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WILLIAM B. CASTLE  
*1897—1990*

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*A Biographical Memoir by*  
JAMES H. JANDL

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*Biographical Memoir*

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*W. B. Austin*

## WILLIAM B. CASTLE

*October 21, 1897–August 9, 1990*

BY JAMES H. JANDL

WILLIAM BOSWORTH CASTLE died peacefully on August 9, 1990, at age ninety-two. Castle's eminence in medicine and physiology was secured early in his career by the celebrated discovery of gastric intrinsic factor, absence of which is the proximal cause of pernicious anemia. Within a very short period, he and his colleagues extracted the active hematopoietic principle of liver, characterized it as a B vitamin, later identified as vitamin B<sub>12</sub> (cobalamin), and formulated an effective parenteral therapy for pernicious anemia. He then demonstrated that tropical sprue was caused by "intestinal impermeability" to this and other hematopoietic factors present in food and in related studies defined the stoichiometric need for iron in hemoglobin synthesis. This body of work transported hematology from a descriptive art to a dynamic interdisciplinary science. In ensuing years Castle and associates characterized the red cell defects responsible for paroxysmal nocturnal hemoglobinuria and hereditary spherocytosis and established the role of heightened hemoglobin viscosity in the pathogenesis of sickle cell anemia.

Castle once attributed his record of achievements to "being in the right place at the right time—especially with the

right people.” In addition, he had the right genes. His father, William Ernest Castle, was professor of zoology at Harvard and a pioneer in the study of mammalian genetics.<sup>1</sup> When W. B. Castle was elected to the National Academy of Sciences in 1939, the two Castles became the first father and son members in history. Examination of the abundant scientific and philosophical writings by and about William Ernest Castle provides uncanny prophecy of the forthcoming character of William Bosworth Castle. The unconventional views of the father, as recorded by L. C. Dunn,<sup>1</sup> resonate marvelously with those to emanate later from the son: “Orthodoxy or easy agreement with generally held notions seemed not to be a normal position for Castle. . . .” “He had a natural aversion to complicated experiments and . . . regarded abstractions with suspicion. . . .” “The memory of him which his former students probably treasure most is that of being treated . . . as intellectual equals.”

#### CASTLE'S EARLY LIFE

William Bosworth Castle was born in Cambridge, Massachusetts, on October 21, 1897, a few months after his father assumed a position as instructor in zoology at Harvard. Insight into some of Castle's boyhood experiences is given in his informal account written in 1986 at the request of the National Academy of Sciences:

My father now exhibited the knacks and interests of the farm boy that he had been by grafting fruit trees and cultivating a kitchen garden bordered by phlox and iris. . . . When in 1909 his animal work was transferred perforce to Harvard's Bussey Institute in another Boston suburb, Forest Hills, a tedious daily commuting trip became a necessity of his academic life. Salvation came at last with the purchase of a 1915 Model T Ford, though not without its perils, as he was a slow learner at the wheel. I was at once interested in the machine and its “planetary transmission,” and being young required no more than a few hundred yards of open road to learn

how to drive and shortly to make elementary repairs. A subsequently purchased Model A Ford of my own ran with few repairs from 1929 to 1953, the only factory-new car I ever owned.

Castle was enamored with the workings and visible logic of the Model T engine and became convinced of the superiority of physical evidence over abstraction. In later years his legendary dedication to the Model A Ford roadster and its rattling successors earned him a local reputation for eccentricity, but for him ownership of a vehicle that he himself could examine, diagnose, and repair was a matter of prudence, a measure of self-reliance. The overt purpose and simplicity of mechanics held a moral authority that conformed with puritanical convictions instilled in his childhood; these rejected the evils of adornment, fashion, and other forms of evasion or conceit. Even in his last years he was never entirely comfortable with the concealment of electronics. This elemental distrust of abstraction, reminiscent of his father's, was to shape his scientific attitudes throughout his career. He did not deny the usefulness of abstract concepts as staging devices but regarded them as the disposable means toward the discovery of facts through scientific investigation.

The world of art did not escape Castle's good-natured but strongly reasoned assessment of the part played by abstraction in viewing the realities of life. An amateur at watercolors who particularly admired Homer, Eakins, and J. S. Sargent, Castle expressed doubts while still a student about the mental status of postimpressionists. He was amused to learn that one producer of abstractions had sued an art museum in New Hampshire for hanging his painting upside down, commenting that no museum should accept paintings in which "up" could not be distinguished from "down."

