The following address is not to be considered as a history of endocrinology dedicated to giving detailed credit and priorities to the various leaders and workers in the field. It attempts merely to paint the picture of the changing concepts and methods of endocrinology and to show the close interlocking of the many disciplines. Due to lack of time the names of many leading contributors have not been mentioned. For these many omissions the writer humbly apologizes and hopes that no personal offense is taken.—L. W.

Members and Guests of The Endocrine Society:

I

KNOW from my own experience that at this time of the evening you, one and all, begin to think of Bed or of Bar while you consider it your painful duty to listen politely, but somewhat drowsily, while a President ruminates about Past, Present or Future. I shall risk being accused of senility by turning my thoughts to the Past of Endocrinology.

I cannot resist the temptation to look back to the years when I was a Medical Student and House Officer and to recall the status of endocrinology at that time. I was a little surprised to recall that the founding in 1918 of The Endocrine Society, then known by the tongue-twisting title of The Association for the Study of Internal Secretions, coincided with the year of my graduation and that the first President was my Professor of Medicine, Dr. Lewellys F. Barker. During my student and hospital days there was a great deal of talk and enthusiasm about the endocrine glands and their relation to certain diseases was well recognized. Indeed, there was a feeling of tense excitement and there were interesting speculations concerning marvelous discoveries which probably lay ahead in the mystic future.

ENDOCRINOLOGY IN 1920

In 1920 the various thyroid disorders were recognized and diagnosed clinically almost as well as they are today. Thyroid substance had been used therapeutically ever since 1893 when Osier administered it to the first cretin in this country one year after MacKenzie and Fox, in England, had demonstrated its effectiveness. The BMR was being used in diagnosis. Thyroidectomies were being performed but there was still a high mortality since Plummer did not demonstrate the preoperative value of Lugol's solution until 1923. Marine was carrying out, in Akron, Ohio, large scale demonstrations of the value of iodine in the prevention of endemic goiter. Kendall had just announced the isolation of crystalline thyroxine.

The relation of the islets of Langerhans to diabetes mellitus had been demonstrated by von Mering and Minkowski in 1889. In histology, we
students were shown the difference between alpha and beta cells, but we did not know their respective functions. The importance of diet and the role of fat in ketosis and acidosis were understood. We had begun to measure CO₂-combining power and we gave our acidotic patients Na-bicarbonate. We had no specific therapy and had never heard of the importance of K.

We knew that the tiny parathyroid glands were important in regulating serum calcium because MacCallum and Voegtlin at Hopkins in 1908 had produced hypocalcemic tetany by parathyroidectomizing dogs. In many other places this relationship was denied and there was much talk about the convulsive effects of guanidine and the detoxifying action of the parathyroids. But we were loyal to our Alma Mater and all for MacCallum and calcium. We were, however, confused a bit by some of the other types of hypocalcemic tetany, and vitamin D had not yet been discovered.

Sex and the sex glands naturally had been of interest since ancient times and the effects of both sexual precocity and castration on somatic growth as well as sexual development had been well described. Although Leydig had observed the interstitial cells of the testes in 1850, their function was still unknown. Prenant in 1898 had suspected the corpus luteum of being an endocrine organ and subsequently the fact that its presence was required for the implantation of the ovum and the maintenance of pregnancy had been established. Gynecologists had studied extensively the endometrial changes of the menstrual cycle and Papanicalou had begun to study the cyclic alterations of the vaginal epithelium.

The adrenals were looked upon as glands of considerable importance; and the embryological and functional differences between cortex and medulla were understood. The first pure hormone, epinephrine, had been isolated in 1899 by our professor of pharmacology, Abel; and it had been synthesized in 1905. Its pharmacologic actions had helped greatly in unravelling the mysteries of the sympathetic and parasympathetic systems. Ampules of adrenalin were at hand on every ward for us internes to use in the treatment of all sorts of shock and we often injected it heroically into the vertricles when the heart stopped beating. We were taught the great importance of the adrenal medulla in preparing the animal to meet acute stress and in adapting to special emergencies as pointed out by Walter Cannon. “Diseases of Adaptation” were not part of our curriculum.

