receptor antibodies play a major part in the autoantibody response. T cells also produce acetylcholine antibodies and are numerous in the thymus of patients with myasthenia gravis.[1]

Basis of Bodily Effects

All the thymic hormones interact with specific cell receptors, leading to the production of cAMP or gAMP. This eventuates in the expression of the T cell actions.

PINEAL GLAND

Structure, Development, and Aging

The pineal gland (epiphysis) originates in the brain. The caudal diencephalic roof plate gives rise to the midline diverticulum which becomes the gland. Proliferation of cells in its walls converts the gland into a solid pine cone-shaped organ, about 8 mm long.

The exact importance of the pineal gland is unknown; its position suggests that it is at least in part the homologue of the third or parietal eye of lower vertebrates. In these vertebrates it has both nerve cells and light receptors, but there are no light-sensitive structures in the human pineal gland.

The gland starts to involute just prior to puberty. It is large in human infants. In the adult, calcium often deposits, allowing the gland to be a landmark on an x-ray of the skull. The pineal gland may retain its production and activity throughout life.

Classification

The major active secretion of the pineal gland is melatonin. This is an indole, *N*-acetyl-5-methoxytryptamine. Melatonin is also known as melanocyte-stimulating hormone.

Biosynthesis

Melatonin is derived from tryptophan through a cascade of stages. The tryptophan is converted enzymatically (tryptophan hydroxylase) to 5-hydroxytryptophan, which changes to 5-hydroxytryptamine (serotonin) by aromatic L-amino decarboxylase. Serotonin *N*-acteyl transferase then changes serotonin to *N*-acetyl serotonin plus hydroxyindole-*O*-methyl transferase. The transfer of a methyl group from *S*-adenosylmethionine to the 5-hydroxyl of *N*-acetyl serotonin yields melatonin.

Release

The pineal gland transduces neural signals into the hormonal melatonin output. The secretion has a circadian rhythm associated with the 24-hour light-dark cycle. Light taken in by the eyes and sent to the brain through the optic nerve radiates to the sympathetic nerves that supply the pineal gland. The light reduces the output of norepinephrine from the nerve endings. Darkness, on the contrary, increases the output.

Normal Bodily Effects

Melatonin lightens the skin of frog tadpoles by an action on melanophores. In mammals its functions are still uncertain. It does not appear to control skin color in man.

In animals, melatonin may detect seasonal changes. It inhibits gonadal function in both sexes by blocking the production of pituitary gonadotropins. It is thought to regulate the onset of puberty, because it drops in concentration as puberty progresses.

The pineal gland is outside the blood-brain barrier because it has fenestrated capillaries and high cell permeability.

Basis of Bodily Effects

Stress activates the sympathetic nervous system to release catecholamines from the nerve endings. The release is increased in darkness and the pineal gland becomes involved. The gland is stimulated by adrenal medullary or neural hormones in that their secretions bind to β-adrenergic receptors. This activates adenylate cyclase and leads to the production of cAMP, then protein kinases, and finally the involvement of enzymes essential to the synthesis of melatonin. Most of the melatonin secretion occurs at night as part of a circadian cycle.

CIRCUMVENTRICULAR ORGANS

The circumventricular organs are sets of neurons situated around the borders of the ventricles of the brain. They include the subfornical organ, organum vasculosum, median eminence, area postrema, and pineal gland.

Their importance is that they lack a blood-brain barrier and contain fenestrated capillaries which permit neurons to receive substances, including certain hormones, to pass directly between the blood and the brain. Thus, the subfornical organ monitors angiotensin-II levels and projects into the hypothalamus. The area postrema monitors cholecystokinin and projects by lower nuclei to the hypothalamus. The organum vasculosum of the lamina terminalis monitors cytokines in the blood and projects to the brain stem and hypothalamus. The median eminence, pineal gland, and pituitary gland, all of which lack a blood-brain barrier, secrete their own hormones from the central nervous system into the general circulation. Some brain circumventricular organs recognize cytokines in the blood, and if the cytokines are transmitted to the brain, they contribute to the production of fever.[2]

ADRENAL GLAND

MEDULLA

Structure, Development, and Aging

The paired adrenal glands are located at the upper pole of each kidney. The adrenal medulla is a sympathetic postganglionic fiber in the fetus and it modifies to a gland. It is supplied only by preganglionic fibers. In the seventh or eighth fetal week, neural crest cells penetrate the adrenal cortex and become the adrenal medulla. The whole gland grows rapidly, peaking at midgestation, after which it grows more slowly and reaches the size found at birth.

Classification

The medulla produces two major hormones, epinephrine and norepinephrine. These are called catecholamines and are biogenic amines. The term "catecholamine" stems from the fact that these substances contain catechol (ortho-dihydroxybenzene) and a side chain with an amino group.

The compound called dopamine is another catecholamine which is in the intermediate synthetic chain in the synthesis of this group of hormones.

Biosynthesis

Catecholamines are produced from the amino acids phenylalanine and tyrosine. The catalysts for them, which are hydroxylases, are in the liver.

Tyrosine enters the adrenal medulla and also into those neurons where it can convert to L-dopa and then to dopamine; these changes utilize tyrosine hydroxylase and dopa decarboxylase. Dopamine is placed into granulated vesicles and changed to norepinephrine by the dopamine-β-hydroxylase.

Some neurons and cells of the medulla release norepinephrine from the vesicles and convert it by the action of phenolethynolamine-*N*-methyl transferase to epinephrine. The transferase is absent in early fetal development.

Release

In the adrenal gland, the medulla secretes norepinephrine and its derivative, epinephrine. Norepinephrine is also secreted by neurons of the hypothalamus and brain stem, and it is put out peripherally by postganglionic sympathetic neurons; some of the receptors affected cause excitation in the cells and others cause inhibition. Both compounds are released probably by exocytosis and are differentially bound to α or β receptors in the target organs.

The compound called dopamine is secreted by neurons of the substantia nigra. Upon release, it acts by way of dopamine receptors. The D_1 receptor activates adenylate cyclase whereas the D_2 receptor inhibits adenylate cyclase. In this process, hydrolysis of guanosine triphosphate is involved as a regulatory subunit for the adenylate cyclase activity. Epinephrine is typically a hormone whereas norepinephrine acts more as a neurotransmitter.

Normal Bodily Effects

Norepinephrine and epinephrine stimulate the nervous system. Their metabolic actions include glycogenolysis in liver and muscle and control over the metabolic rate. Norepinephrine constricts blood vessels via α receptors. Epinephrine dilates vessels via β_2 receptors and regulates cardiac muscle contraction via β_1 receptors.

Dopamine causes renal vasodilation, but vasoconstriction elsewhere. It forms a β_1 receptor complex which increases the cardiac force. Dopamine is also a precursor of norepinephrine. In the basal ganglia it may be a neurotransmitter.

Basis of Bodily Effects

The medulla for the most part releases epinephrine and norepinephrine simultaneously with their comparable neural stimulation. This provides a generalized, supportive action which is widespread. This activity requires only a low frequency of stimulation and a basal energetic tone. If the autonomic neurons are denervated, the tone may be restored by the intrinsic activity of the bodily structures involved.

Stimulation of parasympathetic or sympathetic nerves may cause either excitation or inhibition, depending upon the target organ, and this must be kept in mind for any autonomic effector under study. Norepinephrine excites chiefly α receptors, although β receptors to a lesser degree. Epinephrine excites α and β receptors about equally.

The catecholamines tend to act as first messengers, reacting in the target membranes with specific receptors. These in turn activate the second messengers within the target cells and a cascade of the observable events follows.

CORTEX

Structure, Development, and Aging

The cortex is the outer region of the retroperitoneal adrenal gland. All regions of the cortex secrete hormones, possibly 50 in number, but only a few are of major clinical importance.

The cortex forms in the sixth fetal week by condensation of mesoderm between the root of the dorsal mesentery and the gonad. The adrenocorticoid hormones of the cortex maintain their production and secretion throughout life.

Classification

The cortical hormones are steroids. These have a cyclopentane-hydrophenanthrene nucleus. Most but not all are called 17-ketosteroids because they have a keto group at position 17 on the molecule. Corticosterone does not form a 17-ketosteroid. Both glucocorticoids and mineralocorticoids have 21 carbon atoms.

Biosynthesis of Cortisol and Aldosterone

Cholesterol is the precursor of the cortical steroids. It is cleaved in the adrenal mitochondria to produce a 21-carbon molecule called pregnenolone. To produce cortisol, the pregnenolone is transformed in the mitochondria and forms the cortisol.

To produce aldosterone, pathways involving deoxycorticosterone and corticosterone (both originating from progesterone) occur. The corticosterone is enzymatically changed to 18-hydroxycorticosterone within the mitochondria. The enzyme called 18-hydroxysteroid dehydrogenase activates the chemical changes that produce aldosterone.

Release

The cortex can release any of the five varieties of hormones: (1) glucocorticoids (e.g., cortisol, corticosterone), whose primary action is to elevate blood sugar levels, (2) mineralocorticoids (e.g., aldosterone), which regulate ionic plasma sodium and potassium, (3) androgens, (4) progestins, and (5) estradiol. Groups 3, 4, and 5 are unimportant outputs of the cortex.

The release of aldosterone is regulated by (1) renin, (2) adrenocorticotropic hormone (ACTH; corticotropin) from the anterior pituitary, and (3) a direct effect of plasma sodium and potassium ion levels on the cortex. For cortisol, most that is released is bound to an α globulin and some to albumin. The bound cortisol serves as a reservoir. The free cortisol inhibits the release of ACTH. The latter is a more potent stimulus for the release of cortisol than for aldosterone. Cortisol secretion, like that of ACTH, exhibits diurnal variations in its output. There is little plasma level change with age.

Normal Bodily Effects

Glucocorticoids have many functions. Cortisol is the prime example and it is essential to life. It has a weak effect on electrolyte and water metabolism. It releases liver glucose, increases gluconeogenesis, stimulates protein metabolism in the liver, releases fatty acids from adipose tissue, inhibits fibroblasts and epithelial cell proliferation, lowers serum calcium, and has other effects. The net effect is catabolic.

Mineralocorticoids, aldosterone being the prime example, affect the distal tubules of the kidney, and thus promote resorption of sodium from the urine and excretion of potassium into the urine. These hormones are also antiinflammatory.

Basis of Bodily Effects

Aldosterone secretion is regulated chiefly by angiotensin and potassium, which directly stimulate the adrenocortical cells. Aldosterone exerts most of its effects by occupying a type 1 mineralocorticoid receptor which then binds to DNA and influences the transcription of various genes. Aldosterone may also react with a membrane-bound receptor.

Cortisol secretion is regulated for the most part by ACTH controlled from the anterior pituitary. The ACTH, in turn, is regulated by the corticotropin-releasing hormone (CRH) carried from the hypothalamus in its portal system to the pituitary gland where ACTH is stored and released.

ACTH acts on specific receptors in the adrenal cortex, whereupon adenylate cyclase, acting as a second messenger, induces the formation of cAMP inside the cytoplasm of the cells. In the cascade that follows, phosphoprotein kinases phosphorylate proteins. An important step is the subsequent activation of desmolase; this converts cholesterol esters to pregnenolone, upon which all later steps depend.

