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EDWIN BENNETT ASTWOOD

1909—1976

A Biographical Memoir by

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Biographical Memoir

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Edwin B. Westwood

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December 29, 1909–February 17, 1976

BY ROY O. GREEP AND MONTE A. GREER

DR. EDWIN BENNETT ASTWOOD was born in Hamilton, Bermuda, on December 29, 1909 and died there February 17, 1976. With his passing, endocrinology lost one of its best investigators and one of its most magnetic personalities. Widely recognized and much honored as a brilliant scientist, Dr. Astwood also possessed exceptional personal charm and that mystical human quality, charisma. Though humble in attitude and totally unpretentious, he had a following of peers as well as friends and admirers who held a feeling toward him that bordered on worship. His home, his laboratory, and his clinics were meccas. Few have appreciated privacy more, or endured intrusions upon it with such gentility and good humor, as Dr. Astwood, more popularly known as Ted, and to family and intimate friends as Teddy. Such fame, admiration, respect, and popularity were deserved. Ted had much to give, both intellectually and judgmentally.

Ted's mastery of factual information in biology and medicine seemed limitless, but even more impressive is the range of his sphere of expertise, which extended far beyond these fields. Ted was not only driven by an insatiable curiosity, but by a curiosity that sought answers with willful determination. There are, of course, unanswerable questions

concerning both the natural and physical universe, and these bothered Ted. They also served to stretch his free-ranging imagination and conceptual powers. When no answer existed, Ted had a theory.

Ted's view of life and mortality was untainted by emotion. He considered fear of death a sign of weakness; he abhorred funeral services. Once, however, in a reflective mood, and perhaps overwhelmed by curiosity as he viewed some geologic reminders of the ancient past, he did comment, half jokingly, on how interesting it would be if one could live to see what the world would be like in ages to come.

Ted received his primary and secondary education in Bermuda, where he grew up in a family with long-standing business interests on the island. He lived a normal, happy boyhood, filled with scholastic and athletic achievements of a high order. In sports, he set a Bermuda record in the high jump that held up for many years. His free time was busily occupied with swimming, sailing, and tennis, and he excelled in all three. As a hobby, he fashioned homemade telescopes with which he studied the constellations and their movements. It is characteristic of his independence of thought that he did not share in his family's religious sentiments. His mother and father were followers of different faiths, and both devout.

When it came time for Ted to go to college, it was in deference to his mother's wishes that he attended the Washington Missionary College in Ohio. (Incidentally, Ted received all of his undergraduate and professional education in the United States and Canada.) Ted was never irreverent, but he was an agnostic, a realist, and scrupulously objective. His early exposure to powerful religious influence caused him personal turmoil. Having completed college and made the decision to study medicine, he was again prevailed upon

by his mother to enter the College of Medical Evangelists at Loma Linda University. After two years of struggle with the conflict between family ties and restraints on freedom of thought on the one hand, and a deepening need to master his own destiny on the other, Ted left Loma Linda and completed his medical education at the McGill University Medical School, taking his M.D. and C.M. degrees in 1934. The following year, as a house officer at the Royal Victoria Hospital, he came under the influence of a talented group of endocrine investigators, including J. S. L. Browne, Eleanor Venning, and Hans Selye, with all of whom he maintained enduring personal relationships. They introduced Ted to the challenge of scientific inquiry and set him on a course that was to make medical history.

Ted's departure from McGill was abrupt and sparked by an unpleasant exposure to authoritarianism. It entailed Ted's presentation of a very sick patient he had admitted during the night. The chief of medicine, after hearing the description of the problem, asked for Ted's diagnosis, which was typhoid fever. There followed a blistering attack and an enumeration of reasons why typhoid fever was an indefensible explanation of the patient's illness. Some days later he asked Ted if there were any new developments in this case, and the answer was "Yes, sir, blood cultures show growth." The answer to the next question was, "Typhoid bacillus, sir." To which the weaseling response was, "Now, Astwood, would you not rather have been wrong with my reasoned analysis than have the encumbrance of this meaningless victory?" This incident crystalized Ted's decision to turn to medical research. Although he lacked a firm job offer, he moved his work to Johns Hopkins Hospital and sought an appropriate appointment.

The years 1935 to 1937 were spent at the Johns Hopkins University Surgical Pathology Laboratories, where he

worked with Charles Geschickter, whose interests lay in the interrelationships of nutrition, hormones, and neoplasia. This provided Ted with his first opportunity for a full-scale effort in basic research and promptly resulted in some notable publications on the hormonal control of the mammary gland in rats and on color changes in fish. These studies served to focus immediate attention on this young investigator. In December 1936, he was invited to present his work on hormonal induction of mammary changes before the Harvard Medical Society.

This early excursion in the realm of pure science broadened Ted's horizons and led him to seek a Ph.D. degree. In 1937 he was awarded a Rockefeller Fellowship and was accepted for graduate work in biology at Harvard University. He was to work with Professor Frederick L. Hisaw, one of the great early pioneers in endocrine research. There at the Biological Laboratories, Ted joined a vigorous group of Hisaw associates and fellows, including Harry Fevold, Alexander Albert, Edward Boettiger, Virginia Fiske, Mark Foster, Roy Greep, Clinton Osborne, Charles Pomerant, and M. X. Zarrow. Losing no time, Ted plunged into research, recording a startling early success with his demonstration that the initial action of estrogen on the uterus involved the movement of water.