The diverse manifestations of adrenal disorders puzzled us very much. On the one hand, our professors showed us not infrequently patients with the disease Addison had described with its pigmentation, asthenia, wasting, hypotension, and inevitable death; but offered no satisfactory explanation for these symptoms. On the other hand, it had been known since the paper of Bulloch and Sequeira in 1905 that pseudohermaphroditism, virilization and hirsutism were sometimes associated with tumor or enlargement of the adrenal cortex. Cushing’s syndrome had not been heard of.
The pituitary gland, which Vesalius had accused of secreting nasal mucus, in 1920 attracted attention principally because of its alleged effects on growth. Pierre Marie in 1886 had considered acromegaly due to destruction of the pituitary by a tumor. However, in 1916 Erdheim had emphasized the association of dwarfism and sexual infantilism with destructive lesions of the pituitary. We were quite willing to accept his hypothesis that the pituitary accelerated growth, because our own teachers Samuel Crowe and Harvey Cushing in 1910 had produced dwarfed dogs by hypophysectomy. Skeptics elsewhere contended that the dwarifying probably was due to general debility and malnutrition resulting from the operation and nearly 20 years were to pass before the growth hormone theory was proved by replacement therapy in rats by P. E. Smith and in dogs by Herbert Evans and his colleagues.

The anterior pituitary had not yet assumed its role as the omnipotent "master gland" or the magnificent homeostatic regulator of the endocrine system, although it was strongly suspected that it might have other effects than those on growth and some close relationship to the nervous system. It was recognized that there were interrelationships between the various endocrine glands. However, since potent hormones had not been isolated, and implantation of bits of glandular tissue often gave confused and conflicting results, the interrelationships were based largely on extirpation experiments, or clinical pathologic observations, in which it was found that when a certain gland was removed, some of the other glands hypertrophied while others atrophied. In 1910, Biedl had collected and described these numerous studies in a voluminous book entitled "Innere Sekretione," which long remained the bible of endocrinology. As a somewhat lazy student, I was advised to read a shorter English text entitled "Regulators of Metabolism" by Noel Patton, professor of physiology at the University of Glasgow. I did this with considerable interest, underlining important facts which I resolved never to forget. I dusted off this book the other night and was surprised to learn that there is an interrelationship between the pituitary and the thyroid of such a nature that when the thyroid is removed the pituitary enlarges and when the pituitary is removed the thyroid undergoes considerable hypertrophy apparently in order to take over its job.

Thus, by 1920 there had been sufficient clinical observations and experimental studies to establish convincingly the great importance of the "Secretions internes" which Claude Bernard had postulated in 1857. It was realized, of course, that hormones must exert their effects on metabolic or physiologic processes. Nevertheless, the clinician's interest was attracted mostly by the spectacular morphologic alterations of body build, skin, hair and fingernails which occurred in such syndromes as cretinism, acromegaly, dwarfism, eunuchoidism, Froehlich's syndrome and virilism, which had been so carefully and beautifully described. It was predicted that many new syndromes would be discovered and formes frustes or varia-
tions and combinations of the known ones revealed. My teachers, Lewellys F. Barker and Thomas Futcher, and many other astute diagnosticians were keen in this search and examined their patients minutely, applying the relatively few chemical tests where were available.

ENDOCRINOLOGY IN 1935–1940

Let us jump forward 15 or 20 years. In 1935, when Dr. Edwards Park suggested that I organize a pediatric endocrine clinic, I asked him flip-pantzly whether he wanted to turn an honest but poor pediatrician into a charlatan. I showed my ignorance by this remark but I was influenced by some texts of clinical endocrinology and published papers which I read, and lengthy protocols coming from celebrated physicians. Most diagnosticians were seeking and describing more and more subtle morphologic changes and various unimportant signs and symptoms. More chemical laboratory tests were being made; and these were often in error or misinterpreted. One marvelled, but was not convinced, at the ingenuity with which diagnoses were made. Pluriglandular syndromes were being invented in which there was postulated overactivity of glands A and B with hypofunction of glands C, D and E. This tendency was aided and abetted by some pharmaceutical firms which put out preparations which contained varying proportions of testes, pituitary and thyroid with pinches of thymus, pineal and tonsils thrown in for flavoring. To help the less erudite physician in diagnosis, their advertising contained illustrations such as that shown on the following page.