Castle entered Harvard College in the month after the first firing of the "Guns of August" in 1914. There, as re-

called in his 1986 autobiographical sketch, Castle first heard of and saw the periodic table of the elements in Professor Kohler's course on inorganic chemistry:

Far from its present completeness it gave exciting evidence of a fundamental order of the Universe. The experiments of Jacques Loeb with plants and animals seemed to obey the same laws of Nature.

The sense that human systems might be subject to laws comparable to those so gloriously defined in physics was inspiring; furthermore, it aroused the suspicion that in medicine—somewhat in contrast to surgery—one had a wide-open field for scientific exploration. Medicine had an added appeal in that it was separate and distinct from his father's field of animal genetics. On this precarious point Castle once explained to me:

My disinterest in my father's work did not escape his attention, for when I departed with several college friends for a summertime tour of Europe, he provided me with a letter of introduction and greeting to the distinguished British geneticist, R. A. Fisher. Frankly, I wished to see London museums and the English countryside and cathedrals and was not really interested in visiting his eminent colleague. I returned with the letter undelivered. On opening it myself, I discovered that he had concluded the note by writing, "I think I should tell you that my son is innocent of any knowledge of genetics."

Castle approached postgraduate training warily, harboring doubts that he was bright enough to be a physicist or biologist. In a fuller vein he stated in a 1971 autobiographical note:

Success in most professions leads to a desk job with domination of or by others. It seemed to me that this was not necessarily so for a career in medicine, where, for example, in contrast to law, Nature not man is the adversary. Indeed, I saw that if a doctor wished he could always remain, and usefully so, in direct contact with the object of his endeavors: the sick man, woman, or child.

Spurred by the apprehensions of wartime and government tracts urging that doctors were sorely needed for service in the army, Castle enrolled at Harvard Medical School at the end of his third year of college as a member of the class of 1921. His impression while a student of the state of medical science at the time was expressed in comments made to me in 1978:

After reading the 1910 edition of Osler's textbook, I was impressed with how little could be done for the sick by doctors—other than surgeons, who had long had direct experimental experience. Most of the few specific medical remedies available at the time had been stumbled upon by primitives, witches, milkmaids, and sailors. I thought therefore that even I might have something to offer, either in research or surgery. As an initial step to either I sought a medical internship and was fortunate to be offered one at the Massachusetts General Hospital.

As a twenty-one-month house pupil at the “Old Massachusetts” from 1921 to 1923, Castle had his first direct exposure to some of the great clinicians of the time, including Chester M. Jones, with whom he collaborated in his first medical publication, and the meticulously observant George R. Minot,<sup>2</sup> who later became Castle's mentor and unflinching supporter. Having made a favorable impression as a clinician, Castle was invited to continue on at the MGH, but his consuming interest remained in “finding out how things work,” a passion fired by the great discovery of insulin by Banting and Best, announced in 1922 and applied in the nick of time at the MGH to save Dr. Minot from dying in diabetic coma. With this dramatic example of the raw potential in medical research, Castle could not envision a life of rushing up brownstone stairs to attend to indisposed Boston merchants. Instead, in 1923 he accepted a position in Cecil Drinker's laboratory at the Harvard School of Public Health. Reminiscing on this, he said:

I acquired a respect for accurate experimental protocol and for the private feelings of living tissue. . . . It was there too that I learned from Harold Himwich . . . the meaning of hard work while we investigated the  $\alpha$ -differences in oxygen and carbon dioxide of blood supplying an isolated dog gastrocnemius muscle while at rest. Its R.Q. was found to be 0.71, rather than unity as was then expected.<sup>3</sup>

These observations anticipated by over three decades general recognition that the primary source of energy for muscle was fatty acids, rather than glucose.