Ted was awarded a Ph.D. by Harvard University in 1939 and was immediately called back to Johns Hopkins to work in obstetrics. In a joint effort with George Anna Seegar Jones, a new and vastly improved method for the measurement of pregnanediol was developed; in another study, he described a third gonadotropin in the rat, which he named luteotrophin. Within a year Ted was lured back to Boston at the urging of Soma Weiss, physician-in-chief at the Peter Bent Brigham Hospital, and given a joint appointment as associate in medicine at the Peter Bent Brigham Hospital and assistant

professor of pharmacotherapy with laboratory facilities in Otto Kraye's Department of Pharmacology in the Harvard Medical School. Here he came in close collegial relationship with Edward Dempsey in anatomy, Walter B. Cannon and Robert Morison in physiology, and A. Baird Hastings in biological chemistry. His new duties launched him into a welcome new role as medical educator, a role that was to occupy a significant portion of his time and interest for the remainder of his academic career. It was also during his stay at the Harvard Medical School that Ted made the discoveries that were to revolutionize our knowledge of thyroid regulation and the treatment of thyroid disorders.

At the end of his five years as assistant professor at Harvard, Ted was faced with an "up or out" situation within the year, the result of a new and controversial policy introduced earlier by President James B. Conant. Known as the "eleven-year rule," it allowed only two three-year appointments at the assistant professor level. Promotion to associate professorship would have meant tenure. It might well have been granted, but two events were to intervene. Soma Weiss' death left Ted without one of his staunchest advocates. Also arguing against a permanent appointment was the beleaguered state of the Medical School's financial resources at the end of World War II. Kraye lamented at the time that his departmental funds were adequate for only one instructor. Ted's reputation was soaring; prizes and awards were coming his way. Showered by requests to go elsewhere, an offer to become research professor of medicine at Tufts University School of Medicine, combined with appointments as senior physician with the New England Medical Center Hospital, endocrinologist to the J. H. Pratt Diagnostic Hospital, and physician at the Boston Dispensary, met his needs very nicely and was accepted.

Ted was attracted to the New England Medical Center by

the opportunity of establishing an endocrine research laboratory in a clinical setting. The facilities initially available to him were quite limited, but plans for future expansion had been drawn, although they did not materialize. The hospital purchased an adjoining old factory building for renovation, and eventually most of one floor became Ted's domain. It was here that he established one of the world's most eminent and productive endocrine laboratories. Over a period of twenty-six years, talented young medical scientists came to him for training and experience in endocrine research—ninety-two in all—and many now hold positions of outstanding distinction in this special branch of biomedical science.

Much credit must be given to Dr. Samuel H. Proger, chief of medicine at the New England Medical Center, who had the vision and insight to give Ted unstinting support as he pursued his unusual career virtually free of committee responsibilities and other diversionary administrative activities. He also remained tolerant of Ted's independent *modus operandi*, which occasionally diverged from institutional policy, as on the matter of overhead.

The high point in Ted's remarkable scientific career was reached at the Tufts University New England Medical Center complex, where he spent the major portion of his professional life. He joined that institution in 1945 and was promoted to professor of medicine in 1952, a position he held until he became professor emeritus in 1973 and returned to his homeland to enter the full-time practice of medicine.

In 1937, while Ted was a fellow at the Johns Hopkins Hospital, he married one of the nurses, Sara (Sally) Merritt. Sally, with her stabilizing influence, her encouragement, her devotion, and her understanding of Ted's needs, was the perfect partner. Ted relied heavily on her judgment and counsel on almost everything outside of his experimental

work. Unlike many outstanding investigators, Ted was not totally consumed by his scientific fervor. He found time for a busy home life with Sally and their two children, Philip Merritt and Nancy Bennett.

Shortly after moving to Boston in 1942, Ted and Sally purchased an old, unoccupied stone castle in Brookline. It was in need of considerable repair, but it had exceptional potential. This house, along with many of the other large old homes in a neighborhood that had acquired—for obvious reasons—the label Pill Hill, had been abandoned during the Second World War because of lack of fuel and domestic help. Ted completed all of the repair work with an awesome investment of labor. He installed a new heating system and completely rewired all three floors. Work on the electrical installation had to be approved by the town. The inspector was much impressed by the quality of the work and commented that it was the best job he had seen in a long while. In the front yard there were some large old trees that had been damaged by the 1938 hurricane and had to be removed. Ted dug them out by the roots. It is amazing that he relished tackling jobs requiring much hard physical labor, considering that he was raised in comfortable circumstances where such menial tasks were for others.

Ted's routine was early to bed and early to rise; he awoke at 4:30 a.m. for a few quiet hours of reading, writing, and contemplation of the day's activities. When his research was in an especially exciting phase, it was not uncommon for him to start the day at the laboratory around 2:00 a.m. In the evening he was generally home in time for an hour or so of work about the house or just tinkering in his well-equipped basement shop. Shortly after dinner, he would be off to bed. With company present, he would sometimes have to retire or risk falling asleep in their presence. When Ted came up missing around 10:00 p.m. at a party in his home, everyone

understood that he had retired. He was an immensely practical fellow who did not believe in letting convention interfere with his way of life. He was no epicure. Fancy foods held no fascination for him. He looked upon eating as a necessary intervention in the day's activities solely for the purpose of bodily nutrition. The point can best be made by reference to an incident that happened in 1944 when one of us (R.O.G) stayed overnight at the Astwood home. On our way out at dawn, Ted stopped by the kitchen and gulped down two raw eggs in a glass of cold, leftover coffee. He made an hospitable gesture, but after watching the passage of each egg register on his Adam's apple, I experienced a sudden loss of appetite.