Nevertheless, since 1920 a relatively few but some very important advances in clinical endocrinology had been made. The first parathyroid tumor was removed by Mandl in 1925, a pheochromocytoma by C. H. Mayo in 1927 and an insuloma by Howland in 1929. A few virilizing adrenal tumors had been successfully removed but most patients died.

In July 1921, Banting and Best prepared the first insulin and in January 1922 the first diabetic patient, a doctor from Nova Scotia, was treated. This was a great stimulus to attempts to prepare active hormones. In 1927, Abel isolated pure insulin crystals and in the same year Harrington and Barger announced the structure and chemical synthesis of thyroxine. In 1928, Kamm separated the vasopressor or antidiuretic from the oxytocic factor of the posterior pituitary making possible their therapeutic uses.

In 1925, Rogoff and Stewart, in 1927, Hartman et al. and in 1931, Swingle and Pfiffner prepared extracts of the adrenal cortex which prolonged the survival time of adrenalectomized dogs when they were given abundant NaCl and glucose in addition. Beginning in 1929 these extracts were given to Addisonian patients with some improvement, but the results were far from brilliant. In 1933, Robert Loeb, and shortly afterward George Harrop, treated Addisonian patients with NaCl with some success. Harrop and his group at Hopkins then began to adrenalectomize dogs and were
These types are often hereditary but in all cases are associated with peculiar reactions of the glands of internal secretion.

(Reproduced from Stockard. The illustration typifies the kind of advertising that was used early in the marketing of glandular preparations.)
joined shortly by a sandy-haired boy from Buffalo, named Thorn, who collected a famous pack of bassett hounds, favorites of the rabbit hunters in Maryland. As a result of their careful and tedious studies of electrolytes, long before the temperamental flame photometer was known, the role of sodium and chloride in producing the symptoms of Addison’s disease was thoroughly elucidated; while the importance of potassium was emphasized by Wilder in 1936.

Between 1923 and 1926, Hanson, a U. S. Army surgeon and Collip in Canada, working independently, prepared active extracts of the parathyroid glands. The study of lead poisoning had turned the attention of Joe Aub, tonight’s recipient of the Endocrine Society Medal, toward basic investigation of calcium metabolism and bone physiology. The soil was thus prepared for the study of Collip’s parathyroid extract by Aub and his brilliant coworkers, Walter Bauer and young Fuller Albright. In the years around 1930 an exchange of residents and fellows between Massachusetts General Hospital and Johns Hopkins brought the Promethean fire from Bostonian Olympus to Baltimore where its phosphorescence inspired Read Ellsworth, Palmer Futcher and our Maryland tennis champion, Johnnie Howard. The dual fires, burning brightly ever since and lighting new conflagrations elsewhere, have led to the description and study of hypo- and hyper-parathyroidism, and numerous metabolic bone and renal disorders and the investigation of the effects of parathyroid and other hormones and of vitamin D upon calcium and phosphorus metabolism.