PITUITARY GLAND (HYPOPHYSIS)

POSTERIOR LOBE (NEUROHYPOPHYSIS)

Structure and Development

The pituitary gland is at the base of the brain, in a depression called the sella turcica. It is connected to the hypothalamus above by a hypophyseal stalk. The gland is divided into an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis), and between them a small structure called the pars intermedia. The posterior lobe hormones are manufactured first in the hypothalamus and then transported through a neurosecretory pathway to the posterior lobe where they are stored.

The pituitary develops from two distinctly different areas. For the posterior lobe, a neuroectodermal thickening called the infundibulum in the floor of the diencephalon, and which is composed of neuroglia cells, develops as the stalk and the pars nervosa (posterior lobe) of the neurohypophysis. The hypothalamus sends into the stalk a number of nerve fibers. Then, pituicytes resembling neuroglia cells proliferate in the distal end of the infundibulum.

Classification

The hormones stored in the neurohypophysis are vasopressin (antidiuretic hormone) and oxytocin. Both are polypeptides, with a sulfide link between two cysteines. The arginine vasopressin in man is essential for maximal activity. Both hormones contain eight amino acids; six of them are identical, but oxytocin has leucine and isoleucine instead of arginine and phenylalanine.

Biosynthesis

Both posterior pituitary hormones have been synthesized. The natural compounds are derived from precursor proteins within the hypothalamus. A protein carrier transports them down the axons in membrane vesicles to the neurohypophysis. Appropriate stimuli produce the action potentials within the hypothalamus all the way down the system to the neurohypophysis. There they discharge from nerve terminals.

Release

Vasopressin is synthesized mostly in the supraoptic nucleus of the hypothalamus whereas oxytocin is synthesized primarily in the paraventricular nuclei. Both hormones while still in the hypothalamus are packaged in neurosecretory granules, bound with a protein called neurophysin.

Several factors influence release from the posterior pituitary to the plasma. The hormones dissociate from neurophysin after their secretion. The hypothalamus responds first to any one or more of a great diversity of stimuli and in turn controls the hormonal release. As one example, the release is influenced by extracellular fluid osmolarity. Ingestion of water inhibits release.

Normal Bodily Effects

Vasopressin

The chief effect of this hormone is to maintain the osmolarity of the blood. This is accomplished by a marked antidiuretic effect. Water reabsorption by the kidney distal tubules and collecting ducts is activated.

Vasopressin stimulates smooth muscles of blood vessels, intestine, and uterus. This is a pressor effect. There is peripheral vasoconstriction, but the effect on blood pressure is weak.

Oxytocin

The effects are chiefly on reproductive functions in the female, although it is present in the male in whom the functions are obscure or nonexistent. Oxytocin is a marked stimulant of the pregnant uterus at term and also postpartum. It does not affect blood vessels, water diuresis, coronary arteries, or intestinal smooth muscle.

Basis of Bodily Effects

Vasopressin

Pores for the flow of water along osmotic gradients increase in size. The adenylate cyclase system is activated and the concentration of cAMP is increased.

The hormone promotes water conservation by the renal collecting ducts. In high concentration it causes vasoconstriction. The osmotic pressure of body water is the chief stimulus regulating hormonal secretion. The osmoreceptor cells of the hypothalamus sense the stimuli. This mechanism is the first line of defense in water balance control.

Oxytocin

This hormone causes smooth muscle cells surrounding the alveoli of the mammary glands to contract. Milk then flows from the alveoli to the large sinuses when the milk is to be expressed. The hormonal release is a response to impulses from the nipples during suckling.

For the uterus, the contraction of its smooth muscle cells is highly dependent on estrogen, although the mechanism of action of oxytocin is uncertain.

ANTERIOR LOBE

Structure and Development

The pituitary gland is divided into three parts: (1) anterior lobe, (2) posterior lobe, and (3) infundibulum. The anterior lobe is in turn divided into the pars distalis and pars tuberalis. These two sections plus a pars intermedia are usually termed the adenohypophysis. In the human infant, the pars intermedia can be seen between the pars distalis and the pars nervosa (neurohypophysis), but in adults fusion occurs between the greater lobes and the intermediate lobe becomes obscure.

The anterior lobe in the fetus forms from an ectodermal evagination of the stomodeum (primordial mouth) just anterior to the buccopharyngeal membrane (Rathke's pouch). At the third fetal week, this grows toward the infundibulum, which is a downward extension of the diencephalon. At the close of the second month, Rathke's pouch loses its connection with the mouth and comes into contact with the infundibulum. Cells in the pouch proliferate and form the anterior lobe of the pituitary gland. The pars intermedia develops from the posterior wall of Rathke's pouch. The infundibulum produces the stalk and the pars nervosa.

The hypothalamus develops a portal venous system to transmit its regulatory factors into the anterior lobe of the pituitary gland. The portal secretions are pulsatile. They induce effects through calcium, cAMP, and membrane phospholipid mediators.

Classification

Hormones secreted by the anterior pituitary are generally large proteins or glycoproteins. They include human growth hormone (hGH; somatotropin), ACTH, TSH, gonadotropic hormones (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), and prolactin (PRL).

In addition to the above, the hypothalamus produces releasing and inhibitory hormones (or factors) which regulate the anterior pituitary hormonal secretions. These include TRH,

CRH, growth hormone-releasing hormone (GHRH), growth hormone-inhibiting hormone (GHIH), gonadotropin-releasing hormone (GnRH), prolactin-releasing hormone (PRH), and prolactin-inhibiting hormone (PIH), which is probably dopamine.

Biosynthesis

FSH, LH, and PRL originate from basophilic cells of the anterior pituitary. Growth hormone (GH) comes from acidophilic cells. ACTH also comes from basophilic cells and it is classified as a polypeptide called β-lipoprotein (β-lipotropic hormone; β-LPH). The β-lipoproteins produce the endorphins and enkephalins, which are opioids which simulate narcotics such as morphine.

Although the hormones of the neurohypophysis are synthesized in the hypothalamus with their binding proteins, from which they are later separated, the situation for the anterior pituitary hormones is less well known. Being larger molecules, they probably do not need binding for the transport process.

Release

On the afferent aspect the hypothalamus receives its signals from various areas of the cerebral cortex and also from the lower brain and spinal cord. This releases the neurotransmitters, which link visceral and intellectual stimuli acting by way of the hypothalamus and from there to the anterior pituitary and finally to target organs. Stimulating the release of anterior lobe hormones is the major function of the hypothalamus in its relation to the anterior lobe of the pituitary. The hypothalamic control of releasing factors is a result of both humoral and neural afferent stimuli.

Normal Bodily Effects of the Hormones Produced Within the Anterior Pituitary

Growth Hormone

GH regulates bodily growth, including the skeleton, connective tissue, and visceral organs. This requires synthesis of nucleic acid and proteins. GH lipolyses fat cells and regulates the homeostasis of glucose. GH is inhibited by somatostatin, which comes from the delta cells of the pancreas and from the hypothalamus as GHIH.

Adrenocorticotropin

ACTH stimulates secretion of cortisol and adrenal androgens, stimulates utilization of glucose and release of fatty acids, and enhances release of insulin from the pancreas. It may also have an effect on behavior.

Thyroid-Stimulating Hormone

TSH is a polypeptide glycoprotein produced and released by the anterior pituitary gland. Its function is to produce and release T_3 and T_4 within the thyroid gland. The thyroid hormones are essential for bodily growth, development, and metabolism. The hypothalamus controls the TSH level through its TRH.

Gonadotropins (FSH and LH)

FSH activates the proliferation of ovarian follicles during the follicular phase of the ovarian cycle. In the male, it increases the activity of the seminiferous tubules.

LH is involved in the maturation of the ovarian follicles and their transformation to corpora lutea in the luteal phase of the nonpregnant ovarian cycle. In the male it stimulates the Leydig cells and the output of testosterone.

Prolactin

PRL is a peptide hormone stimulated mostly by pregnancy, nursing, sleep, and stress. It is produced in both sexes. In the female, its lactogenic and mammotropic effects involve

ovarian and adrenal steroids, insulin, and probably the thyroid hormones. It can produce an antigonadal action, such as the absence of the menses. Some effects are similar to those of GH.

Basis of Bodily Effects of Hormones Produced Within the Anterior Pituitary

Growth Hormone (GH)

GH is regulated by the GHRH and the GHIH, both originating in the hypothalamus. The ventromedial nucleus of the hypothalamus releases GHRH. The nutritional status of the body tissues may be a prime regulator of this release.

GH increases transport of amino acids through cell membranes. It enhances protein synthesis through RNA translation on the ribosomes and the transcription of DNA in the nuclei of cells. It also has a diabetogenic effect.

An adjunctive substance called somatostatin may act by inhibiting secretion of thyrotropin and other substances. It induces liver synthesis of peptide factors called somatomedins, which mediate the effects of GH on skeletal tissues.

Adrenocorticotropin

The activation of the rate of synthesis of adrenal cortical steroids by ACTH is by its stimulation of cholesterol to pregnenolone. ACTH brings about skin darkening by dispersing skin melanin. It has a lipolytic action by activating triglyceride lipase. It stimulates adenylate cyclase, producing a cascade of reactions.

Thyroid-Stimulating Hormone

TSH acts by binding to its specific receptor in cell membranes within the thyroid gland. Adenylate cyclase is activated and cAMP is increased, followed by the stages leading to thyroid development and functions.

Although TSH secretion is stimulated by TRH from the hypothalamus, it is inhibited by somatostatin and by T_3 and T_4 levels in the thyroid gland.

Gonadotropins (FSH and LH)

One of the substances in this category called human chorionic gonadotropin (hCG) produces effects similar to those of LH, but it is a placental hormone and will not be discussed at this point.

The receptors for FSH and LH are distinct. FSH activates adenylate cyclase in the membranes of the Sertoli cells of the testes and in the granulosa cells of the ovaries. LH activates adenylate cyclase, with the subsequent generation of cAMP followed by the appropriate cellular cascade of events.

Prolactin

PRL exerts its actions by binding to glycoprotein receptors, followed by augmented synthesis of mRNA for casein and α-lactalbumin. The lactogenic and mammotropic effects involve the adjunctive action of the hormones that follow. Estrogen and progesterone in the postpubertal ovary enhance proliferation of the mammary glands and this is facilitated by thyroid hormones and adrenal cortical steroids. Placental output of estrogens, progesterones, and gonadotropins is the final stage in the maturation of the mammary glands. Suckling is the mechanism in the production of milk. Suckling causes the release of oxytocin, thus producing contraction of the mammary myoepithelial cells.

Although secretion of most anterior pituitary hormones is controlled chiefly by stimulating hormones, PRL secretion is tonically inhibited by dopamine.

KIDNEY HORMONES

RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system, along with aldosterone from the adrenal cortex, is the prime regulator of sodium and potassium balance and of blood pressure-fluid volume homeostasis. Renin is the enzyme that initiates the synthetic processes leading to the formation of the active hormone, angiotensin-II (AT-II). In this synthesis, the release of aldosterone occurs. In turn, aldosterone acts on the renal distal tubules to bring about sodium resorption from tubules to plasma. In the process, plasma potassium levels become stabilized. The regulation of aldosterone output is controlled to a lesser degree by ACTH from the anterior pituitary.

Structure of the Kidney for Renin Output

Most renal nephrons lie close to the surface of the kidney and are called cortical nephrons. Those nephrons extending from the glomeruli that lie deep in the cortex are called juxtamedullary; these extend far down into the medulla of the kidney and then return to the cortex. Their epithelial cells in the distal tubule are called the macula densa; these send secretions toward the arterioles. Thus arterioles in close contact with the epithelial cells are packed with renin and are called juxtaglomerular cells. These cells plus the macula densa are called the juxtaglomerular complex. A paucity of sodium and chloride ions at the macula densa stimulates the juxtaglomerular cells to release active renin. This catalyzes angiotensin to increase the glomerular filtration rate. The ion concentrations may then return to normal levels and thus provide a feedback mechanism for constancy in renal function.