Despite his popularity, Ted was not an easy social mixer. He was not shy or timid, but he was not comfortable among strangers, and he detested making small talk. He enjoyed parties at his own home where the guests were all close friends. He also disliked traveling alone. With Sally, however, he would unhesitatingly go anywhere—and did. They traveled extensively and with much mutual enjoyment.

As a focus for his creative energies, Ted's shop was second only to his laboratory. He turned out elegant pieces in woodworking and built radio sets, but nothing quite matched his accomplishment in that novelty of the times, high-fidelity audio transmission. Each production was a bigger, better, and more powerful Hi-Fi. The final one would have served an amphitheater quite nicely. At home it could shiver the timbers. Ted had a slight hearing problem, but he had no difficulty with the high notes from his own equipment.

ACCOMPLISHMENTS IN BIOMEDICAL RESEARCH

Astwood's first two publications were straight case reports based on patients treated while he was a house officer at the

mecca of Canadian medicine, the "Royal Vic" in Montreal. They did not typify nor portend what was to follow, but they did reveal keen medical insight. These were succeeded in sharp contrast by a report showing that the nuptial coloration induced by pituitary extracts in the minnow *Phoxinus laevis* was brought about by a specific hormone that Zondek and Krohn had recently described and named intermedin. Although intermedin was known to produce pigmentary changes in amphibia by expanding the melanophores, in *Phoxinus* it caused expansion of the erythrophores. Astwood found that blood from a patient with advanced melanosarcoma also contained this same erythrophore-expanding activity.

Ted could not have entered this field of pigmentary changes in lower forms at a more propitious time. As a result of many earlier classic studies, interest was at an all time high, and Ted, a medical graduate, was welcomed into the ranks of biology.

Simultaneously, Ted was venturing into a less explored area—hormonal control of the mammary gland. It had been reported that growth and development of the rat mammary gland was under the control of ovarian hormones from the day of birth onward. Astwood and Geschickter found this not to be true. They gonadectomized male and female rats at birth and found that for the first six weeks of life the glands developed with the same rapidity as those of controls. Exogenous estrogen had no effect until after the third week, when it accelerated duct growth. On extending the estrogen treatment to six months or more, they found that the stimulatory action remained confined to the duct system and that excessive proliferation of the ductal epithelium resulted in localized cyst formation. The glands from animals on high dosage were strongly reminiscent of the changes seen during chronic cystic mastitis in women. These localized pathologi-

cal changes were also found in animals receiving both estrogen and progesterone but were prevented by prior or simultaneous treatment with gonad stimulating preparations. Long-term treatment of intact or castrated female rats with testosterone produced a male-type gland with a profusion of lobule-like structures. Lactogenic hormone produced no structural changes, but secretion of milk was seen in the terminal buds. These authors were also first to note that cessation of mammary growth and regression following hypophysectomy was not repairable by estrogen and could be duplicated in intact rats by dietary deficiencies. Using gonad-stimulating hormones, they produced in intact immature female rats the same full-blown duct and lobule development that is characteristic of late pregnancy.

These early studies were based on use of the newly available pure steroid hormones (progesterone in 1934; estradiol and testosterone in 1936) and provided a foundation for the multitude of succeeding studies that have so greatly extended our knowledge of the hormonal control of mammary growth and function in a wide variety of mammals.

As a Harvard graduate fellow, Ted decided to examine the temporal relationship of uterine events following a single injection of estrogen into immature female rats. He found that during the first six hours, the uterus increased in wet weight from the imbibition of water; there was no increase in dry weight. On further study, he found this initial response in uterine weight to be directly proportional to the dose of estrogen and that this could serve as a sensitive method for the quantitation of estrogenic substances. This new "six-hour assay" reduced the time of available bioassay systems from days to hours.

When the changes in uterine weight and water content were followed over a period of twenty-four hours, it was

found that during the second six-hour period the uterus lost most of the weight gained in the first six hours, and much of its newly acquired water. Over the next twelve hours there was another gain in weight, but this time it was the result of normal growth involving mitotic activity and accumulation of protoplasm.

Ted found that the water-imbibition reaction could be prevented by severe dehydration, as by an intraperitoneal injection of twenty percent glucose, and augmented by alimentary hydration, but only in proportion to the increase in body weight. Progesterone also suppressed the reaction. Since the reaction was not blocked by atropine, it was concluded that acetylcholine is not an essential factor in mediating the response. Nathan Talbot and Oliver Lowry joined Ted in demonstrating that marked changes also occur in electrolyte patterns during the first six-hour period. They found a significant extracellular accumulation of Na and Cl and a slight decrease in extracellular K and phosphate. These changes in electrolyte concentrations turned to normal values during the ensuing phase of normal tissue growth. None of these shifts in electrolytes was observed in either blood or hearts.

On histologic examination of uteri taken during the first six hours, the mucosa was found to be edematous and the cells swollen, but lacking in evidence of mitotic activity. During the second six-hour period the edematous condition faded and was followed by a burst of mitotic activity.