During this same period work was being carried out which seemed less spectacular but was even more important in laying the foundation for the future progress of endocrinology. Anatomists and physiologists, working painstakingly in their laboratories on small animals were devising ingenious new methods of hypophysectomy and of parabiotic union, which were to reveal the basic relationships of the endocrine system and techniques of bioassay which were to lead to the isolation of pure hormones and to more accurate diagnosis of clinical disorders. A long series of investigations finally clarified the role of the pituitary as the “master gland.” As early as 1916, Philip E. Smith studied the effects of hypophysectomy and implanting pituitary tissue in tadpoles and in 1921 Herbert M. Evans was observing the effect of injecting crude pituitary extracts on the growth of rats. By 1926 Smith had perfected the technique for hypophysectomizing rats. In 1926 both Smith and Zondek were carrying out experiments which showed that crude pituitary extracts repaired the gonadal atrophy which resulted from hypophysectomy. In 1928 Ascheim and Zondek discovered that the injection of the urine of pregnant women exerted gonadotropic effect on the ovary of the rat and thereby laid the foundation for the future development of gonadotropic assay. The lists of the pioneers who studied the tropic hormones of the pituitary during the 1930’s is too long to enumerate. In the gonadotropic field there were Smith, Fevold, Hisaw,
van Dyke, Greep, Evans and his coworkers, Riddle, Lyons and others too numerous to mention. At the same time Collip, Pugsley, Evelyn Anderson and others were studying thyrotropic hormone and the Evans group growth hormone. Later these pioneer workers were joined by skillful protein chemists such as Choh Haoh Li, A. White, Cierezsko, Wilhelmi and others. George Sayers and others began to measure the ascorbic acid and cholesterol content of the adrenal as an index of its activity, thereby developing a method for the measurement of ACTH. This phase of work continued for another decade, during which prolactin was isolated by Lyons in 1937 and identified as luteotropin by Astwood in 1941; L. H. was separated from FSH, identified with ICSH, and isolated in 1940; thyrotropin was isolated in 1942; ACTH in 1943; and growth hormone in 1944.

During this era of great discoveries, there occurred a happy union between the endocrinologists and steroid chemists which bore much fruit. The development by Allen and Doisy in 1923 of a method for bioassaying estrogen led to the isolation of estrone by Doisy et al. and by Butenandt in 1929, and the synthesis of estradiol by Schwenk and Hildebrant in 1933. Similarly the perfection of the capon-comb androgen assay by Koch and his coworkers enabled his pupil, McGee, to obtain an active alcoholic extract of bull’s testes in 1927 and led to the isolation of crystalline testosterone by David, Dingemanse, Freud and Laqueur in 1935 and its synthesis by Butenandt and by Ruszika in the same year. The pioneer studies of the corpus luteum by George W. Corner and the development of a bioassay method by Corner and Allen in 1929 led eventually to the isolation of progesterone by Wintersteiner and Allen in 1934 and its synthesis by Butenandt and by Fernholz within the same year. In the meantime the chemists were studying the steroids of the adrenal cortex, but it was not until 1936 that Mason, Kendall et al. isolated Compounds A and B and Reichstein isolated B and named it corticosterone. The following year Steiger and Reichstein synthesized desoxycorticosterone.

The isolation from the urine of steroids shown later to be the degradation products of the sex hormones was likewise of the greatest importance. Pregnanediol was isolated from pregnancy urine by Marrian in 1929 and Butenandt obtained androsterone in 1931. The Zimmerman reaction was discovered in 1935, and in 1938 Callow and coworkers described the method now used with various modifications for the measurement of 17-keto-steroids.

Thus, by the end of the 1930’s the basic relations of the endocrine system had been clarified; bioassay and chemical methods which could be applied for studying hormonal secretion in patients with various disorders had been devised; and biologically potent hormones were available to study their metabolic and other actions in the human subject. Tools and methods were now ready to be applied by the clinical investigator.
During the years between 1935 and 1943, the daily output of urinary gonadotropins and sex hormones were measured and the norms established for childhood, adolescence and adult life by Catchpole and Greulich; Nathanson, Towne and Aub, Talbot and coworkers and by the Albright group. Hormonal measurements made by Rakoff and Canterow, by G. W. and O. W. Smith, by Venning and others combined with the careful observations of vaginal and endometrial changes on monkey and man by Carl Hartman, Corner, Hisaw, Earl Engle and others clarified most of the mysteries of the menstrual cycle, the menopause and pregnancy.