#### SCIENTIFIC ACHIEVEMENTS

In 1925 Castle was enticed back into a clinical setting at the Thorndike Memorial Laboratory, Boston City Hospital, by the luminous Francis W. Peabody. A profoundly admired and gifted man and physician, Peabody had within several years attracted to the Thorndike a remarkable nucleus of talented young men destined soon to become leaders in academic medicine; these included Joseph Wearn, Perrin H. Long, Henry A. Jackson, Jr., Alberto A. Hurtado, Herrman Blumgart, Charles Doan, Chester Keefer, Soma Weiss, and the young Castle. Peabody retained a favorable impression of Castle gained several years earlier during the latter's third-year clinical clerkship. This came about, interestingly enough, because Castle had flunked the previous year's examination in hematology owing to an inability to count red cells. Peabody granted the flunkee an opportunity to redeem himself via an interview, and Castle's performance was sufficiently memorable to gain him an historic appointment. At this time Peabody was deeply interested in the cancer-like marrow morphology of pernicious anemia, and Castle assisted him in the collection of tibial marrow biopsy specimens obtained by surgeons employing mastoid trephines and cuvettes. Peabody took the slides to Northeast Harbor, Maine, during his escapes from administrative duties and

described the specimens presciently as showing “inefficient erythropoiesis.” Suddenly, the following year pernicious anemia became a focus of international attention, with Minot’s stirring discovery that this dread, uniformly fatal ailment could be cured by feeding patients odious quantities (300 grams daily) of raw or lightly cooked liver. With Peabody’s untimely death in 1927 and public awareness of Minot’s pending arrival as his successor as director of the Thorndike, patients flocked to the City Hospital. Minot’s grand achievement, which later earned him the Nobel Prize (shared with Whipple and Murphy), was an empirical consequence of his fastidious attention to strict dietary regimens and meticulous reliance on reticulocyte levels as a quotidian measure of therapeutic response. But Minot, a nineteenth-century prototype, was scientifically unprepared to pursue his great discovery. Castle’s mechanistic mentality was perfect for grappling with this lingering riddle: If normal people do not have to eat any liver to maintain normal blood counts, why should ingestion of liver in large quantity cure pernicious anemia?

#### INTRINSIC FACTOR, THE SPUR TO FAME

In the fall of 1927 Minot was scheduled to give an address before the American Academy of Arts and Sciences in Boston to present the latest bulletins on the new therapy of pernicious anemia. Apprehensive as to how Minot would look upon his uneventful first two years at the Thorndike, Castle attended the talk. While descending to the ground floor of the Thorndike via the back elevator en route to Minot’s lecture, Castle experienced a flash of insight. If it was true, as had been recorded most convincingly by S. A. Levine and W. S. Ladd, that all pernicious anemia patients lack gastric juice, the trouble must be that—deprived of effective digestion in their stomachs—they were unable to

“make” their own liver extract. The essentials of Castle’s experiments to explore this fanciful thought were deceptively simple. Castle, who slept in a room next door to the Thorndike ward kitchen, resolutely fed himself 300 grams of raw beef patties every morning while in fasting state and after one hour induced regurgitation by pharyngeal stimulation. The captured semiliquid contents were adjusted to pH 2.5 to 3.5 with HCl and incubated for six hours at body temperature, after which the liquefied material was passed through a fine sieve and neutralized before introduction via Rehfuß tube into the stomach of the unwitting patient. Patients who were unresponsive to beef muscle alone (or to gastric juice alone) showed brisk reticulocyte responses when this sour admixture of predigested beef muscle was administered. These indelicate but “classic” studies were amplified and confirmed in every conceivable way in a series of fifteen papers bearing the heraldic banner, “Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia.” In the fifth paper (1936) of this memorable series, Castle and T. Hale Ham summed up experiments performed in sixty-one consecutive cases, and silenced critics of the Castle hypothesis, in a succinct synopsis of their long labors:

If beef muscle and gastric juice are administered without opportunity for contact, they are not effective. It is obvious, therefore, that the activity of mixtures of beef muscle and gastric juice cannot be due to the simple addition of two subthreshold substances but requires an interaction between them.

Castle called the essential gastric secretion “intrinsic factor” because it was formed in the body and could not at the time be chemically identified. Indeed, it was not until the 1970s that the primary structure of this essential glycoprotein secreted by gastric parietal cells was elucidated. In the

tenth paper of the “Observations” series, published in 1948, Castle and associates showed by therapeutic trial (in a study confirmed independently by Randolph West) that “extrinsic factor” was identical to the B vitamin now known as cobalamin, which had been purified earlier that year by Karl Folkers’s group and by E. L. Smith and L. F. J. Parker on the cis and trans sides of the Atlantic. This was capped off by Dorothy Hodgkin’s three-dimensional crystallographic analysis of cobalamin structure in 1956, for which she received the Nobel Prize in chemistry in 1964.