Classification

Renin is a proteolytic enzyme produced when the juxtaglomerular cells of the kidney are stimulated by reduction in (1) sodium concentration or (2) blood volume.

Angiotensin is an octapeptide hormone containing eight amino acids.

Biosynthesis

The enzyme renin is synthesized in the juxtaglomerular cells where it is stored as an inactive form called prorenin. A drop in arterial pressure plus other factors stimulate renin release. The ensuing cascade involves splitting of angiotensinogen to angiotensin-I (AT-I), a decapeptide, and then to AT-II by an enzyme in the lung and also in the brain and kidney.

AT-II does not remain long in the body. It is converted by aminopeptidases to des-Asp-heptapeptide (AT-III), and this is changed to inactive substances by angiotensinases.

Release of Renin and Angiotensin

Renin

One mechanism of renin release may involve pressure or stretch-sensitive receptors in the renal afferent arterioles. A second mechanism may be the macula densa receptors responding to changing sodium concentrations. Disturbances in potassium balance may be a stimulus. Plasma angiotensin levels act as another feedback mechanism. Even autonomic nerves can take part in the mechanisms of action.

Angiotensin

Renin in the blood reacts with a protein that is an α_2 globulin protein fraction. This fraction is produced in the liver and is called angiotensinogen. This substance is hydrolyzed by renin to release AT-I, a decapeptide. A converting enzyme in the vascular epithelium, primarily in the lungs and called depeptidyl carboxypeptidase, changes AT-I to AT-II. AT-III, along with AT-II, is released into the plasma.

Normal Bodily Effects of Angiotensin-II

AT-II is a powerful vasoconstrictor for systemic arterioles. It affects the vasomotor centers in the medulla, involving the sympathetic postganglionics to release catecholamines. This elevates both systolic and diastolic blood pressures. Thus, it is an extremely potent pressor compound. It has a minor stimulating action on the heart. Its potency on the vessels is much greater than that of AT-III.

The compound stimulates aldosterone synthesis by the adrenal cortex. Renal tubular sodium ion resorption is increased. Aldosterone-III may have a similar effect.

AT-II induces platelet aggregation, inhibits plasminogen activity, and is chemotactic to mononuclear cells. It activates the circumventricular organs to increase water input, vasopressin secretion, and ACTH action. This compound may be a central transmitter because all its components are also found in the brain.

Basis of Angiotensin-II Bodily Effects

AT-II actions are mediated by specific receptors located on the cell surface of target organs such as arterioles, adrenal cortices, kidneys, and sympathetic nerve endings. Its binding to arterial smooth muscle cells activates cellular phopholipase C. This produces second messengers, e.g., inositol phosphate and diacylglycerol. Calcium ions increase and muscle contractile force is enhanced.

The compound has a growth promoting effect due to activation of protein kinase C; this accelerates gene transcription and protein synthesis in cells.

The action of the compound to produce retention of salt and water is to constrict kidney blood vessels and to activate tubular resorption. By increasing the rate of aldosterone secretion, sodium resorption is increased greatly.

The arteriole pressure increases because of the osmotic effects in the blood vessels from salt and water retention.

ERYTHROPOIETIN (HEMOPOIETIN)

Structure, Development, and Aging

Red blood cells, platelets, and white blood cells after birth are produced in the bone marrow. Erythropoietin is a hormone that acts in the bone marrow to increase the rate of red blood cell production in response to hypoxia. Lymphocytes can also form in the thymus and lymph organs after birth. In the third fetal week, the blood cells appear in the splanchnic mesoderm of the yolk sac and this region is called the angioblast. About the same time, blood cells develop in the extraembryonic mesoderm of the placental villi and in the connecting stalk (basis of the future placenta) of the mother. In late fetal life, blood cell production is transferred to the liver, spleen, and lymph nodes. About 25% of the blood cells manufactured by the marrow are red cells in the process of maturing to their final erythrocyte stage. At about 20 years of age the marrow is no longer active, except for the vertebrae, sternum, ribs, pelvis, calvaria, and the ends of the long bones. The yellow marrow, which accumulates fat, becomes inactive, but it can regain function in certain hematologic disorders.

The average life of the mature erythrocytes in a person's circulation is about 120 days. There is an endocrine control of the production and release of the erythrocytes that maintains the constancy of these processes. The hormone is erythropoietin, produced in the kidneys, but the liver is the chief site in the first few weeks of life.

Classification

Erythropoietin is a glycoprotein having a molecular weight of about 34,000.

Biosynthesis

Erythropoietin is produced chiefly in the kidneys, although the liver may be a source. In the kidney, the glomerular epithelium is one probable site of formation. Another site is the

juxtaglomerular cells. Nephrectomy, however, does not always abolish the formation of the hormone.

There is a substance called renal erythropoietic factor (erythrogenin), secreted by the kidneys from a precursor plasma globulin, that may have originated in the liver or kidneys; this is involved in the synthesis of erythropoietin.

Release

In bleeding, very high elevation, or any disorder causing hypoxia, synthesis and output of red blood cells from the bone marrow is increased. If the red cells increase considerably, as in certain polycythemias, then the natural production and release may be variably lowered. The mechanism involves erythropoietin. A polycythemia can occur if a malignant tumor, usually renal, is overproducing the hormone. The condition called polycythemia vera may occur when red cell precursor cells arise from regulatory failures during cell-line maturation.

Normal Bodily Effects

The rate of red cell production is not regulated directly by the red cell concentration but indirectly by the capacity to transport sufficient oxygen to tissue cells. Red cell production must be significantly involved as a mechanism of adaptation. Erythropoietin does respond to oxygen lack from any cause by increasing red cell production in the bone marrow. In the absence of the hormone, the marrow does not respond. Hypoxia in that case does not display a stimulating effect.

The half-life of erythropoietin is about five hours in the circulation, but its effects on obtaining maximal red cell numbers in the blood may take several days.

There is a growing literature on the role of extracellular factors in the proliferation and differentiation of hemopoietic cells. The mechanisms involve hemopoietic growth factors, cytokines, and oncogenes.[3]

Basis of Bodily Effects

Erythropoietin stimulates the stem cells in the bone marrow to convert to proerythroblasts. This requires mRNA synthesis. The hormone increases the rate of cell division of the stem cells and hastens differentiation of these cells through a line of successive cells that end as mature erythrocytes. The entire process is closely coordinated with iron metabolism, which is essential for hemoglobin production. Lipoproteins are also needed for the construction of the red cell membranes.

CARDIAC HORMONES

ATRIAL NATRIURETIC FACTOR

Site of Origin

Although there may be other cardiac hormones, the atrial natriuretic factor (ANF) is the one most completely defined. The ANF is located in cells in both the right and left cardiac atria but chiefly in the right atrium. It is produced within the myocardial cells. The ANF, in contributing to blood volume control, acts as a set of stretch receptors in the atrial muscles.

Classification

ANF in the human is a polypeptide derived from a molecule with 151 amino acid residues. ANF is probably only one of several natriuretic factors.

Biosynthesis

ANF is produced in both atria of the heart under conditions when it is necessary to increase water excretion because of high blood volume.

Release

ANF is released when an increase in blood volume stretches the atrial wall; this occurs, for example, when blood enters the right atrium from the venae cavae. The hormonal release is a response to augmentation of extracellular fluid volume and to sodium loading.

Normal Bodily Effects

ANF produces an increased rate of glomerular filtration, thus causing both salt and water excretion at the outset of kidney function.

ANF inhibits the release of renin, vasopressin, and aldosterone. Blood pressure and volume are decreased. It exerts a marked inhibition of vessel contraction that may have been caused by epinephrine and AT-II. It is an important regulator of sodium chloride and water distribution in tissues. Overall, ANF is an important regulating agency for blood volume.

Sodium ion excretion is one of its major effects. It does not affect sodium transport mechanisms across cell membranes. It stimulates guanylase cyclase activity, particularly in kidney glomeruli. This enzyme helps form guanosine monophosphate (GMP), a second messenger that inhibits smooth muscle contraction. The inhibition involves changing the degree of phosphorylation of several enzymes. Intracellular calcium ion concentration is reduced.

Basis of Bodily Effects

There are ANF-containing neurons in the brain, with a pathway from the hypothalamus to the medullary area of the brain that regulates blood vessel diameters. If the blood volume increases, so do cardiac output, blood pressure, and urinary flow, although only over the first few hours. The concomitant elevated pressure in the right atrium causes pressure augmentation within that atrium. This becomes the stimulus for afferent impulse transmission to the brain. On the efferent side, nerves to the kidney exert an effect on the vessels, which results in elevated urine flow.

When ANF dilates renal blood vessels, sodium output is increased. ANF inhibits tubular resorption and the ADH of the posterior pituitary, adding to the increased urine output. These adjustments may not be long term.

Another adjunctive mechanism involves the simultaneous responsiveness of the carotid sinus baroceptor; this adds to the effects of the atrial volume receptors.

Overall, the right side of the heart has adaptive reactions to the volume flow of blood through it. Because of the local mechanisms that exist, the cardiac chambers pump out a volume of blood equal to the venous input.

GASTROINTESTINAL HORMONES

The gastrointestinal hormones considered herein are cholecystokinin (CCK; pancreozymin), gastric inhibitory peptide (GIP), gastrin, motilin, secretin, substance P, and vasoactive intestinal peptide (VIP). These are manufactured and released from the mucosa of the stomach and/or small intestine.

CHOLECYSTOKININ (PANCREOZYMIN)

Structure

The lining of the small intestine secretes CCK. The hormone is put out in the duodenum and jejunum.

Classification

CCK is a polypeptide containing 33 amino acids. This is its physiologic form in the gastrointestinal tract. It has the same C-terminal tetrapeptide as gastrin. A sulfate group on the seventh C-terminal amino acid is important for its biologic activity. CCK is found in certain neurons of the central nervous system.

Biosynthesis

The formation of CCK involves the usual steps in the synthesis of proteins.

Release

The alimentary form of CCK is released in response to the presence of certain fatty acids, but other foodstuffs are also stimuli. These include some single amino acids, proteoses, and peptones. Undigested protein is an ineffective releaser whereas phenylalanine is a potent releaser.

The chyme in the intestine evokes the secretion of CCK. The hormone directly stimulates the acinar cells of the pancreas to release its contents of zymogen granules, but there is very little activation of the pancreatic duct epithelium.

Normal Bodily Effects

CCK is the chief endocrine stimulus of enzyme secretion from the acinar cells of the pancreas. Large amounts of pancreatic enzymes and the aqueous components of pancreatic juice are secreted. This simulates vagal nerve action. CCK importantly promotes the emptying of bile from the gallbladder, the presence of fats being essential in the meal. CCK diminishes secretory activity of the stomach when gastric emptying is taking place. The endocrine effect on emptying is aided by the enterogastric reflex in which duodenal acidity activates vagal afferents to decrease gastric motility and emptying. CCK stimulates glucagon release as well as the release of insulin.

Basis of Bodily Effects

CCK is the most important mediator of the pancreatic exocrine response to the digestive products of certain lipids and proteins. CCK may produce its effects by increasing intracellular calcium efflux from pancreatic acinar cells.