Having found that the initial rise in uterine weight and water content in response to estrogen could be suppressed by progesterone, Ted was able to study the ovarian output of these two hormones during the estrous cycle and pseudopregnancy. First he gathered data on the uterine weight and water content at closely graded stages throughout the estrous cycle and pseudopregnancy. Next he made single injections

of estradiol at these same stages and measured the uterine responses after six hours. Contrary to the widely held assumption that the increase in uterine weight occurred evenly during the estrous cycle, Ted found sharp increases in both uterine weight and water content over a brief period leading up to proestrus. This was followed by equally sharp declines in both parameters with the approach of estrus. These values remained low through estrus and metestrus. During diestrus the uterus increased in both wet and dry weight. The same pattern of changes occurred during the first three days of pseudopregnancy, after which uterine wet and dry weight rose through day five and declined to basal level by day eight. Piecing this information together, Ted reasoned that the rise in uterine weight and water content at the beginning of the cycle was the result of greatly enhanced estrogen output from a rapidly growing set of follicles and that the subsequent decline was due not to cessation of estrogen production but to secretion of progesterone by preovulatory follicles. Indeed, in animals killed six hours after a single injection of estrogen at various stages of the estrous cycle, he found an augmented increase in water content early in the cycle, but a much reduced response during proestrus and estrus, showing that the known inhibitory action of the luteal hormone progesterone was at work. An interesting point here is that the cyclic corpora lutea of the rat were then believed to be nonfunctional. Ted was the first to suggest otherwise, and subsequent studies have established beyond question that the preovulatory and luteinizing follicles of cycling rats do indeed secrete progesterone for a brief period.

Ted was never one to be deterred from attacking a problem because of obstacles that some would find discouraging. The discovery of a hitherto unknown corpus luteum-stimulating substance in rat placenta is a good example. Such

substances had been found in the human, horse, and chimpanzee, all sizeable animals with large placentae for extraction purposes. This study was carried out with one of the authors (R.O.G.), who supervised a large breeding colony of rats that met the needs of all the people in Hisaw's group. Ted was not unaware of its potential for the daily supply of fresh rat placentae of known gestation age. The available information concerning the endocrinology of pregnancy in the rat pointedly suggested that some substance from the fetal placenta was playing a key role in maintaining luteal function during the second half of pregnancy. Hypophysectomy before the eleventh day of gestation, and thus before the fetal chorion had become established, always resulted in luteal failure and abortion. When the operation was performed after the evening of the eleventh day, the pregnancy continued to term in normal fashion.

The obvious thing to do was to see if rat fetal placentae would maintain formed deciduomata in pseudopregnant rats following hypophysectomy. Fresh placentae were collected daily from rats on the twelfth to fourteenth day of gestation, homogenized in saline, and the mush injected subcutaneously. Despite the somewhat sickly appearance of the hypophysectomized test animals at autopsy after four or more days of this drastic regime, the deciduomata were robust and thriving. Some were maintained well beyond the normal span of pseudopregnancy. With this encouraging preliminary outcome, a variety of extraction procedures were employed. At this point the colony yield of weanling young plummeted, much to the consternation of our colleagues, but not before evidence had been gathered to show that the rat fetal placentae produced a luteal-stimulating factor that was unlike any other known gonadotropin. That finding has now been abundantly confirmed.

As indicated earlier, Ted tended to be of practical bent,

and this was often reflected in his choice of problems for investigation. He was impatient with many of the cumbersome, costly, and protracted bioassay procedures then available. The only means of measuring progesterone required rabbits that were expensive and often not readily available in quantity, several days of treatment, and the necessity of preparing uterine tissue for histologic examination. Ted turned to the pseudopregnant rat and demonstrated that the injection of graded doses of progesterone following ovariectomy on the fourth day produced deciduomata that varied in size with the dose of hormone administered. This simple test involving rats and no histology served as a satisfactory measure of the progestins.

It is well known that the effectiveness of the conventional oral contraceptive, the Pill, is based on the ability of progesterone and related steroids with progestational activity to inhibit the release of LH from the pituitary, and thus block ovulation. The discovery of this action of progesterone predates the birth of the Pill by about twenty years. By 1936 it was known that progesterone inhibited estrous cycles in rats, and in 1937 came the historic discovery by Makepeace, Weinstein, and Friedman that an injection of progesterone would block ovulation in mated rabbits. This was followed a year later by Astwood and Fevold's striking demonstration that progesterone injected into immature female rats with FSH for as long as ten days prevented the appearance of luteinization. In the absence of progesterone, luteinization was a constant finding after the fourth day. Thus the progesterone had suppressed release of luteinizing hormone, LH, from the test animal's own intact pituitary.

The possibility of using such information for fertility control in humans was not given much consideration at this early time. Progesterone was both extremely expensive and effective only by daily injections. Such findings did, however,

provide the background data for the later development of the Pill.

In his brief stay (1939–1940) at Johns Hopkins in obstetrics, Ted chalked up two more achievements of exceptional importance, one in clinical chemistry and another in reproductive endocrinology. In association with George Anna Seegar Jones, he developed a much improved method for the quantitative determination of the urinary excretion of pregnanediol, a breakdown product of progesterone and a universally used indicator of luteal function in the human female. Pregnanediol is excreted in the form of sodium pregnanediol glucuronide, for which Eleanor Venning had developed an assay procedure. Adequate refrigeration facilities were often quite limited at that time, and Venning's procedure did not allow for the spontaneous hydrolysis that might occur during the twenty-four-hour collection period. This difficulty was overcome by measuring free pregnanediol after complete hydrolysis and using a predetermined conversion factor that expressed the yield in pregnanediol from a given amount of sodium pregnanediol glucuronide. Their method was promptly adopted on a wide scale, and it served as an important diagnostic aid in both obstetrics and gynecology.