It became clear in retrospect that Castle’s seminal experiments had been correct in targeting an interplay between intrinsic and extrinsic factors and in identifying extrinsic factor as a B vitamin, but he had not pinpointed the role of intrinsic factor as an intestinal transport vehicle for this essential nutrient. Nonetheless, Castle’s series of papers established for the first time that nutritional deficiencies can result not only from defective diets but also from faulty absorption or metabolism of nutrients. The latter mechanisms Castle grouped together as “conditioned deficiencies.” Pernicious anemia, in his words, was a form of “starvation in the midst of plenty.”

In the present time, when clinical observation is tightly regulated by public agencies and strict human studies’ protocols, it is unlikely that Castle’s benign but covert experiments would pass muster. It would, indeed, be an interesting fantasy to listen in as Castle, with his flare for euphemism, explained his regurgitation studies to round-eyed patients gripping consent forms. When he submitted his initial studies of intrinsic factor to the Warren Triennial Prize Committee at the MGH in 1928, Castle was bound by rules requiring anonymity. He identified his winning entry with the regal disclaimer, “Honi soit qui mal y pense.” In a larger view, taken by Yale University when in 1933 it conferred on

Castle his first honorary degree, Professor Phelps commented on both the brilliance and heroism of the awardee, adding that "Prometheus showed no greater self-command."<sup>4</sup>

After affirming and extending his studies of intrinsic factor, Castle wasted no time in attempting to prepare an injectable form of liver extract containing the active ingredient. Minot and the physical chemist Edward J. Cohn were engaged in systematically fractionating liver using heat, alcohol, and acidification and came up with an effective oral preparation that reduced the daily requirement from 300 grams of liver to about 12.5 grams of yellow powder ("fraction G"). Knowing from Cohn's work that the active factor was not a protein, Castle minced up liver in capacious crucibles, added water, boiled his brew, stirred it with paddles, and strained off the strange soup through cheesecloth. From this crude beginning, with simple modifications, Castle and F. H. Laskey Taylor produced a "domestic liver extract" that could be injected safely either intramuscularly or (given slowly) intravenously. This discovery was not only of great practical merit but also led to the provocative finding that the protein-free, water-soluble principle was far more potent, unit for unit, when given parenterally than when taken orally.

#### LESSONS FROM THE TROPICS: SPRUE, IRON, AND SHOES

Stimulated by George C. Shattuck and aided by his influence in the field of tropical diseases, Castle in 1931 enlisted the interest of the Rockefeller Foundation in underwriting an expedition to Puerto Rico to assess the efficacy of his liver extract in patients with tropical sprue. Under Rockefeller auspices, an entourage consisting of Castle, Cornelius P. (Dusty) Rhoads, and a group of assistants set sail for this subtropical island, which at that time was no paradise, for a majority of its citizens were laid low by the coendemic rav-

ages of tropical sprue and hookworm-induced anemia. At the Presbyterian Hospital in San Juan, in which their laboratories were located, Castle and Rhoads were at first fascinated by the rich aromas borne by the breeze, “a nostalgic mixture once you have breathed it—compounded of the smell of moist humus and humanity, burning coconut husks, and a trace of ginger. . . . On a nearby beach . . . deep blue shoaled to bright green towards the yellow sand gently fingered by the moving shadows of palm fronds. . . .”<sup>5</sup>

But there were also darker shadows and the hovering stench of sickness caused by tropical sprue, a dispiriting disease endemic to this island. Tropical sprue patients had megaloblastic anemia and severe glossitis similar to that of untreated pernicious anemia, but these patients failed to respond to oral liver extract or to combinations of beef muscle and normal gastric juice. Furthermore, many of them had ample amounts of acid gastric juice, which contained normal concentrations of intrinsic factor, as determined with the “human reticulocyte assay” performed on frozen specimens mailed to the expedition’s anchor man in Boston, Maurice B. Strauss. In the treatment of sprue, Castle’s home-brewed parenteral liver extract paid off wonderfully, patients responded promptly, and the debilitating anemia of sprue was established as resulting from “intestinal impermeability,” later referred to as malabsorption syndrome. The pathogenetic mechanisms responsible for initiating tropical sprue, and its curiously spotty distribution, still have no tidy explanation, but since the Castle-Rhoads expedition empirical prophylaxes with folate and cobalamin have eradicated this melancholy menace in Puerto Rico.