CCK competes with gastrin for receptor sites on target cells, thus blocking the action of gastrin. CCK inhibits the parietal cells that produce stomach acid secretion. In general, hormones that stimulate pancreatic acinar cells do so by raising cAMP or the ionic calcium levels.

GASTRIC INHIBITORY PEPTIDE

Structure

GIP is produced by the mucosal cells of the duodenum and jejunum. It was once considered to be a hypothetical hormone called enterogastrone.

Classification

GIP is a peptide containing 43 amino acids. Chemically, it resembles secretin.

Biosynthesis

The synthesis of proteins in general holds for GIP.

Release

Carbohydrates such as glucose in the duodenum and proximal jejunum are prime stimulants for the release of GIP. There is also a stimulating effect of fat and protein products in the duodenum and upper jejunum. The vagus nerve may secrete GIP as a final transmitter to the target cells.

Normal Bodily Effects

GIP is an inhibitor of stomach acid secretion, motility, and emptying. It also regulates the release of insulin from the pancreas.

Basis of Bodily Effects

The hormone acts directly on the islet cells of the pancreas. It inhibits gastric acid secretion by preventing gastrin release and also by inhibiting parietal cell acid secretion.

GASTRIN

Structure

There are several types of productive cells in the gut. The G cells secrete gastrin in the duodenum and proximal jejunum.

Classification

Gastrin is a polypeptide. One form, G-34, contains 34 amino acids. A second form, G-17, has 17 amino acids and is the more abundant species; G-17 is also called gastrin I or little gastrin. G-34 is called big gastrin and is much less important than gastrin I.

Biosynthesis

Gastrin is not only produced by G cells in the pyloric stomach and in the intestinal mucosa, but is also found in the pituitary gland and in some peripheral nerves.

Release

Gastrin secretion is regulated by food in the stomach and small intestine. Mechanical wall distention activates stretch receptors, which in turn increase motility and secretion. The chemical stimuli are chiefly the peptides of protein hydrolysis. These act on the G cells and release gastrin in the very active or second (gastric) phase of stomach digestion. Stimulation of the vagal nerve fibers also helps to release gastrin.

Normal Bodily Effects

Gastrin has a positive motor effect on the stomach muscles. Whether the hormone plays a part in the early cephalic phase of gastric digestion is uncertain.

The upper intestine, which contains G cells, releases gastrin upon stimulation by amino acids and peptides. The hormone can stimulate the stomach parietal cells to increase their secretion of hydrochloric acid; the acid is built from the reaction of hydrogen ions and chloride ions, both compounds having entered the mucosa from the blood.

Basis of Bodily Effects

The activity of gastrin lies in its terminal four amino acids. Also, the pH of the gastric juice importantly determines the ability of gastrin to stimulate secretion. A pH of 2.0 blocks the exit of gastrin from the mucosa to the lumen. A low acidity inhibits the neurally active secretion which is a regulatory feedback system.

MOTILIN

Structure

The cells in the lining of the upper small intestine produce and release motilin.

Classification

Motilin is a polypeptide containing 22 amino acids. It is classified as a neuroactive, gut-brain peptide.

Biosynthesis

In general, neuropeptides may be produced in the cell bodies of neurons. Following encoding by DNA, they are transcribed to mRNA and this is translated on polyribosomes bound to the endoplasmic reticulum. Transport to the Golgi complex then occurs.

Neurohormones may be produced as preprohormones and then converted to prohormones, after which they are cleaved to peptide sequences.

Release

Secretory vesicles pass from the Golgi complex to axon terminals. The stimulus for hormonal release is uncertain. The cleavage of the substance within the vesicles as a neurohumor is followed by its release to an active peptide.

Normal Bodily Effects

Motilin acts as both a hormone and a neurotransmitter. It is widely distributed in the body, as seen by its presence in the central nervous system where it excites most corticospinal neurons. In animal experiments, the hormone increases the motility of the stomach and intestine and it activates contraction of the lower esophageal sphincter.

Motilin may be the hormone that initiates the migrating myoelectric complexes that travel intermittently from the stomach through the ileum and which, as electrical outbursts, clean the intestine down as far as the cecum. During feeding, motilin is not released.

Basis of Bodily Effects

There is much uncertainty in this category. Whatever stimuli cause the glands to secrete motilin, it is the release from the vesicles that produces the target effects.

SECRETIN

Structure and Development

Secretin is a hormone derived from the mucosa of the duodenum and also from the jejunum. It is among the gut compounds that originate in the ectoblast of the embryo.

Classification

Secretin is a hormone containing 27 amino acids, all of which are needed for adequate activity. The compound exists in more than one form.

Biosynthesis

The synthesis of secretin follows the usual sequence for that of proteins in general.

Release

The hormone is contained in granules concentrated close to capillaries. It is released chiefly in response to the low pH of the gastric contents entering the small intestine. The release from the small intestinal mucosa is especially great when the pH drops below 4.5. Fatty acids are another set of releasing stimuli.

Normal Bodily Effects

The primary action of secretin is to stimulate in the duodenum a copious secretion of pancreatic fluid and bicarbonate. It also stimulates the growth of the exocrine pancreas. In these functions, it is assisted by CCK. Secretin stimulates secretion of biliary fluid and bicarbonate, an activity also complemented by CCK. Secretin and CCK stimulate the chief cells to secrete pepsinogens.

Basis of Bodily Effects

The activity of secretin requires its binding with a specific receptor on the membranes of appropriate digestive cells. This involves the activation of adenylate cyclase and the conversion of ATP to cAMP. The cascade of target events follows.

SUBSTANCE P

Structure

Substance P is produced and released in several areas of the body. Its hormonal status is uncertain. It occurs both in the brain and the digestive tract mucosa.

Classification

Substance P is a polypeptide containing 11 amino acids. Its name comes from the fact that it was originally extracted and stored as a powder. It is a neuroactive gut-brain peptide.

Biosynthesis

The basis of formation of substance P is the general synthesis of proteins.

Release

Substance P can be released in the salivary glands by nerve terminals in the mouth. It is also present in the intestine. Additionally, substance P is found in the nervous system, in the brain and spinal nerves. It is released peripherally by nerve pain fibers situated in the dorsal horns of the spinal cord, from which it travels contralaterally to the brain.

Normal Bodily Effects

Substance P is generally excitatory in the body. It may mediate the myenteric reflex and increase the motility of the small intestine. It stimulates gallbladder contraction. It is a potent salivary secretagogue. It may bring about axon reflexes. It causes vasodilation, thus lowering the blood pressure. It may act as a neurotransmitter in the central and peripheral nervous system. In the brain, it may cause neurons in the substantia nigra to release dopamine.

Basis of Bodily Effects

Substance P exerts its effects by increasing intracellular calcium levels along an inositol phosphate pathway. The release of calcium increases cyclic gAMP, which activates the subsequent cascade of events to the target. Substance P, acting as a neuropeptide, may produce its effects as a hormone or as a neurotransmitter.

VASOACTIVE INTESTINAL PEPTIDE

Structure

The endocrine glands throughout the GI tract include VIP in their secretions. Nerve endings in the gut also contain the hormone.

Classification

VIP is a polypeptide chemically related to secretin and GIP. It contains 28 amino acids.

Biosynthesis

VIP is widely distributed in the central nervous system and in the intrinsic gut neurons. Its synthesis is essentially that for proteins in general.

Release

Stimulation of the vagus nerve, apparently acting as a neurotransmitter, releases VIP from the gut. Other sources of release are uncertain.

Normal Bodily Effects

VIP vasodilates certain blood vessels during secretory activity. It stimulates the release of pancreatic bicarbonate and inhibits the secretion of gastric juice. It also stimulates secretion of intestinal enzymes, pancreatic hormones, glycogen breakdown in the liver, and fat metabolism.

Basis of Bodily Effects

Although VIP is classified as a neuroactive, gut-brain peptide, it is uncertain whether it acts as a true neurotransmitter, a hormone, or a neuromodulator (which regulates synaptic transmission). It may be an inhibitory transmitter to smooth muscle and an excitatory transmitter to glandular epithelial cells.

The hormone appears to be a potent activator of the adenylate cyclase complex in liver, fat cells, and pancreas. The usual cascade of events succeeds the enzyme activity.

PANCREATIC HORMONES

INSULIN

Structure and Development

The pancreas is both an endocrine and exocrine organ. The endocrine aspects, secreted by the islets of Langerhans, are the more prominent. The principal hormones are insulin and glucagon. Other hormones are somatostatin and pancreatic polypeptide. The endocrine cells develop from the endodermal pancreatic ducts. Insulin secretion begins significantly at about the fifth fetal month although the islets develop as early as the 60th to the 90th day.

Classification

Insulin contains two straight chains of polypeptides joined by two disulfide linkages. One chain contains 21 amino acids and the other 30. The molecule is originally a monomer that forms dimers (molecular weight 12,000).

Biosynthesis

Insulin is synthesized in a gene in islet β cells and is transcribed by mRNA to preproinsulin, after which proinsulin is formed. The synthesis occurs in the ribosomes of the endoplasmic reticulum. The proinsulin is cleaved by a protease in the β cells. The insulin formed is stored in granules within the Golgi apparatus. Another fragment that is formed is called C-peptide, but this lacks biologic activity. The granules upon demand travel to the β cell membranes and release their contents into the extracellular spaces. The insulin reaches the tissues by way of the blood. Most of the hormone is inactivated as it passes through the liver.

Release

The release of insulin is by exocytosis. After a meal, insulin blood levels may increase markedly because of the excess of food. The most important stimulus for release is glucose. Protein digestive products are significant stimuli, especially arginine and lysine.

Insulin is normally transported unbound. Carbohydrates cause its dissociation from any protein carrier. The half-life in the plasma is 5 to 8 min. Release does not appear to involve any regulating factor such as the pituitary or any direct feedback mechanism. However, insulin synthesis and release are increased by the growth hormone, glucose levels, glucagon, secretin, and pancreozymin. Release is inhibited by epinephrine and α-adrenergic receptors, whereas it is stimulated by interaction with β-adrenergic receptors. Insulin is metabolized chiefly in the kidney and liver by a specific protease and a transhydrogenase.

Normal Bodily Effects

Insulin is the prime regulator of metabolic processes which are anabolic. It influences the metabolism of carbohydrates, fats, and proteins. The organs affected most are adipose tissues, liver, and muscles. In the liver, insulin increases glucose uptake and its storage as glycogen. In muscle, insulin is necessary to transport glucose from plasma to cells, and it has a similar action in adipose tissues. Insulin facilitates transport of magnesium, phosphate, and potassium

into muscle, and phosphate and potassium into liver, all for the purposes of glycogen and protein storage.

The metabolism of fat from all sources is greatly affected. Storage is increased. Both mobilization and oxidation of fatty acids are inhibited. Insulin induces the enzymatic secretion of lipoproteins from capillaries to tissues by lipoprotein lipase, thus facilitating fatty acid entrance to the tissues.

Recombinant insulin-like growth factor I (IGF-I) appears to be a potent stimulator of bone growth. It may accomplish this by influencing bone remodeling. Insulin is necessary for the normal liver production of IGF-I.