In his final study at Hopkins, Ted scored one of the two most outstanding successes of his investigative career—the identification of a third pituitary gonadotropin, which he termed luteotrophin. This much-cited paper represents a masterpiece in experimental design, documentation, and interpretation. It revised concepts concerning the hormonal control of ovarian function in the rat and is clearly one of the landmarks of that early period in research on reproduction.

The problem that Ted tackled was the puzzling observation that while LH induced luteinization, it did not elicit secretion of the luteal hormone, progesterone. In essence,

what he did was to induce the formation of corpora lutea with exogenous gonadotropins and then start long-term estrogen treatment. If no further treatment was administered, the vaginal smear would shift from cornified to mucified, showing that the intact pituitary under estrogen stimulation was producing something that induced the corpora lutea to secrete progesterone. This condition was sustained for two to three weeks. If, however, the pituitary was removed after the corpora lutea had become functional, the vaginal smear, under the continuing influence of estrogen, would shift back to the cornified state. This, of course, offered an excellent opportunity for replacement therapy to test for maintenance of luteal function. Ted set about preparing pituitary extracts by both existing and modified methods. As anticipated, neither FSH nor LH nor any combination of the two sustained the mucified vaginal smear, but a crude extract of the residual tissue left after the extraction of FSH, LH, and TSH was effective. Purification studies were carried out, but the active luteotrophic fraction continued to show contamination with lactogenic activity. Ted argued, on the basis of physiological evidence, that luteotrophin and lactogenic hormone were most likely separate hormonal entities, and he cited several instances of nonparallelism between lactogenesis and luteal function in both pregnant and nonpregnant mammals. He agreed, however, that the question of the identity of the lactogenic and luteotrophic hormones remained unanswered. The methodology for purification of protein hormones was inadequate at the time for definitive answers to questions such as this one. It is now well established that pure lactogenic hormone prolactin and Ted's luteotrophin are one and the same, hence the need for the term luteotrophin no longer exists.

Ted's versatility was never in question, and never more

evident than in his brief but early venture into the field of sex behavior following his return to Boston. In this effort, Ted joined with Ed Dempsey, who had a background of experience in research on sex behavior in guinea pigs. The problem was to try to delineate the separate roles of estrogen and progesterone on the induction of mating behavior in adult female rats that had been hypophysectomized for two months. Of the rats treated with estrogen alone, about fifty percent mated at around forty-eight hours, whereas among those receiving both estrogen and progesterone, mating occurred within four hours. Their conclusion that progesterone hastens and facilitates mating behavior, but is not essential, has now been amply substantiated.

THE RESHAPING OF THYROID RESEARCH MANAGEMENT OF THYROID DISEASE REVOLUTIONIZED

It is not an exaggeration to say that Astwood had a greater influence on the development of thyroidology in the twentieth century than any other individual. Although he did not participate in the isolation and structural identification of the thyroid hormones, thyroxine and triiodothyronine, his laboratory provided the solid foundation for understanding the basic mechanisms of thyroid physiology and established rational therapeutic regimens for most thyroid diseases. Although the majority of the ideas and the physical work in his laboratory came from Astwood himself, the free spirit of inquiry that permeated his establishment and his willingness to give advice permitted the younger members of his group to develop and validate their own ideas in a manner that would not have been possible in a more tightly directed organization. Because of his modesty, Astwood's name was withheld from many of the pioneering publications on the thyroid that came from his laboratory, even though he supplied the funds and space and contributed to

the development of the ideas that generated the studies. Such self-effacement is uncommon among scientists.

Astwood's initial interest in the thyroid was probably stimulated during his second sojourn at Johns Hopkins, when two independent Hopkins laboratories noted that two chemically unrelated substances being studied for other purposes produced goiter in rats. Sulfaguanidine was being investigated as an inhibitor of intestinal bacterial growth, and phenylthiourea as a rat poison. The cause of the thyroid hypertrophy was unknown.

Upon returning to Boston, Ted set to work to unravel the unifying chemical group that caused thyroid enlargement and its mechanism of action. From an exhaustive study with large numbers of compounds, he was able to deduce that three primary classes of substances possess what was termed "antithyroid" activity. These were thionamides, sulfonamides, and aniline derivatives. All of these were found to inhibit the synthesis of thyroid hormone by interfering with the organic binding of iodine in the thyroid; they also caused thyroid hypertrophy by lowering plasma thyroid hormone concentration, and thus reducing negative feedback on pituitary TSH secretion. Goiter could be prevented by administering thyroxine or by hypophysectomizing animals treated with the drugs. An unrelated class of compounds, monovalent anions, typified by thiocyanate and perchlorate, was found to act in a quite different manner by inhibiting the activity of the iodide pump that concentrates iodide in the thyroid cell. The pump inhibitors decrease thyroid hormone synthesis by reducing the amount of iodide substrate in the thyroid, but they do not interfere with organic binding of intrathyroidal iodine to form thyroid hormone.

Having concluded that the mechanism of action of the antithyroid compounds was to inhibit thyroid hormone formation, Ted was quick to realize their potential value in

treating hyperthyroidism, a relatively common clinical problem. Several drugs were tested and found to be effective in the human, but a high incidence of toxic reactions made their widespread use seem impractical. He then began a trial of propylthiouracil, a drug that was extremely potent in producing goiter in the rat, and thus might be less toxic because it could be employed in a smaller dose than the drugs tried earlier. Propylthiouracil was indeed much less toxic than some of the earlier materials tested, and it is still one of the two drugs commonly used in treating hyperthyroidism in the United States today.