The diagnostic value of gonadotropic assays was demonstrated in 1942 when Varney, Kenyon and Koch and Albright and his colleagues, showed that they served to differentiate primary gonadal defects from hypogonadism due to pituitary deficiency. Albright then elucidated the syndrome described by Henry Turner, which subsequently became known incorrectly as "ovarian agenesis and stunted growth." Shortly afterward the Albright group and Heller and Nelson applied gonadotropic studies to the diagnosis of primary testicular disorders. During this period Albright was blazing the pathway for more rational diagnosis by showing the importance of studying gonadotropins, urinary 17-ketosteroids and carbohydrate metabolism in suspected pituitary deficiency.

In the early 1940's clinical investigators began to study intensively the metabolic actions of the recently discovered hormones which were now available. J. S. L. Browne, Kenyon and his group, McCullagh, and Albright et al. and Wilkins and Fleischman studied the protein-anabolic action of testosterone and methyltestosterone and were seeking unsuccessfully new steroids which might be anabolic without virilizing. The metabolic actions of the adrenocortical hormones, aside from their effects on electrolytes, were being studied also. As early as 1927, Cori and Cori had shown that liver glycogen was depleted in adrenalectomized animals, and in 1932 Britton and Silvette had emphasized the role of the adrenal in carbohydrate metabolism. Between 1936 and 1940, C. N. H. Long and his coworkers carried out careful animal experiments elucidating the gluconeogenetic action of the adrenocortical steroids and demonstrated that they increased the deamination of the amino acids. Cushing first described his syndrome in 1932 at a lecture which I attended at Hopkins; but this disorder was thought then to be due to a pituitary disorder. In 1938 Anderson and Haymaker suggested that the symptoms of Cushing's syndrome could all be accounted for by the overproduction of the various adrenocortical hormones. Nevertheless, the manifold symptomatology remained a mystery to most clinicians until it was beautifully elucidated by Albright in his Harvey Lecture of 1942. During the early 1940's there was
also intense interest in the role played by the metabolic effects of both adrenocorticoids and androgen in acute and chronic illness and in various forms of injury and stress.

The Josiah Macy, Jr., Conferences, organized by Dr. Fremont-Smith under the inspiring leadership of Fuller Albright, brought together the various groups of clinical investigators working on these metabolic problems, such as the groups of Albright, John Browne, Bassett, Kenyon, Kochakian, Shorr, Howard and myself, with leaders in steroid chemistry such as Dobriner and Gallagher, Kendall and Mason, and Pincus and Dorfman. These conferences afforded a rare opportunity for interesting and stimulating discussion and interchange of information concerning work in progress. The peak of intellectual activity generally was reached after midnight in Dobie's apartment aided by alcoholic extraction. This conference was concerned also with Ca and P metabolism, the composition of bone, and the effects on bone of parathyroid and other hormones being studied by Albright and Reifenstein, J. E. Howard, Armstrong and others. We were kept informed by Dobriner and Gallagher of their pioneering work in the column fractionation of steroids and the patterns found in carcinoma and various conditions. In these meetings many of us first learned from Dent about paper chromatography and from Stettin about the use of radioisotopes in the study of intermediary metabolism.

During this period, Selye had been studying the effects of stress on the rats' adrenals and in 1946 he elaborated his theories concerning the role of the adrenal cortex in adaptation to stress. The hypothalamic-pituitary-adrenocortical system then assumed its place as the homeostatic regulator of metabolism which enables the organism to meet the needs of stressful influences.

In 1949 a tremendous stimulus to the study of adrenal physiology and of the effects of adrenal hormones upon the peripheral tissues resulted from Hench's discovery that rheumatoid arthritis was favorably affected by cortisone, recently synthesized by Kendall. Within a short time effective preparations of ACTH were made available through the efforts of John L. Mote of the Armour Laboratories. The experimental use of these substances in innumerable diseases and the study of their antiallergic and antiinflammatory actions have shown that the effects of adrenal hormones are not confined to regulating carbohydrate, protein and fat metabolism but have still poorly-understood effects upon collagen, cells and enzyme systems. Dr. Mote deserves great credit for organizing the ACTH Conferences of 1951 and 1952 so that the rapidly accumulating knowledge of scores of investigators could be promptly pooled and evaluated.