Basis of Bodily Effects

Insulin action is initiated at the plasma membrane receptors before the hormone enters the cells. Uptake of glucose across the membranes and into cells is increased, thus lowering sugar in the blood. The hormone apparently hastens the activity of a carrier molecule in the membranes. Pyruvate and lactate increase because of greater utilization of glucose. Organic phosphate decreases as glucose is phosphorylated. Plasma potassium decreases because the liver storage of glycogen is accompanied by potassium entrance to the liver. The actions of insulin on fat and protein metabolism are independent of the actions on glucose. The storage of foodstuffs is a major function of insulin.

Glucose is continually released from its storage in the liver, a process which importantly involves glucose-6-phosphatase. Glucose is convertible to α-glycerophosphate, which changes in turn to free fatty acids and triglycerides. Overall, insulin is active in many of the processes occurring in the intermediate metabolism of foodstuffs. Receptors for insulin have been identified in osteoblasts.

GLUCAGON

Structure and Development

There are several types of cells in the pancreas. The acinar cells contain the zymogen granules for exocrine secretion. The islets of Langerhans produce the endocrine secretion. The islet β cells manufacture insulin, whereas the islet α cells manufacture glucagon. The islets also have γ and δ cells whose functions are uncertain.

Classification

Glucagon is a polypeptide. It is composed of a single straight chain of 29 amino acid residues. The molecular weight is about 3500.

Biosynthesis

Glucagon in humans is synthesized on chromosome 2 by α cells in the islets. A prepro-hormone is converted to a prohormone called glycentin, which is localized to the peripheral area of the secretory granules whereas glucagon is in the core of the granules. In several animal species, glucagon is synthesized in the GI tract.

Release

Glucagon is synthesized and released from secretory storage granules by exocytosis in the α cells of the islets of Langerhans. In humans, the release occurs mostly if glucose is low in the circulation. This contrasts with the effect of glucose on insulin secretion. Glucagon is also secreted in response to a protein meal, especially if it contains alanine and arginine.

The secretion of glucagon is increased by generalized stress and by autonomic nerve stimulation. High levels of circulating fatty acids inhibit glucagon secretion. The hormone circulates mostly unbound in the plasma.

Normal Bodily Effects

Glucagon actions are for the most part opposite to insulin actions. Thus, it makes energy available to tissues, especially between meals. It promotes mobilization but not storage of energy sources, e.g., glucose. It is called the hyperglycemic factor, protecting against hypoglycemia.

The primary target organ of glucagon is the liver in which it maintains the ouput of glucose. This is its most important effect. It influences the rates of hepatic glycogenolysis, glycolysis, lipolysis, and gluconeogenesis. Epinephrine, in particular, is a similar promoter of liver glycogenolysis. Glucagon may not stimulate glycogenolysis in muscle and it does not appear to have an effect on the peripheral tissue utilization of glucose.

Glucagon is ketogenic as well as hyperglycemic. It also activates adipose tissue lipase. It inhibits sodium resorption by the kidney tubules. It activates adenylate cyclase in the cardiocytes and increases both cardiac contractility and rate.

The hormone is degraded mostly in the liver and kidney. The half-life of pancreatic glucagon is about 6 min.

Basis of Bodily Effects

Glucagon initiates metabolic processes by binding in the liver to a specific receptor, which couples to adenylate cyclase by a guanine nucleotide binding protein. There also appears to be an inhibitory guanine nucleotide binding regulatory protein whose functions are unclear. Cyclic AMP in the liver quickly increases. Protein kinases are activated, which in turn lead to the formation of phosphorylase b and then phosphorylase a kinases. The end result is the enhancement of glycogenolysis. Glucagon can also elevate liver gluconeogenesis and inhibit glycolysis. These actions involve cAMP and an increase in protein kinase activity.

Glucoreceptors in the hypothalamus respond to rapidly falling glucose concentration. It may be that stimulation of glucagon involves the activation of the sympathetic nervous system through fibers descending from the hypothalamus and ending in the pancreas. There may be an effect of glucose deprivation in the α cells, or even an effect secondary to circulating epinephrine.

MALE SEX HORMONES

ANDROGENS

Structure, Development, and Aging

All male sex hormones are called androgens. The testes are the principle source for their syntheses. The important androgen produced in the testis is testosterone. A second, less potent hormone is androsterone. In certain states, the adrenal cortex may secrete significant amounts of androgens.

The testes are composed mainly of seminiferous tubules wherein the sperm are produced by a succession of maturing germ cells. Interstitial cells of Leydig are located between the tubules and they produce the hormonal secretions of the testes. Sertoli cells are supporting epithelial cells in the tubule system. They gain contact with the developing sperm and provide or exclude nutrients to and from the fluid surrounding the germ cells and the tubules, thus acting as a blood-testis barrier.

The fetal testes produce androgens, which stimulate growth of the penis, formation of the penile urethra, and development of the prostate gland and seminal vesicles. Although the Y chromosome of the sperm is male-determining, all developing structures pass through an indifferent stage and may differentiate in either a male or a female direction.

The testicular production of androgen is low before age 10 and increases greatly at male puberty. The hormonal secretion is fairly constant throughout the life of the adult male and sexual development and its functions are maintained under the control of the pituitary gonadotropins. The hormone production declines in very old age.

Classification

The precursor for all adrenocortical hormones is cholesterol, a 27-carbon molecule. The androgens are C-19 steroids and testosterone is the prototype. The androgens are excreted in the urine as 17-ketosteroids, whose origin is chiefly the testis and adrenal cortex in the male and the ovary and adrenal cortex in the female.

Biosynthesis

Testosterone synthesis and release by Leydig cells are regulated by LH, which is controlled by LHRH. The synthesis of gonadal steroids closely resembles that in the adrenal cortex, and this is true in both sexes. The initial precursor is cholesterol, delivered by plasma lipoproteins. LH stimulates the gonads to secrete androgens. In this process, LH binds to membrane receptors, which activate adenylate cyclase, resulting in elevated cAMP levels. There is a subsequent activation of protein kinases, and protein steroidogenesis occurs.

Within the mitochondria, the following scheme of steroid forming events occurs: acetyl coenzyme A produces cholesterol in the Leydig cells and these convert to Δ^5-pregnenolone. The following chain of successive compounds are 17-α-OH-pregnenolone, dehydroepiandrosterone, androstenedione, and testosterone.

In the above steps within the testes, the cholesterol is synthesized and stored as esters in the Leydig cells. Some cholesterol is sent to the endoplasmic reticulum for chemical completion to testosterone.

Release

The release of testosterone by the interstitial cells of Leydig requires that these cells be activated. This is accomplished by a feedback system to the anterior pituitary gland. The pituitary secretes the gonadotropin, LH, also known as the interstitial cell stimulating hormone. The response of the cells of Leydig to the LH action catalyzes spermatogenesis. Other hormones, including FSH, and probably estradiol, prolactin, and growth hormone, are mutually interactive in the control of spermatogenesis.

The hypothalamus is involved in a regulatory manner because it transports releasing factors to the anterior pituitary, which in turn releases its gonadotropins that are transported in the blood to the testes. The action of FSH is to stimulate the germinal epithelium of the seminiferous tubules. The androgen feedback exerts a negative effect on the central centers and this in turn regulates the synthesis of FSH.

Normal Bodily Effects

Testosterone develops and maintains male secondary sexual characteristics that have been markedly activated at the time of puberty. Even in the fetus, the hormone has already initiated differentiation of the male phenotype.

Testosterone, by feedback, regulates pituitary gonadotropin secretion. It has an anabolic action on proteins. It favors growth of epiphyseal cartilage and closure of the bone epiphyses; closure is also regulated by androgens in the female.

The Sertoli cells of the testes are important. In the fetus, they control the development and descent of the testes, the germ cells, and the cells that secrete hormones responsible for masculinization. In adulthood they nourish the early germ cells as they mature into sperm. Also in the fetus, a hormone named mullerian inhibiting substance is produced by Sertoli cells and is claimed to cause the regression in the male of the fetal structures called the mullerian ducts at about eight weeks. These ducts in the female differentiate into the fallopian tubes.

The androgens of the adrenal gland are not important in males, because testosterone is produced chiefly in the testes.

Basis of Bodily Effects

Activation of protein synthesis results from an effect of testosterone on microsomal ribonucleic acid. Testosterone from the Leydig cells stimulates the epithelium of the seminiferous tubules, thus providing the androgens needed for sperm production. In prostate gland chemistry, testosterone converts to dihydrotestosterone, the active compound in the prostate gland. The enzyme involved is 5-α-reductase. The mechanism of testosterone control of Leydig cells involves cAMP and its sequelae of chemical changes.

FEMALE SEX HORMONES

ESTROGENS

Structure, Development, and Aging

Estrogens are synthesized in the ovaries, placenta, and adrenal cortex. In the male, synthesis is in the testes, liver, and other tissues. The ovary in the nongravid female is the primary source. Its follicles in the first half of the ovarian cycle secrete estrogens by its granulosa cells. The estrogens include β-estradiol, estrone, and estriol. Estradiol is the most important for development of the female phenotype. At ovulation, the second half of the cycle begins and the empty follicle becomes a new endocrine producer called the corpus luteum; this secretes progesterone and some β-estradiol. The growth of the follicles as well as its estrogen secretions are stimulated by FSH from the anterior pituitary. Toward the close of the follicular phase, two to three days before ovulation occurs, LH is stimulated to secretion by way of positive feedback on the hypothalamus but mainly on the anterior pituitary. Between ovulation and menstruation, the hormones exert a negative effect on the hypothalamus and pituitary and this suppresses FSH and LH; these will increase again beginning with menstruation.

FSH causes growth of the follicle and its production of estrogens. LH stimulates interstitial cells in the ovary and thus the corpus luteum. Ovulation is stimulated and FSH secretion is inhibited. In pregnancy the placenta becomes the source of progesterone.

The primordial germ cells develop in the walls of the yolk sac at about the fourth embryonic week. They proliferate and migrate to the ovaries in which they convert to oogonia and some to primary oocytes. Further development ceases until puberty. During menopause the follicles and their eggs begin to disappear.

Classification

All estrogens and progesterone are steroids. A controlling hormone from the hypothalamus, LHRH or GnRH, is a decapeptide. The anterior pituitary FSH and LH are proteins. LHRH controls the release of FSH and LH. In turn, FSH is the major control of the follicular phase of the ovarian cycle and LH is the major regulator of the luteal phase.

Biosynthesis

In the nongravid female, in the production of estrogens, the precursor is cholesterol, brought in from the plasma. Under the influence of LH, pregnenolone is synthesized. From there, one pathway will lead to the formation of progesterone. The other can convert to 17-hydroxyprogesterone, then androstenedione. This last compound can convert to estrone, estradiol, and estriol.

In pregnancy, estrogen precursors are formed in the adrenal glands and transported to the placenta where they are built to estradiol, estrone, and estriol. The female also produces testosterone. To do this, the ovary and adrenal cortex utilize steroid prohormones such as androstenedione and dehydroepiandrosterone; these are finally converted to testosterone in the liver and peripheral tissues.

Release

Estrogens are secreted by precursors of the follicular cells called granulosa cells and by another layer of follicular cells called the theca interna. Another source, of lesser importance, is the adrenal cortex.

Normal Bodily Effects

In the nongravid female, estrogens are essential for the growth and development of the sex organs. They aid uterine development and promote cyclic changes in the endometrium. They are necessary for maturation of secondary sexual characteristics. In pregnancy, they stimulate development of the mammary glands and uterine enlargement and relax pelvic ligaments. They promote deposition of fat in subcutaneous tissues. They regulate bone growth in length, more so than androgens do in males.