The relative potency of antithyroid drugs in the rat and in man proved to be different. Although propylthiouracil is eleven times as potent as thiouracil in the rat, it is somewhat less potent than thiouracil in man. Ted was trying to develop an optimal drug for treating hyperthyroidism at the end of World War II, at the time the Atomic Energy Commission began making various isotopes available to the general biomedical community. Although he had not worked with radioisotopes previously, he taught himself the principles of nuclear physics, obtained an isotope license, and began basic studies of thyroid physiology employing radioactive iodine. One of his goals was to devise a technique for the acute assessment of relative potency of antithyroid drugs in man, because using the rat as a test model did not always project the drug potency in unfeathered bipeds. Although instrumentation for isotope measurement was extremely crude in the late 1940s, he invented a technique for measuring the thyroid accumulation of radioiodine over short periods of observation. After trial and error, he discovered that a straight-line relationship would hold for about eight hours if a plot were made of the accumulation of thyroid radioactivity against the square root of time. This straight-line was called the "accumulation gradient." He showed that ingestion of

antithyroid substances of the thionamide type would prevent further accumulation of radioactive iodine by the thyroid, with the degree of inhibition proportional to the potency of the compound tested. This relationship could easily be seen because of the deviation from linearity when the thyroid radioiodine uptake was plotted as an accumulation gradient. With this technique, it was found that another thionamide derivative, methimazole, was approximately 100 times as active as propylthiouracil in man. Methimazole is the only other antithyroid drug generally used for treating thyrotoxicosis in the United States. As delineated above, clinical employment of both of these came from Astwood's laboratory.

Further studies with radioactive iodine in Astwood's laboratory determined that a single injection of TSH dramatically increased thyroid radioiodine uptake in man after a latency period of about eight hours. In a separate study, it was found that if a thionamide-type antithyroid compound is given before administration of radioiodine, thyroid uptake of radioiodine is normal for about the first hour, before plateauing off. This early uptake is the result of the unimpaired activity of the thyroid iodide pump. The accumulated radioiodide is promptly discharged from the thyroid by administration of a thiocyanate-type antithyroid substance that inhibits the iodide pump. Both of these phenomena are still widely used in clinical medicine to study the ability of the thyroid gland to respond to TSH, to differentiate primary from secondary hypothyroidism, and to determine if there is a biosynthetic block of organic binding of iodine by using a thiocyanate of perchlorate discharge test.

Having accumulated the basic tools required, Ted turned his attention to a reinvestigation of the identity of naturally occurring goitrogens. In the late 1920s, Chesney and his collaborators in Baltimore had discovered that a cabbage diet

produced goiter in laboratory rabbits. Subsequent unsuccessful studies throughout the world had attempted to identify the responsible agent in cabbage. With characteristic intuition, Ted thought that the problem might be solved by using the thyroid accumulation gradient to determine if certain foods showed antithyroid activity in the same way that chemical compounds had. Accordingly, a large variety of foodstuffs were tested in human volunteers. Although cabbage was inactive, a related vegetable, rutabaga, markedly inhibited the thyroid accumulation of radioiodide. Astwood was able to isolate and identify the active substance, goitrin, as a thionamide closely related to methimazole. It is released from a thioglycoside precursor (progoitrin) and has a potency in man slightly greater than that of propylthiouracil. Although goitrin and other naturally occurring antithyroid substances have not been proven responsible for a widespread occurrence of goiter in man, foods containing goitrin and related substances are often eaten in sufficient quantity that, in combination with a marginal supply of iodine, they may be a contributing factor to endemic goiter.

Astwood's work on the mechanism of action of antithyroid compounds brought home to him the importance of the pituitary-thyroid axis in the control of thyroid size. In the late 1940s and early 1950s, there was increasing concern about the significance of nodular goiter, and especially about the single thyroid nodule, as a potentially fatal cancer. There was a general consensus at that time that single thyroid nodules, in particular, should be surgically removed because of the high incidence of malignancy in these nodules. The death rate from thyroid cancer, however, is so small compared with the large number of thyroid nodules present in the population that indiscriminate operation would statistically be more likely to result in a patient's demise than if nothing were done.

Since administration of thyroid hormone prevents, or causes regression, of goiter in rats treated with antithyroid drugs, Astwood hypothesized that the same thing might happen in nontoxic "simple" goiter of unknown etiology in man, including that characterized by single thyroid nodules. In a large-scale trial it was found that this was indeed the case and that a majority of nontoxic goiters and single nodules decreased in size when thyroid hormone is administered. Treatment of goiter with thyroid hormone had been common in the late nineteenth century, but at a time when thyroid physiology and the pituitary-thyroid axis were unknown. Although reports at the time had indicated that it was quite efficacious, for some reason its employment had gradually died out, and it was not a recommended therapy at the time of its reintroduction by Astwood. As with antithyroid drugs, the use of thyroid hormone, instead of routine surgical excision, quickly gained worldwide acceptance as the first line of treatment of single thyroid nodules and nontoxic goiter that are not the result of iodine deficiency.

Astwood's investigations in the thyroid took place within a period of about ten years, between 1942 and 1952. The sustained impact of his studies from this relatively short burst of activity is remarkable. It is no exaggeration to state that as a result of the work on the thyroid by Astwood and associates (J. Sullivan, A. Bissell, A. M. Hughes, W. P. VanderLaan, M. M. Stanley, M. A. Greer, M. C. Ettlinger, D. H. Solomon, J. Hershman, and C. E. Cassidy), thousands of lives have been saved, suffering from hyperthyroidism has been reduced, and an inordinate number of unnecessary operations has been prevented.