While contending with tropical sprue, Castle, Rhoads, and company confirmed B. K. Ashford’s observation that 90 percent of the island population was infected with hookworm. Vermifuges expelled the worms and stopped intestinal bleed-

ing, but hematologic responses were uneven and subject to relapses attributed to obscure wormborne toxicities. Blood morphology was identical to that of the iron deficiency characteristic of bleeding Bostonians. Both in the hospital and in the small cooperative town of Cidra, Castle's group showed that removing hookworms from anemic patients did nothing to improve hemoglobin levels, but that iron induced a rapid rise whether or not hookworms were removed. With a characteristic canny blend of logic and social pragmatism, Castle convinced public health authorities that their emphasis on priority for purging parasites was not as sensible as a direct attack on the anemia. Hematologic remissions he recounted ". . . would quickly restore subjective health and return the patient to work. He could then learn the value of a better diet and could build a latrine in the backyard, buy shoes, and have his worms eliminated without the likelihood of recurrence." For his contributions to the well-being of Puerto Ricans, Castle was awarded the key to the city of San Juan.

Castle's interest in pernicious anemia and other megaloblastic anemias persisted throughout his lifetime, engendering scores of papers dealing with assays of liver extracts; identification of cobalamin (vitamin B<sub>12</sub>) with "extrinsic factor"; recognition that pernicious anemia of pregnancy responded to a different vitamin, later identified as folate; interactions between folate and ascorbate; and the mechanisms of absorption and metabolism of pteroylpolyglutamates. When receiving the Kober Medal, Castle reminisced that he had been privileged to experience several great moments of insight and promise for the future. Foremost among these were the appearance of the first reticulocyte response in pernicious anemia to autodigested beef muscle, the dramatic improvement in tropical sprue induced by parenteral liver extract, and the startling increase in viscosity of deoxy-

generated sickle cell anemia blood that he and T. Hale Ham first witnessed.

#### HEMOLYTIC ANEMIAS

One afternoon in the late 1930s Castle and Ham were methodically observing the effects on red cell volume of changes in  $O_2$  and  $CO_2$  tensions. Among the several varieties of hemolytic anemia blood so studied was that from a patient with sickle cell anemia. As he recalled it later, "We discovered that when the  $pCO_2$  was held constant, and the  $pO_2$  was lowered in one sealed tube and not the other, deoxygenated sickle blood failed to sediment in the centrifuge. It immediately occurred to us that this was because the elongated, sickled red cells had become tangled up 'like haywire.'"

From this Ham and Castle deduced a general theme that stagnation ("erythrosthesis") and packing ("erythroconcentration") of red cells were primary mechanisms in many kinds of hemolytic anemias, including hereditary spherocytosis (HS) and possibly immunohemolytic anemias. The genetically defective cells of HS were shown by Castle, Ham, Charles P. Emerson, Jr., and their associates to lose control of volume, shape, and surface area when subjected to erythrosthesis for long periods *in vitro*, unless the cells were repeatedly reinvigorated by additions of glucose or fresh serum. The vulnerability of these cells to packing and substrate depletion led to origination of the "incubation fragility test." More importantly, spherocytosis and cell membrane loss observed *in vitro* during erythrosthesis and erythroconcentration were shown to correspond with changes in red cells recovered from blood and spleens of patients with HS; this both defined the essential role of splenic vasculature in expressing the latent cell defect and explained the efficacy of splenectomy in curing the anemia despite persistence of

the membrane abnormality. These observations, first recorded in general and in abstract form by Ham and Castle in 1940, had a profound influence on the direction of research on nonimmune mechanisms of hemolytic anemias in the late 1940s, although publication of the full body of experimental evidence and clinical specifics (gathered mainly by C. P. Emerson) was delayed by a Darwinian sixteen years.