Basis of Bodily Effects

The estrogens bind to specific receptors that are present in the target organs. There are nuclear receptor sites in which the initial complexes are transferred to the nucleus. Processes occur such as the production and utilization of rRNA and this becomes involved in the synthesis of enzymes and proteins. DNA is activated. The overall processes that are essential for the action of progesterone are similar to those for estrogens.

The normal cyclic regulation of ovarian activity, characteristically beginning with puberty, involves first the hypothalamus and its LHRH, the subsequent production of FSH and LH from the pituitary, and the ovarian secretion of female and male hormones.

PROGESTERONE

Elements of the preceding discussion primarily on estrogens apply to the progestins, the major one being progesterone. This hormone is a 21-carbon steroid that is a precursor to other steroids. It is secreted cyclically in nonpregnant women under the influence of LH. In this process, cAMP synthesis in the corpus luteum increases. The testes and the adrenal cortex may be additional sites of progesterone formation. The corpus luteum, which is the chief source of progesterone, develops and its endocrine output in pregnancy is increased by hCG, which starts to be secreted by trophoblast cells of the embryo. At about the 80th day, hCG secretion falls rapidly and remains at a low level throughout pregnancy. However, the placenta takes over and secretes large quantities of estrogen and progesterone. The corpus luteum involutes gradually after the 13th to the 17th week of gestation and its endocrine output is small.

Progesterone is to a great extent a hormone of pregnancy. It prepares the uterus for the implantation of an ovum and maintains the uterus during pregnancy. It inhibits FSH and LH, and this suppresses ovulation during gestation. The hypothalamus is a primary, central, suppressive center because it keeps all the gonadotropins in check until puberty.

Progesterone stimulates maturation of the mammary glands in preparation for lactation. It depresses uterine contractility in pregnancy until a late phase when estrogens dominate and increase the excitability which favors birth at parturition. Progesterone stimulates the decidual cells of the pregnant uterus to synthesize prolactin. Whereas estrogens prime the target tissues, progesterone decreases the number of estrogen receptors, thus favoring anti-estrogen actions. In the nonpregnant female it promotes the changing phases within the uterine cycles.

RELAXIN

The functions of relaxin are limited to the period of pregnancy, at which time the ovaries secrete this peptide hormone. Its actions are to loosen the ligaments of the pubic symphysis and to soften the cervix. These activities importantly assist the delivery of the fetus at parturition.

INHIBIN

Structure, Development, and Aging

Inhibin is a hormone that inhibits the secretion of FSH. The origin of the hormone is most likely the Sertoli cells and probably the seminiferous tubules in males and the ovarian follicles in females.

At the time of birth in males, germ cells have developed in the sex cords of the testes, surrounded by supporting cells which become the Sertoli cells. The sex cords also develop a lumen and become the seminiferous tubules.

Circulating levels of FSH and LH in males increase with aging. After age 40, gonadotropin levels are increasing. Seminiferous tubule degeneration with a decreased inhibin production occurs to a greater extent than decreases in Leydig cell function.

In women, a loss in the secretion of inhibin could explain the higher follicular-phase levels of FSH in the perimenopausal state. In general, inhibin may provide a mechanism to regulate the number of follicles that are maturing during each cycle.

Classification

Inhibin is a polypeptide hormone and a glycoprotein. The compound that has been extracted from ovarian follicular fluid contains three polypeptide subunits. One is an alpha compound with a molecular weight of 18,000. There are two beta subunits, $beta_A$ and $beta_B$, both with molecular weights of 14,000. Subunit alpha can form dimers with $beta_A$ or $beta_B$.

Both $inhibin_A$ (alpha $beta_A$) and $inhibin_B$ (alpha $beta_B$) inhibit FSH secretion. There are other subunits that may stimulate FSH secretion.

Biosynthesis

In the male, inhibin is produced most likely by the Sertoli cells of the testes, although there is a view that the seminiferous tubules can be regions of production. In the female, inhibin is produced by the ovarian follicles and perhaps by the corpus luteum.

Release

The hormone in the male that was produced by the Sertoli cells is also secreted by them. In the female, granulosa cells of the follicles secrete the hormone.

Normal Bodily Effects

Inhibin inhibits FSH secretion in response to GnRH stimulation, without influencing to any marked degree the secretion of LH. The FSH effect is the major function of inhibin. In males the FSH produced acts in turn on the Sertoli cells. LH, however, acts on Leydig cells. It is probable that inhibin is also a factor in the functioning of the seminiferous tubules.

In females, inhibin decreases secretion particularly of the FSH of the anterior pituitary and even LH (controversially). The action is complemented by estrogen and to a lesser degree by progesterone. The inhibition is a negative feedback process. It occurs during the luteal phase of the ovarian cycle, at about the 12th day of the life phase of the corpus luteum. The resultant loss of gonadotropic maintenance from the hypothalamus and pituitary, a short number of days prior to the start of a menstrual cycle, removes the pituitary feedback, whereupon the pituitary again secretes FSH (and LH); the next ovarian cycle then begins.

Basis of Bodily Effects

FSH is inhibited in both males and females by estradiol and testosterone; both block the pituitary response to LHRH. Inhibin is the third blocker. The inhibition is produced in males particularly in the Sertoli cells and in females in the ovarian follicles.

FSH increases the synthesis of inhibin, which produces a feedback loop that helps regulate the availability of FSH according to the demands of specific aspects and stages of gametogenesis. In the male, if the seminiferous tubules do not produce sperm, then the anterior

pituitary increases its secretion of FSH. However, if the rate of spermatogenesis increases greatly, FSH secretion decreases. These actions result from activation of the Sertoli secretion of inhibin. There appears to be a simultaneous, although weaker secretion of the hypothalamus.

PLACENTAL HORMONES

The placenta takes care of the food and waste exchange between fetus and mother. It is also an endocrine gland. The hormones secreted are estrogens, progesterone, and the anterior pituitary polypeptide and protein hormones, which include hCG and human chorionic somatomammotropin (hCS; also called placental lactogen [hPL]); hCS consists of a single polypeptide chain containing 191 to 199 amino acid residues. Other placental hormones are also produced.

Human Chorionic Gonadotropin

hCG is a glycoprotein with two subunits. An alpha subunit is identical to that of TSH, FSH, and LH. A beta subunit closely resembles that of LH and has a molecular weight of about 28,000.

hCG is produced and secreted by the syncytiotrophoblast cells of the embryo. These cells are the forerunners of the placenta. The biochemical steps in producing hCG follow that of general protein synthesis.

hCG is detectable in the plasma and urine of pregnant women when the trophoblast structure is well developed. Urine testing about the seventh day measures the beta subunit and is a test for pregnancy. The hCG levels reach a peak at 9 to 12 weeks and decline to a constant level thereafter.

The hCG in pregnancy maintains the growth of the corpus luteum and its secretions and prevents its involution before the 13th to 17th week of pregnancy. The placenta then takes over, secreting estrogen and progesterone.

There is a normal stimulating effect of hCG on the thyroid glands, resulting in an increased production of thyroid hormones. This is reinforced by another TSH secreted by the placenta called human chorionic thyrotropin. Still another hormone called relaxin is secreted by the placenta and also within the corpus luteum under the influence of hCG. Relaxin is a polypeptide whose molecular weight is about 9,000. In certain animals it is claimed to relax the ligaments of the symphysis pubis during the estrous cycle. This effect is weak or missing in pregnant women.

Placental hCG stimulates ovarian functions in the female fetus. When there is reproductive immaturity after birth, hCG no longer acts as a stimulating agent.

hCG is sometimes used clinically to correct failure of ovulation that results from hyposecretion of pituitary gonadotropic hormones. hCG maintains the functions of the corpus luteum in pregnancy for most of its gestation period.

hCG stimulates testosterone production and secretion in the male fetus by activating the production of Leydig cells. These effects are similar to those of LH, which also stimulates Leydig cells to produce testosterone. Another testosterone-producing hormone is PRL, which potentiates the effects of LH.

Human Chorionic Somatomammotropin

hCS (or hPL) is a hormone unique to pregnancy. hCS is a protein with a molecular weight of about 30,000. It is structurally similar to hGH and PRL.

The hormone is formed in the placental syncytiotrophoblast in the fourth or fifth week after ovulation and fertilization. It can be detected in the serum of pregnant women at about six weeks of gestation. Its levels increase progressively to about the 35th week of pregnancy after which they plateau. The levels of hCS in the plasma of the fetus are far less than those

in the plasma of the pregnant mother. After delivery of the fetus the hormone disappears quickly from the maternal blood.

In normal function hCS in lower animals, such as sheep and goats, helps stimulate their mammary development, partly supporting the action of PRL. hCS also stimulates milk secretion in these animals. The human female appears to be far less responsive in these actions.

hCS has properties similar to those of hGH, adding protein mass to the body. However, it is much weaker in potency.

hCS probably plays a role in the nutrition of the fetus, particularly in regard to fat and glucose metabolism. Glucose is diverted to the fetus in pregnancy by decreasing the mother's capacity to utilize this sugar. Fatty acids in the maternal adipose tissue are lipolyzed and released, providing the mother with an important store of bioenergetic fuel. The hormone thus directs the metabolic traffic in the fetus, but with special importance in the mother so that she may maintain an appropriate flow of nutrients to the fetus.

APPENDIX I: QUANTITATIVE ASPECTS OF RECEPTOR BINDING

Drugs, including hormones, interact with receptors in the body, and these complexes include a wide variety of structures. Not all drug actions are mediated by receptors, however.

In hormone-receptor interactions the selective nature of the effect on the target organ depends not only on the hormonal messenger but also on the specific receptor involved. A drug acts by triggering a response via an action on that part of the cell called a receptor. A deficiency of receptors or hormones may explain a pathologic effect. The nature of the response may also be determined by a changed concentration of elements in the hormone-receptor complex or by the rate of the drug-receptor events.

The binding forces in a drug-receptor complex are covalent, ionic, hydrogen bonds, and van der Waals forces.[4] In covalent bonds the electrons are shared between atoms. The high-energy covalent bonds are irreversible. Antagonistic drugs with covalent binding produce a noncompetitive antagonism. Ionic bonds are important because many drugs have an anion and cation content with attractive forces. For hydrogen bonds, a hydrogen atom is shared between two reacting polar groups, which strengthens the bond. In van der Waals bonding, the interaction occurs weakly between any two atoms or groups of atoms, but it is effective only over a very short distance.

The reactions occurring in a hormone-receptor system may be quantitatively expressed by dose-response curves. These can show the magnitude of the response as a function of the concentration of the constituents of the complex at the receptor sites. The log of the dose is plotted against the effect, if the dose and the effect are known.

In drug effects, the terms *affinity* and *efficacy* are used frequently and can be differentiated in graphs. Affinity expresses the tendency of a drug to combine with receptors. The magnitude of the response is determined by the number of receptors that react and this is expressed as efficacy, i.e., intrinsic activity or power. The term *power* indicates the amount of transformation in a given time or place. A drug that has both affinity and efficacy is called an agonist. A drug that is called a competitive antagonist has affinity but not efficacy; such a drug competes with another for space on the same receptor.

One can show quantitatively the binding of a drug (D) with the available receptors (R) where there is continual occupation by the drug.[5] The effect of (D) is a function of the concentration of the drug-receptor complex.