THE ROUNDING OUT OF AN ILLUSTRIOUS CAREER

In the heady aftermath of the 1949 discovery of the ameliorative action of cortisone on a variety of inflammatory

diseases by Hench and Kendall, interest in the possible beneficial effect of the pituitary adrenal cortex-stimulating hormone, corticotropin, on these same disease states suddenly became acute. Active cortical stimulating extracts of bovine and porcine pituitaries were prepared by several different methods, but the yield and potency were rather low. Contaminated by protein contaminants that led to immunologic resistance, these preparations were not suitable for long-term clinical use. The yield from acetone-dried glands was better than from fresh frozen glands, and in vitro tests showed that the hormone was quickly inactivated by blood. The cruder the product, the more difficult it was to maintain an effective level of corticotropin in the bloodstream. The presumption was that the activity of the hormone was reduced by proteinases, but virtually nothing was known about the nature of the hormone itself.

It was at this point that Ted entered the field; with his magic touch he eliminated these difficulties in a few months through the introduction of two simple procedures. Although he had been totally engaged in thyroid research for nearly a decade, he recalled some unpublished observations made in the early 1940s when he and Tyslowitz were experimenting with the effect of pH on the extraction of pituitary hormones. This led him to test the extraction of dried pituitary powders with hot glacial acetic acid—a bold step for the extraction of a hormone assumed to be a protein. It worked. The yield was nearly 100 percent, and the activity, highly resistant to enzymatic inactivation, was suitable for effective clinical use, as Ted himself demonstrated. The second major advance involved the use of oxidized cellulose as a step in the purification of corticotropin. This acted to selectively absorb corticotropin that could be eluted with 0.1 N hydrochloric acid. As a result of the forty-fold purification achieved by this oxycellulose method, the daily dose for

clinical use could be reduced from 50 mg in divided doses to 0.1 mg in a single injection!

These methodological advances introduced by Ted and associates, Maurice Raben, Richard Payne, Isadore Rosenberg, A. P. Cleroux, A. B. Grady, and V. W. Westermeyer, were adopted worldwide and provided starting material for the later isolation, determination of structure, and synthesis of ACTH by others. Thus, the many problems and controversies associated with the pituitary adrenocortical-stimulating hormone were resolved within a period of ten years following the remarkable advances contributed by the Astwood laboratory. Moreover, Ted's observations on the chromatographic, electrophoretic, spectrophotometric, and biologic behavior of corticotropin after treatment with a variety of different agents was an important cornerstone in the foundation of subsequent studies on the other peptide hormones. The physical-chemical properties of corticotropin were elaborated to a degree not previously known for any peptide hormone, with the exception of insulin. The extensive clinical studies by Astwood and his associates helped define the usefulness of corticotropin in medical practice. He was able to use his experience in purification gained with the corticotropin studies to further the elegant work of Gerald D. Aurbach in his laboratory in purifying parathyroid hormones.

In the last phase of his research career, Astwood turned his attention to the metabolic action of corticotropin and growth hormone and to the hormonal regulation of fat metabolism. He had a thorough mastery of the thinking and voluminous literature on the interrelationships of growth hormone, corticotropin, insulin, glucagon, thyroxine, and androgens on the growth and regulation of carbohydrate, protein, and fat metabolism, as shown by his monumental 1955 review published in *The Hormones* (vol. 3). An array of

data, including the finding that the fat mobilizing action of different preparations of growth hormone varied from batch to batch and was sometimes absent, led Astwood to speculate that the lipolytic function of the anterior pituitary may be explained by a separate principle. This became the object of intensive investigation by Astwood and colleagues, R. J. Barrett, Maurice Raben, Henry Friesen, Charles Hollenberg, Maurice Goodman, and Ruth Landolt. From extraction studies it became apparent that much lipolytic activity remained after the removal of corticotropin and growth hormone. From the residue they succeeded in isolating two highly potent lipolytic peptides from both porcine and human pituitary glands, using anion exchange chromatography and molecular sieving. These peptides, termed peptide I and II, led first to the release of free fatty acids and later to gross lipemia in experimental animals. Although Astwood did not succeed in accomplishing the ultimate objective, which was to find a substance that would "burn fat" in humans, his pioneering studies shed light on this complex and still clouded field of adipose tissue metabolism.

The Astwood laboratory was also the site of independent work of distinction by his associates—work that does not appear in his bibliography for the simple reason that he declined to coauthor any paper unless he had participated significantly in the gathering of data. Some of the studies that were carried out in the Astwood laboratory deserve mention in the context of this memoir, including the extraction, purification and clinical application of human growth hormone by Maurice S. Raben and John Beck; the extraction and purification of human placental lactogen by Henry Friesen; the development of a simple and reliable assay for long-acting thyroid stimulator (LATS) and its significance in Grave's disease by J. M. McKenzie; and the hypothalamic control of TSH secretion by Monte Greer.

In addition to his specific research contributions, Dr. Edwin B. Astwood succeeded to an extent achieved by few in spanning the broad area between the natural sciences and clinical medicine. The perspective gained from the breadth and exactness of his knowledge contributed both to his own research and to that of the many who had the benefit of his wise counsel.