#### THE VISCOUS CYCLE

The potential for hematologic havoc through erythrosthiasis was most grippingly evident in sickle cell disease. Using the Ostwald viscosimeter and sealed cylindrical flasks containing blood equilibrated with gas mixtures, Ham and Castle observed in 1940 that reduction of  $PO_2$  to levels approximating that of mixed venous blood dramatically increased the viscosity of sickle cell (but not normal) blood. This led to Castle's famed postulation that the painful crisis, organ infarcts, and hemolytic anemia of sickle cell disease were the consequence of a vicious cycle initiated by increased viscosity, the endpoint being vascular occlusion by ensnared rigidified red cells. This 1940 interpretation of events at the cellular level took wing in 1945 during a legendary conversation between Castle and Linus Pauling, as they traveled together by overnight train from Denver to Chicago. As recorded by Castle's former colleague in megaloblastic matters, M. B. Strauss,<sup>6</sup> Castle sketched out to Pauling some of the work he and Ham had been doing since 1940 on sickle cell disease, adding that ". . . as stated by Dr. I. J. Sherman in 1940, when the cells were deoxygenated and sickled they showed birefringence in polarized light. This, I stated, meant to me some type of molecular alignment or orientation, and ventured to suggest that this might be 'the kind of thing in which he would be interested.'"

It was indeed the kind of thing, for in the following year,

Pauling, Harvey A. Itano, and others began studies using moving boundary electrophoresis that showed sickle cell hemoglobin to be intrinsically abnormal in its electrophoretic migration. The report<sup>7</sup> of this finding ushered the age of molecular biology into clinical medicine. Knowledge of the discovery by Pauling's group inspired John W. Harris, then a fellow of Castle, to investigate the physical properties of sickle cell hemoglobin solutions divested of cell membranes. When sufficiently concentrated, deoxyhemoglobin S was shown by Harris using phase optics to form long, watery crystals or tactoids;<sup>8</sup> these rigid and birefringent bodies, created by cable-like growth of filaments of polymerized hemoglobin S, account for the vascular impactions by sickled cells. Our elaborate knowledge today of the molecular biology and pathogenesis of sickle cell anemia stems directly from Castle's bold inference based on viscosity plus birefringence.

CASTLE'S INFLUENCE AS A TEACHER:  
THREE GENERATIONS OF TRAINEES

The Minot-Castle era of hematology research began before hematology had become a business. It started with W. C. Townsend, M. B. Strauss, C. W. Heath, J. H. Burchenal, R. W. Heinle, and F. H. Laskey Taylor, a gifted group of investigators who overlapped with T. Hale Ham, followed by P. F. Wagley, J. Watson, F. H. Gardner, and C. P. Emerson, Jr. Castle's first generation of trainees, which included several of these, ended with the departure in the early 1950s of Ham, J. W. Harris, Robert F. Schilling (author of the Schilling test), S. C. Shen, and others schooled by Castle in learning from the "mistakes of nature." Clearly, Thorndike hematology under Castle was immensely productive but physically restricted, forcing newly spawned investigators to swim off to less crowded waters, where their activities could

be amplified. Consequently, a brief lull in scientific productivity set in, occasioned in part by Castle's increasing administrative responsibilities. Progressively hampered by complications of diabetes, Minot had gradually transferred the reins of office to Castle during the 1940s, a process made official by Castle's appointment as director in 1948.

Thorndike tradition had strongly nurtured a do-it-yourself philosophy, often placing outrageous demands on the investigator, and Castle and his chancellor of the exchequer, Maxwell Finland, kept a keen watch on the number and quality of incoming fellows and the resources grudgingly allotted them. In 1952 hematology was represented by only three fledgling fellows (M. S. Greenberg, J. H. Jandl, and A. A. Lear), and Castle was seldom at liberty to roam the laboratories or fuss with the various gadgets, such as the mechanical fragility machine, which he had invented, assembled, and hitherto kept in good repair. Nevertheless, those of us starting then were peculiarly fortunate, for while we spent most of our time learning the techniques of science the hard way, we were repaid for our labors by access to frequent, informal conferences with this legendary man, who treated us all as his intellectual equals.