In the following equation, R* is an activated receptor and $\underline{R}$ is an unavailable receptor.

$$[D]+[R]\underset{k_2}{\overset{k_1}{\longrightarrow}}[DR]\xrightarrow{k_3}DR^*\xrightarrow{k_4}[D]+[\underline{R}];[\underline{R}]\xrightarrow{k_5}R \qquad [1.1]$$

The ratio k_1/k_2 expresses the affinity of the receptor for a drug. The ratio k_3/k_2 expresses the efficacy.

Where the response is thought to be proportional to the number of receptors occupied, this is called an occupation theory.[5,6] In a view called the rate theory, the response is directly proportional to the rate of association of the drug with the receptor.[7]

$$\text{Drug} + \text{Receptor} \underset{k_2}{\overset{k_1}{\longrightarrow}} \text{Complex} \longrightarrow \text{Response} \qquad [1.2]$$

For an antagonist, in the rate theory, this type of drug may dissociate slowly from the complex. This explains the persistence of effect for such drugs.

A graphic treatment can be used to illustrate the difference between efficacy and potency (degree of biologic activity). Potency can be expressed by the site along an X-axis, in relation to an intensity effect along a Y-axis. To elaborate, two different drugs may have maximal effects that appear to be equal. However, it is possible for one of these drugs (A) to have a larger peak effect than the other (B) does. In this instance, A has both greater potency and efficacy. Thus, drug A in a dose of 0.1 g may have the same effect as 1.0 g of drug B.[6]

Drugs may display a competitive or noncompetitive antagonism. A competitive antagonist combines with a receptor similar to the way that an agonist drug does. However, the formation of the complex is weak or ineffective. Increasing the concentration of the agonist usually breaks through the blockade, making the blockade reversible.

There are other types of antagonism. A response to a drug may be variably reduced by another drug with a reverse effect, or abolished by inducing a chemical alteration of a drug's molecular structure.

In noncompetitive antagonism, the antagonist combines irreversibly with a receptor. This produces an inhibition, which prevents any concentration of a drug from exerting a maximum effect. This can be illustrated in log-dose response curves, in which the number of drug-receptor interactions is seen to be decreased. The reader is referred to Schild,[8] who introduced a scale to measure drug antagonism in relation to potency. In this scale, the term potency refers to the concentration of a substance that effectively competes for a target site. Another term, IC_{50}, is used to denote the concentration that inhibits binding by 50%.

The effects of a drug involve its absorption, distribution, metabolism, and excretion. Membrane interactions are highly involved at all stages of these processes. A discussion of the binding problems in the drug-receptor interactions at membranes can be found in many texts. The reader is referred to a succinct review in Neubig.[9]

In models relating drug concentration to effect, the law of mass action is useful to analyze the factors determining receptor occupation. This is because with most drugs the binding to receptors is not absolutely tight so that a reversible dissociation may occur. This means that drugs may not have excessively long persistence and duration of activity.

A Scratchard plot is useful in drug-receptor studies. It is a method to determine values for the binding of drugs to independent sites in which all have the same K_D for the drug, the K_D being the free drug concentration at which DR is 50% of the $(DR)_{max}$. The Scratchard plot converts curves of linear or semilogarithmic plots of binding data into straight lines.[9]

Following a positive interaction between a drug and its receptor, the drug is absorbed and distributed to target organs. The volume of distribution (V_D) is used to describe the relationship between the dose given and the concentration of the drug reached in the blood.

$$V_D = \text{Amount of drug in the body/concentration of drug in plasma} \qquad [1.3]$$

In determining the distribution of a drug in the body, a single compartment model involving drug kinetics has been a promising device. However, it oversimplifies conclusions drawn from it because it assumes that there is a homogeneous and instantaneous distribution of a drug. A two-compartment model is better in that it considers the phase in which the decrease of drug concentration in the body is reflecting the gradual distribution of a substance from the plasma to the tissues.[10]

Drugs are eventually cleared (excreted) from the body. This is an important process in that it determines the quantity of a drug needed to maintain a steady-state drug concentration in the tissues. There are many interacting factors; among them, the rate of elimination determines the regimen of the dose. In the period of disappearance of a drug from the body, exponential decay curves and the so-called half-life of a drug are productive methods of visualizing the internal persistence in time of the drug in the body (see Figure 1).[6]

In the temporal phases of the passage of drugs through the body, cell membranes are involved at each transfer area and their importance cannot be overemphasized. In the case where a drug ionizes, the Henderson-Hasselbalch equation is a measure of the capacity for passage; this is a function of the pH of a cell's interior and the so-called pK_a of the drug. The pK_a, or negative log of the acid dissociation constant, is the pH at which numerator and denominator quantities (seen in the following equation) are equal.

$$\text{pH, negative log } [H^+] = pK_a + \log \text{ base/acid} \qquad [1.4]$$

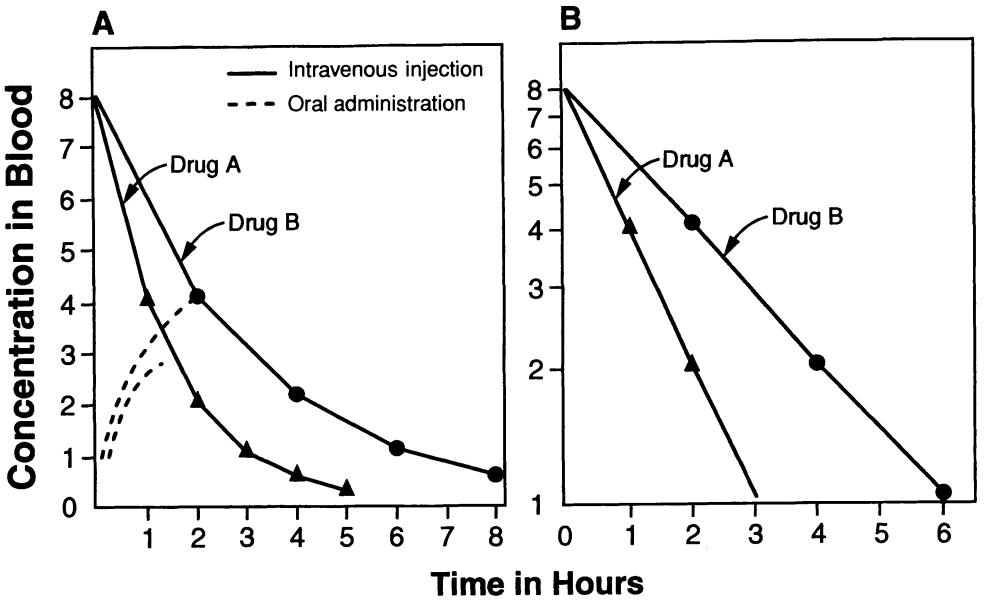

FIGURE 1. Schematic representation of drug disappearance curves and biologic half-life. The Y-axis is on the arithmetic scale in **A** and on the logarithmic scale in **B**. Drug A has a biologic half-life of one hour. The biologic half-life of drug B is two hours. *(Reprinted with permission. Data from Clark, W. G., Brater, D. C., and Johnson, A. R., Eds.,* Goth's Medical Pharmacology, *13th ed., Mosby-YearBook, St. Louis, 1992, 28.)*

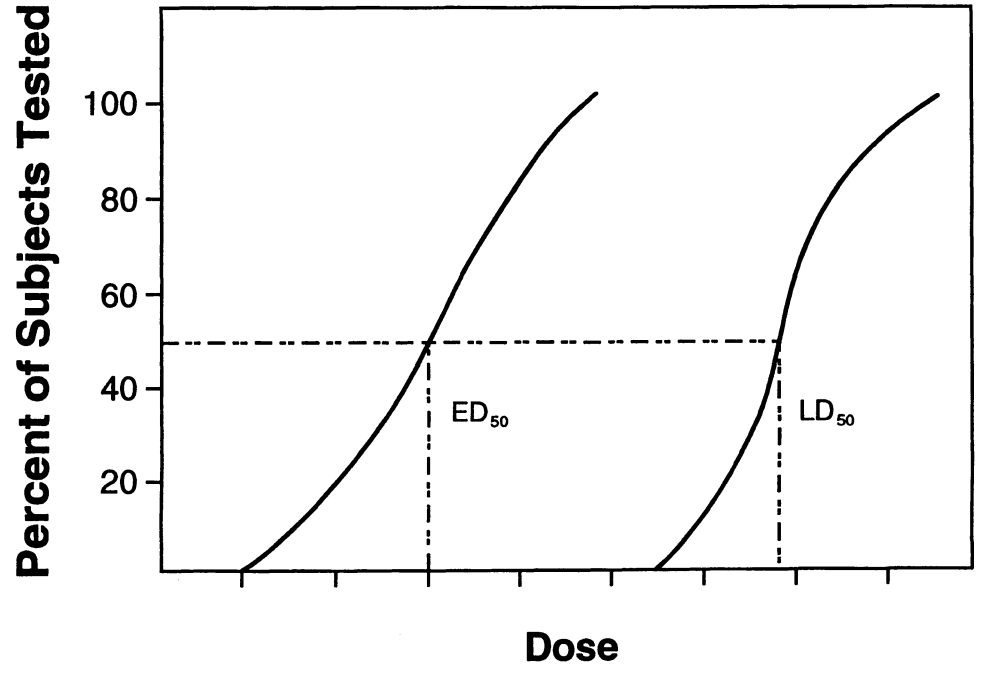

FIGURE 2. Therapeutic index. *(Reprinted with permission. Data from Clark, W. G., Brater, D. C., and Johnson, A. R., Eds.,* Goth's Medical Pharmacology, *12th ed., C. V. Mosby, St. Louis, 1988, 40.)*

Acids with low pK_a are absorbed well from the stomach and bases with high pK_a have to reach the more alkaline small intestine to be absorbed well.

Another process to be considered is that after a drug passes through cell membranes, a concern arises about how much of a therapeutic dose should have been given before toxicity is a likely possibility. This can be evaluated by the use of a concept called the therapeutic index (TI_{50}), a ratio between the median lethal dose (LD_{50}) and the median effective dose (ED_{50}).

$$TI_{50} = LD_{50} / ED_{50} \qquad [1.5]$$

where the numerator is the median lethal dose and the denominator is the dose required to produce a specified effect, whereas the lethal dose is the dose that kills 50% of animals in a given population of experimental animals.[6] The graph herein (Figure 2) illustrates this modality. It is noted that no drug produces a single effect. Several TIs can be calculated for each effect. The TI is thus a measure of selectivity or margin of safety.

Only a few concepts have been discussed herein relevant to the quantitation of receptor binding. An abundant literature exists, however, on the applications of mathematics to the problems at hand. Many of these data were published between 1950 and 1960 and emphasize the use of quantitative models. The problem with models is that they need to correspond to the facts. The model is a hypothesis and it can be tested by perturbations in a system to find if it truly applies. Also, it acts as an economical condensation of the observations.

Because pharmacokinetics is drawn upon in many quantitative studies, the reader is referred to a useful chronological bibliography listing literature prior to 1963 and ending in 1971.[10]

APPENDIX II: TABLE OF NORMAL REFERENCE LABORATORY VALUES

The reference values herein are for endocrine chemistry tests commonly ordered at the Massachusetts General Hospital (MGH) and recorded in the case records of the MGH.