HONORS AND DISTINCTIONS

FELLOWSHIPS

- 1935–1937 Fellow, Surgical Pathology Laboratory, Johns Hopkins Hospital
1938–1939 Rockefeller Foundation Fellow, Harvard University

ACADEMIC POSITIONS

- 1939–1940 Associate in Obstetrics, Johns Hopkins Hospital
1940–1945 Assistant Professor of Pharmacotherapy, Harvard Medical School
1945–1952 Research Professor of Medicine, Tufts University School of Medicine
1952–1972 Professor of Medicine, Tufts University School of Medicine
1958–1959 Visiting Professor of Biological Chemistry, Harvard Medical School
1972–1976 Professor of Medicine Emeritus, Tufts University School of Medicine

HOSPITAL APPOINTMENTS

- 1934–1935 Medical House Officer, Royal Victoria Hospital, Montreal
1939–1940 Assistant Obstetrician, Johns Hopkins Hospital, Baltimore
1940–1945 Associate in Medicine, Peter Bent Brigham Hospital, Boston
1945–1948 Physician, New England Medical Center Hospital, Boston
1945–1972 Physician, Boston Dispensary, Boston
1945–1972 Endocrinologist, New England Medical Center, Boston
1948–1972 Senior Physician, New England Medical Center, Boston

SOCIETIES

American Physiological Society
American Chemical Society
The Endocrine Society

American Thyroid Association
 Society for Endocrinology (British)
 American Society for Clinical Investigation
 American College of Physicians
 American Academy of Arts and Sciences
 American Association for the Advancement of Science
 Association of American Physicians
 National Academy of Sciences
 American College of Clinical Pharmacology and Chemotherapy
 Alpha Omega Alpha

PRIZES AND AWARDS

1944	Ciba Award, Association for Study of Internal Secretions
1948	Cameron Prize, University of Edinburgh
1949	John Phillips Memorial Award, American College of Physicians
1952	Borden Award, Association of American Medical Colleges
1954	Lasker Award, American Public Health Association
1966	Gordon Wilson Medal, American Clinical and Climatological Association
1967	Koch Medal, The Endocrine Society
1967	Sc.D., University of Chicago
1974	Named Master, American College of Physicians
1975	Named Distinguished Thyroid Scientist, Seventh International Thyroid Conference
1975	Distinguished Leadership Award, The Endocrine Society

LECTURES

1945	Harvey Lecture, Harvey Society, New York
1948	Addison Lecture, London
1954	Lecturer, Australian Post Graduate Federation of Medicine
1959	Centennial Lecturer, 100th Anniversary, E. R. Squibb & Sons
1962	Presidential Address, The Endocrine Society
1965	Lecturer, Fiftieth Anniversary, American College of Physicians

- 1967 Gordon Wilson Lecture, American Clinical and Climatological Association
1968 Pfizer Lecture, Clinical Research Institute of Montreal

OTHER PROFESSIONAL ACTIVITIES

- 1941–1942 Editor, *Endocrinology*
1956–1959 Member, Endocrine Society Study Section, National Institute of Arthritis and Metabolic Diseases
1957–1959 Chairman, Endocrine Study Section, National Institute of Arthritis and Metabolic Diseases
1957–1960 Member, Board of Science Counselors, National Institute of Arthritis and Metabolic Diseases
1960 Editor, *Clinical Endocrinology I*
1962–1972 National Institute of Arthritis and Metabolic Diseases Career Award
1962 President, The Endocrine Society
Chairman, The Endocrine Study Section, National Institute of Arthritis and Metabolic Diseases
1964 Coeditor, *The Hormones*, Volumes 4 and 5
1965–1969 Member, National Advisory Council, National Institute of Arthritis and Metabolic Diseases
1967–1972 Chairman, Laurentian Hormone Conference, Committee on Arrangements
1968 Coeditor, *Clinical Endocrinology II*
1972–1976 Coeditor, *Handbook of Physiology*, Section 7: *Endocrinology*, American Physiological Society (seven volumes)

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1937

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1938

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1939

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1940

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1941

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With J. M. Flynn and O. Krayner. Effect of continuous intravenous infusion of glucose in normal dogs. *J. Clin. Invest.*, 1:621.

With G. E. S. Jones. The physiological significance of the estrogen:progesterone ratio on vaginal cornification in the rat. *Endocrinology*, 30:295.

1943

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- With A. Bissell. Changes in the iodine content and weight of the thyroid gland produced by thiouracil. *Fed. Proc.*, 3:5.
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- With A. Bissell. Effect of thiouracil on the iodine content of the thyroid gland. *Endocrinology*, 34:282.
- With A. M. Hughes. Thyroid function and resistance to anoxia in the rat. *J. Aviat. Med.*, 230:1.
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1957

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1958

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1959

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1960

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1961

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- With R. J. Barrett and H. Friesen. Electrophoresis of pituitary hormones in starch gel. Fed. Proc., 20:1836.
- With O. Kraymer, R. Waud, and M. H. Alper. Rate-increasing action of corticotropin and of α -intermedin in the isolated mammal heart. Proc. Natl. Acad. Sci. USA, 47:1525.
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1962

- With R. J. Barrett and H. Friesen. Characterization of pituitary and other peptide hormones by high-voltage starch gel electrophoresis. J. Biol. Chem., 237:432.
- With H. Friesen and R. J. Barrett. Metabolic effects of two peptides from the anterior pituitary gland. Endocrinology, 70: 579.
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1963

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1964

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1965

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