Associating with Castle, exchanging ideas, debating data, absorbing tactful corrections, and learning to search the entire natural universe if necessary for clues to disease processes challenged every neuron in our bodies. Castle's curiosity was insatiable, his mind was never idle, and it seemed almost impossible to get enough of him. He conveyed the power to think more clearly, observe more sharply, and function more effectively than we ever had on our own. I think this was because he could see in us potentials we did not know we had. Certainly his incorruptible example served as our gold meter bar, by which we could measure ourselves and direct our endeavors. If Castle had approved our ex-

periments and interpretations, we felt no nervousness whatever on reporting them before national societies. Soon to share in this heady atmosphere was Allan J. Erslev and, on an informal basis, Rudi Schmid. Castle's preoccupation with the mechanisms of anemias (rather than further development of their remedies) led him to sustain his lifelong interest in pernicious anemia and allied processes. Under his benign direction, experimental observations were resumed through the efforts of a succession of colleagues, including Bernard A. Cooper, Hendrick O. Nieweg, and later Victor Herbert; Herbert in turn shared the responsibilities of training and collaborating with Louis W. Sullivan, Ralph Zalusky, and Richard R. Streiff. Jandl and co-workers already had launched a broad attack on the mechanisms of hemolytic anemias, bearing out many of the predictions made earlier by Ham and Castle, and then conducted increasingly independent studies that among other things defined the role of Fc receptors in immune hemolysis and demonstrated the existence of transferrin receptors. With characteristic magnanimity, Castle transferred responsibility for the hematology division to Jandl in 1962, and the following year stepped aside as Minot Professor and director of the Thorndike enabling Finland to take on these titles and duties in recognition of his extraordinary contributions in funding and remodeling the aging facility. These maneuvers, involving Castle's appointment as Francis Weld Peabody Faculty Professor of Medicine, led to a second generation of Castle fellows, his scientific grandchildren. Jandl ran the division under Castle's sparkling firmament. From this lively and collegial arrangement spilled forth a remarkable new crop of talented investigators, all of whom became doyens in hematology or deans of medicine: David W. Allen, Harry S. Jacob, Manuel E. Kaplan, Richard H. Aster, H. Franklin Bunn, Christian Gulbrandsen, Richard

A. Cooper, Herman A. Godwin, Albert F. LoBuglio, Neil Abramson, and Sanford J. Shattil.

In 1968 the hard rules of retirement then in force had already been stretched by five years in Castle's case through his appointment as faculty professor. Castle's own mental faculties at this time had remained so much livelier than those of most younger colleagues that it was unthinkable to let him go. Through the collusion of benevolent admirers Castle was appointed distinguished physician by the Veterans Administration and assigned to the West Roxbury V.A. Hospital. Here he was welcomed by old friends (T. A. Warthin and R. P. Stetson) and stirred excitement and strong loyalties among the young staff and residents of that hospital and of members of the Brigham and Women's Hospital staff who rotated through this V.A. affiliate. As he had done at the Boston City Hospital, Castle soon imbued the staff of the West Roxbury V.A. Hospital with his view that in both patient care and research the patient is the essential analyzer and the clinical investigator should never abandon the unique, often heuristic, experiences arising during direct patient care. Castle resigned as distinguished professor to become senior physician at West Roxbury V.A. Hospital in 1972, and for several years thereafter he conducted regular tutorial sessions, clinic rounds, and conferences in hematology. After Harvard's withdrawal from Boston City Hospital in 1974, the epicenter of the Castle mystique shifted back to Harvard Medical School, where one of the four educational pathways (programs) was designated the William B. Castle Society.

#### HONORS

Honors came to Castle early on as well as late. He received nine honorary degrees, fifteen honorary memberships, and two dozen special awards, including the Walter

Reed, Leonard Wood, and George Kober medals. Conferers of awards were usually rewarded in return by the felicitous phrasing characteristic of Castle's speech. In addressing a prestigious gathering of gastroenterologists in 1959, he explained that, "The human stomach is a convenient receptacle for food in both savage and civilized man who, for quite different reasons, must often eat and run."

#### PERSONAL PROPERTIES

Physically, Castle was tall and angular, moved about restlessly, and gestured with long sinewy arms and spidery but powerful hands. His deep, penetrating voice imparted authority, and his leveled eyes held their focus attentively on the subject or person at hand. However impatient with interruptions by telephones and by the impositions of administrative persons, whom he classified collectively as "chronophages," Castle was always generous with his time in discussing scientific matters with colleagues. This was for him a pleasure, not a duty—or perhaps deep in his good-natured and conscientious soul, helping out on research problems, like lending a hand, was a pleasurable duty. Long after official retirement, while at home or when attending rounds, seminars, or scientific programs (many of which were held in his honor by various generations of the "Castle family"), his astute comments and biological or philosophical excursions invariably added sparkle as well as insight.