The availability of cortisone and related compounds made adequate substitution therapy possible and resulted in therapeutic advances such as the operative cure of Cushing's syndrome and the employment of hypophysectomy for the palliation of cancer. Nothing in medicine is more
spectacular and gratifying than the prevention or control of virilization in female pseudohermaphrodites which resulted from the discovery in 1950 that virilizing adrenal hyperplasia can be suppressed by physiologic doses of cortisone.

Simultaneously with clinical investigations during the 1940’s and 1950’s, chemists had been perfecting methods for the fractionation and isolation of minute amounts of individual steroids in both plasma and urine. These techniques and the use of radioisotopes made possible experiments on the conversion of steroids by tissue slices and homogenates, the perfusion of glands, and the measurement of steroids in blood coming directly from the adrenal or spermatic veins of intact animals. Such experiments carried out by Dorfman, Hechter, Pincus and others of the Worcester group, by Leo Samuels and his pupils, by Dobriner and Gallagher and by Libermann have increased our knowledge concerning the nature of the active hormones secreted by the glands and have established the probable pathways of their biosynthesis, metabolism, degradation and excretion. The preliminary work of Luetscher and the further application of refined chemical and bioassay techniques led to the isolation of aldosterone and the determination of its structure by Simpson, Tate, Wettstein, Neher and Reichstein in 1954.

It should be emphasized that the clinical investigators have made important contributions to basic knowledge by studying the “experiments of nature” which he encounters and which cannot be reproduced in animals. A notable example is virilizing adrenal hyperplasia. The suggestions of Bartter, of Jailer and of Kelley that this disorder might be due to a defect in the normal synthesis of hydrocortisone resulting in the excessive production of androgenic steroids gave a great impetus to the study of steroidal patterns before and after treatment with cortisone. The studies of Dorfman and of Bongiovanni and Eberlein have demonstrated that there are two different defects in the hydroxylation of progesterone, one of which accounts for the coexistence of hypertension in certain cases of the virilizing syndrome. Similarly the discovery and study of goitrous cretinism in regions where there is no deficiency of iodine has led to renewed interest in the pathway of synthesis of thyroid hormones and the demonstration by Stanbury, McGirr and Hutchinson, Pitt-Rivers and others that hypothyroidism can be caused by enzyme defects. These findings in virilizing adrenal hyperplasia and in goitrous cretinism lead to the new concept that some endocrine disorders may be due to inborn, genetically-determined defects of enzymes necessary for normal hormone synthesis.

Time does not permit an enumeration of the many advances of endocrinology during the last few years. I can only mention the culmination of du Vigneaud’s work of 30 years in the determination of the exact structure and in the synthesis of vasopressin and oxytocin. Attention has focused again on the neurohumoral secretions of the hypothalamus and on attempts
to localize in this tiny structure the exact areas of specific functions. The works of experimental embryologists such as Jost and Wells who studied the effects of castration in very young embryos, and of cytologists such as Barr, who studied sex chromatin patterns, have combined with the observations of endocrinologists and clinicians in helping elucidate some of the mysteries of hermaphroditism and gonadal dysgenesis.

Thus, the embryologist, anatomist and cytologist; the physiologist and clever animal experimenter; the enzymologist and geneticist; the chemist skilled in steroidal methodology and synthesis, in protein structure and fractionation or working on the structure of iodinated compounds; the clinical diagnostician or investigator interested in electrolyte or carbohydrate metabolism, in bone disorders and calcium metabolism, or in renal physiology, have all combined to advance endocrinology. I know of no scientific organization other than our Endocrine Society, which combines in common interests so many experts with totally different skills and disciplines as I see before me tonight. Your work has not only elucidated the endocrine disorders and facilitated their diagnosis and treatment but has contributed greatly to the advancement of all physiology and biochemistry and the understanding and treatment of disease.