TABLE 1
Endocrine Chemistry

Analyte	Fluid	MGH Units	SI Units	Method or Machine	Factor to Convert to SI Units
Aldosterone					
Standing (normal-salt diet)	S, P	4–31 ng/dl	111–860 pmol/L	Immunoassay	27.74
Recumbent (normal-salt diet)	S, P	<16 ng/dl	<444 pmol/L	Immunoassay	27.74
Normal-salt diet (100–180 meq of Na)	U	6–25 μg/day	17–69 nmol/day	Immunoassay	2.774
Low-salt diet (10 meq of Na)	U	17–44 μg/day	47–122 nmol/day	Immunoassay	2.774
High-salt diet	U	0–6 μg/day	0–17 nmol/day	Immunoassay	2.774
Androstenedione	S	60–260 ng/dl	2.1–9.1 nmol/L	Immunoassay	0.0349
Antidiuretic hormone	P	1.0–13.3 pg/ml	1.0–13.3 ng/L	Immunoassay	1
Calcitonin	S			Immunoassay	
Female		0–20 pg/ml	0–20 ng/L		
Male		0–28 pg/ml	0–28 ng/L		
Catecholamines					
Dopamine	U	65–400 μg/day	424–2612 nmol/day	Liquid chromatography	6.53
	P	0–30 pg/ml	0–196 nmol/L	Liquid chromatography	6.53
Epinephrine	U	1.7–22.4 μg/day	9.3–122 nmol/day	Liquid chromatography	5.458
Supine	P	0–110 pg/ml	0–600 pmol/L	Liquid chromatography	5.458
Standing	P	0–140 pg/ml	0–764 pmol/L	Liquid chromatography	5.458
Norepinephrine	U	12.1–85.5 μg/day	72–505 nmol/day	Liquid chromatography	5.991
Supine	P	70–750 pg/ml	0.41–4.43 nmol/L	Liquid chromatography	0.005911
Standing	P	200–1700 pg/ml	1.18–10.0 nmol/L	Liquid chromatography	0.005911
Chorionic gonadotropin (hCG) (nonpregnant)	S	<10 mIU/ml	<10 mIU/ml	Immunoassay	1
Corticotropin (ACTH)	P	6.0–76.0 pg/ml	1.3–16.7 pmol/L	Immunoassay	0.2202
Cortisol	P			Immunoassay	27.59
Fasting, 8 a.m.–noon		5.0–25.0 μg/dl	138–690 nmol/L		
noon–8 p.m.		5.0–15.0 μg/dl	138–410 nmol/L		
8 p.m.–8 a.m.		0.0–10.0 μg/dl	0–276 nmol/L		
Cortisol, free	U	20–70 μg/day	55–193 nmol/day	Immunoassay	2.759

TABLE 1 (continued)
Endocrine Chemistry

Analyte	Fluid	MGH Units	SI Units	Method or Machine	Factor to Convert to SI Units
C-Peptide	S	0.30–3.70 µg/L	0.10–1.22 nmol/L	Immunoassay	0.33
11-Deoxycortisol (after metyrapone)	P	>7.5 µg/dl	>216 nmol/L	Immunoassay	28.86
1,25-Dihydroxy-vitamin D	S	16–42 pg/ml	38–101 pmol/L	Immunoassay	2.4
Erythropoietin	S	<19 mU/ml	≤19 U/L	Immunoassay	1
Estradiol	S, P			Immunoassay	3.671
Female					
Premenopausalj		23–361 pg/ml	84–1325 pmol/L		
Postmenopausal		<30 pg/ml	<110 pmol/L		
Prepubertal		<20 pg/ml	<73 pmol/L		
Male		<50 pg/ml	<184 pmol/L		
Gastrin	P	0–200 pg/ml	0–200 ng/L	Immunoassay	1
Growth hormone	P	2.0–6.0 ng/ml	2.0–6.0µg/L	Immunoassay	1
Hemoglobin A	P	3.8–6.4%	0.038–0.064	Liquid chromatography	0.01
Homovanillic acid	U	0.0–15.0 mg/day	0–82 µmol/day	Liquid chromatography	5.489
17-Hydroxycortico-steroids	U			Colorimetry	2.759
Female		2.0–6.0 mg/day	5.5–17 µmol/day		
Male		3.0–10.0 mg/day	8–28 µmol/day		
5-Hydroxyindole-acetic acid (lower in women)	U	2–9 mg/day	10–47 µmol/day	Colorimetry	5.23
17-Hydroxypro-gesterone	S			Immunoassay	3.026
Female					
Prepubertal		0.20–0.54 µg/L	0.61–1.63 nmol/L		
Follicular		0.02–0.80 µg/L	0.61–2.42 nmol/L		
Luteal		0.90–3.04 µg/L	2.72–9.20 nmol/L		
Postmenopausal		<0.45 µg/L	<1.36 nmol/L		
Male					
Prepubertal		0.12–0.30 µg/L	0.36–0.91 nmol/L		
Adult		0.20–1.80 µg/L	0.61–5.45 nmol/L		
25-Hydroxyvitamin D	S	8–55 ng/ml	20–137 nmol/L	Immunoassay	2.496
Insulin	S	0–29 µU/ml	0–208 pmol/L	Immunoassay	7.175
17-Ketogenic steroids	U			Colorimetry	3.467
Female		3.0–15.0 mg/day	15–52 µmol/day		
Male		5.0–23.0 mg/day	17–80 µmol/day		
17-Ketosteroids	U			Colorimetry	3.467
Female and male ≤10 years old		0.1–3.0 mg/day	0.4–10.4 µmol/day		
Female and male 11–14 years old		2.0–7.0 mg/day	6.9–24.2 µmol/day		
Female ≥15 years old		5.0–15.0 mg/day	17.3–52.0 µmol/day		
Male ≥15 years old		9.0–22.0 mg/day	31.2–76.3 µmol/day		
Metanephrines, total	U	0.0–0.90 mg/day	0.0–4.9 µmol/day	Spectro-photometry	5.458

TABLE 1 (continued)
Endocrine Chemistry

Analyte	Fluid	MGH Units	SI Units	Method or Machine	Factor to Convert to SI Units
Parathyroid hormone	P	10–60 pg/ml	10–60 ng/L	Immunoassay	1
Parathyroid-related protein	P	>1.5 pmol/L	>1.5 pmol/L	Immunoassay	1
Pregnanediol	U			Gas chromatography	3.12
Female		0.2–6.0 mg/day	0.6–18.7 μmol/day		
Follicular phase		0.1–1.3 mg/day	0.3–5.3 μmol/day		
Luteal phase		1.2–9.5 mg/day	3.7–29.6 μmol/day		
Pregnancy		Gestation period dependent	Gestation period dependent		
Male		0.2–1.2 mg/day	0.6–3.7 μmol/day		
Pregnanetriol	U	0.5–2.0 mg/day	1.5–6.0 μmol/day	Gas chromatography	2.972
Prolactin	S			Immunoassay	1
Female		0–15 ng/ml	0–15 μg/L		
Male		0–10 ng/ml	0–10 μg/L		
Renin activity	P			Immunoassay	0.2778
Normal salt intake					
Recumbent 6 hr		0.5–1.6 ng/ml/h	0.14–0.44 ng/(L · s)		
Upright 4 hr		1.9–3.6 ng/ml/h	0.53–1.00 ng/(L · s)		
Low salt intake					
Recumbent 6 hr		2.2–4.4 ng/ml/h	0.61–1.22 ng/(L · s)		
Upright 4 hr		4.0–8.1 ng/ml/h	1.11–2.25 ng/(L · s)		
Upright 4 hr, with diuretic		6.8–15.0 ng/ml/h	1.89–4.17 ng/(L · s)		
Somatomedin C	P			Immunoassay	1
Female					
Preadolescent		60.8–724.5 ng/ml	60.8–724.5 μg/L		
Adolescent		112.5–450.0 ng/ml	112.5–450.0 μg/L		
Adult		141.8–389.3 ng/ml	141.8–389.3 μg/L		
Male					
Preadolescent		65.5–841.5 ng/ml	65.5–841.5 μg/L		
Adolescent		83.3–378.0 ng/ml	83.3–378.0 μg/L		
Adult		54.0–328.5 ng/ml	54.0–328.5 μg/L		
Testosterone, total, morning sample	P			Immunoassay	0.03467
Female		20–90 ng/dl	0.7–3.1 nmol/L		
Male, adult		300–1100 ng/dl	10.4–38.1 nmol/L		
Testosterone, unbound, morning sample	P			Equilibrium dialysis	34.67
Female, adult		0.09–1.29 ng/dl	3–45 pmol/L		
Male, adult		3.06–24.0 ng/dl	106–832 pmol/L		
Thyroglobulin	S	0–60 ng/ml	0–60 μg/L	Immunoassay	1
Thyroid-hormone-binding index		0.83–1.17	0.83–1.17	Charcoal resin	1
Thyroid-stimulating hormone	S	0.5–5.0 μU/ml	0.5–5.0 mU/L	Immunoassay	1

TABLE 1 (continued)
Endocrine Chemistry

Analyte	Fluid	MGH Units	SI Units	Method or Machine	Factor to Convert to SI Units
Thyroxine, free	S	0.8–2.7 ng/dl	10–35 pmol/L	Direct equilibrium dialysis	12.87
Thyroxine-binding globulin	S	Age and sex dependent	Age and sex dependent	Immunoassay	
Thyroxine, free, index		4.6–11.2	4.6–11.2	Calculation	1
Thyroxine, total (T_4)	S	4–12 μg/dl	51–154 nmol/L	Immunoassay	12.87
Triiodothyronine, total (T_3)	S	75–195 ng/dl	1.2–3.0 nmol/L	Immunoassay	0.01536

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APPENDIX III: SMITHKLINE BEECHAM CLINICAL LABORATORIES PERFORMING ENDOCRINE DIAGNOSTIC TESTS

The editors and chapter author wish to thank Ms. Barbara Wickersham, Quality Assurance Manager at SmithKline Beecham Clinical Laboratory in St. Louis, for providing a geographic list of the major SKB diagnostic laboratories.

ATLANTA
1777 Montreal Circle
Tucker, GA 30084
(404) 934-9205
(800) 877-8805

Drugs of Abuse Testing
3175 Presidential Drive
Atlanta, GA 30340
(800) 729-6432

BALTIMORE
11425 Cronhill Drive
Owings Mills, MD 21117
(301) 581-2400
(800) 729-7525

BOSTON
343 Winter Street
Waltham, MA 02154
(617) 890-6161
(800) 669-4566

CHICAGO
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Schaumburg, IL 60173
(708) 885-2010
(800) 669-6995

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Valley View, OH 44125
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(800) 854-1774 (OH only)

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Dallas, TX 75247
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(800) 442-2102

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(800) 356-2142

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(800) 882-7012

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Nashville, TN 37203
(615) 327-1855
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(800) 251-2633 (outside TN)

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(800) 452-7669

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Syosset, NY 11791
(516) 677-3800
(800) 877-7530

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Norristown, PA 19403
(215) 631-4200
(800) 523-5447

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(800) 829-7225 (AZ only)

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San Antonio, TX 78207
(512) 225-5101
(800) 292-7466

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San Diego, CA 92126
(619) 536-1338
(800) 479-2121 (within San Diego Co.)

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6511 Golden Gate Drive
Dublin, CA 94568
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(800) 228-3008 (Northern California)

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(800) 877-0051

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(800) 669-7525
(800) 669-8077 (client response)

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Tallahassee, FL 32308
(904) 877-5171

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Tampa, FL 33617
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AFFILIATED LABORATORIES
Scripps Immunology Reference Laboratory
11107 Roselle Street
Suite A
San Diego, CA 92121
(619) 453-7155

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