#### HIS LANGUAGE AND PHILOSOPHY

Castle's facility with words added immeasurably to the impact of his written and spoken thoughts, which nearly always contained one or more graceful phrases lastingly treasured in the memories of rapt listeners. This gift not only enabled him to link human values to dry facts but served to deflect and neutralize those awkward moments or phrases

incidental to human intercourse. When a visiting dignitary holding forth on grand rounds once expressed patronizing amazement that “such splendid science was being conducted here—at the Boston City Hospital,” Castle uncoiled slowly to his feet during the dead silence to remark in his deep rumbling tones, “at last Mohammed has come to the mountain.” This gift for recasting adversity was his first weapon of defense when expenditures loomed, for the generosity of the great man was equaled only by his parsimony. For him the most pleasurable of all situations occurred when resourcefulness could be substituted for expense. When in the 1950s impecunity forced me to make periodic demands for incremental levels of support, my requests were received with visible agitation, followed by a well-paced stream of anguished propaganda that issued forth for weeks. After dropping handbills in my letterbox advertising \$7 pants and \$3 shirts, and then extolling the thrift of powdered milk as a solution available to the impecunious, Castle’s final stratagem on one occasion was to send me a copy of a communication from Francis Peabody written in 1925. In this letter Castle was offered a stipend of \$1,000 per year; on the margin he penned the words, “As are you, Jim, so once was I.” Frugality and abhorrence of waste were ironed into his soul, but with the resources possessed by him—his scientific instincts, his language skills, use of his aged cars, the summer house he and Louise made available to friends and fellows—with these he was always generous. For years the Castles offered to our enlarging family vacation use of their spacious home on the Cape. An annual preliminary ceremony was the vernal installation of their dock, a process Castle preferred to perform personally. Among the most unnerving experiences of memory was that of standing on the cross-member of a sawhorse, wielding a 16-pound maul to drive in the vertical posts grasped beneath me by Castle,

neck-deep in river water. On one occasion I hesitated while apprehensively studying the famous but fragile cranium below, spaced inches from the post. "Anything wrong?" he asked. "No, just shifting my position." His smiling response left me dumbfounded. "I thought perhaps you were pondering the future directorship of the Thorndike!" After sweaty tasks of this kind, we generally cooled off in the river and then resumed discussions of how skunk cabbages melt their way through hard ice or other mysteries of nature that invited exploration.

For anyone with broad interests in the external world (Castle had no use for introspection and almost none for psychiatry), his panoramic appraisals of "all the uses of this world" were astute and fearless. As recorded by his son, William Rogers Castle,<sup>9</sup> he wanted to know, after reading a few pages of *Portrait of the Artist as a Young Man*, whether Joyce suffered from eye disease. "I thought so," he said; "there was all that emphasis on losing his glasses." A naturalist by habit, he was irked by Thoreau for "misidentifying a few birds in his nature writing." Castle loved steam engines both for their working parts and for their efficiency in transporting people in a state of productive privacy and was outraged at the dismemberment of railroads by financiers. He once burst into the lab exclaiming that it no longer was possible to go by train from Boston to Cincinnati. He feared and disapproved of airplanes, especially the supersonic Concorde, and brooded over the inequity of a privileged few gaining dubious minutes while we earthlings lost our hearing.

#### A GIFT FOR GIVING

Castle's sharp eye for particulars and gift of insight remained with him until his final days. Thanks to the indispensable and inspiring efforts of his remarkable wife, Louise

Muller Castle, to whom he had been married since 1933, and with encouragement from their daughter, Ann Castle Morris, and son, Castle was able to receive a procession of friends and colleagues until the week of his death. Visitors made pilgrimages to the venerable Victorian edifice at 22 Irving Street more to receive than to give. Time spent with Castle, even as congestive heart failure shortened his sentences (but not his wits or comprehension), continued to be an adventure. As recently as 1988 he journeyed to the medical school to participate with characteristic zest and nimble humor in a special hematology research session convened by H. F. Bunn. Then, as throughout his long life, William Castle was stimulating, original, inquisitive, tactful, humorous, courtly, considerate, and constantly interesting. One could never get enough of his company. That company we shall forever miss.

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