NATIONAL ACADEMY OF SCIENCES

ABRAHAM WHITE

1908—1980

A Biographical Memoir by

EMIL L. SMITH

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March 8, 1908–February 14, 1980

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ABRAHAM WHITE was born in Cleveland, Ohio, and died suddenly in Santa Barbara, California, where he had gone that morning from his home in Palo Alto to deliver a lecture at the University of California. Despite earlier cardiac episodes, he had continued active laboratory investigations and teaching and was full of plans for future activities. Thus there came to an end the life of this versatile and distinguished scientist and educator, whose pioneering investigations in metabolism, endocrinology, and immunology will long continue to influence these fields.

Abe White's parents (Morris and Lena White) came to the United States in 1900 on their honeymoon and settled first in Pittsburgh, Pennsylvania, but later moved to Cleveland. When Abe was one year old, the family moved to Lafayette, Colorado. They lived in this town of about 1,800 for nine years. Abe's father worked first as a coal miner, but a few years later he organized a casualty insurance company specifically for coal miners. When Abe was nine years old, the family moved to Denver, where he completed his schooling and later attended the University of Denver. During his school years he helped to finance his education by working during vacations in the fields picking strawberries, apples, and cherries. Later, as a college student in Denver, he

worked odd hours, weekends, and summer vacations as a streetcar conductor and, when he qualified at the age of eighteen, as a motorman.

At the University of Denver, White enrolled as an anthropology major "despite an interest in science and mathematics—possibly because both my sister and brother who preceded me at the University, majored in chemistry." It should be noted that his sister, Essie White Cohn, had a long career at the University of Denver, where she was professor of chemistry until her death in 1964. His older brother Julius ("Jay") White was an organic chemist who worked at the National Cancer Institute in Bethesda, Maryland, until his retirement.

During his third year in college, White changed his major to chemistry. His interest in biochemistry was aroused by the late Reuben G. Gustavson (then professor of chemistry at Denver), who gave him the opportunity to do summer research between his junior and senior college years. After completing his undergraduate work in 1927, White remained with Gustavson for his M.A., which was awarded in 1928 for studies of the active estrogen in ovarian follicular fluid. A graduate fellowship at the University of Michigan led to Ph.D. thesis research with the late Howard B. Lewis.

Two years of postdoctoral fellowships at Yale allowed him to work with Hubert Bradford Vickery at the Connecticut Agricultural Experiment Station. He was then invited by Lafayette B. Mendel to join the faculty of the Department of Physiological Chemistry at the Yale School of Medicine, where he remained for the next fifteen years for a very fruitful period of research and teaching.

MAJOR SCIENTIFIC WORK

White's work at Michigan was devoted to studies of the amino acid composition of proteins and to the metabolism of sulfur-containing amino acids. These fields continued to be

his main interests for some years, but his focus was to change gradually after his appointment to the faculty at Yale. Under the influence of Mendel, he began to pursue nutritional and growth studies in animals. In 1936, when C. N. H. Long became chairman of the Department of Physiological Chemistry, White was influenced to use his knowledge and experience in protein chemistry in investigations of the protein hormones of the pituitary. This change resulted in a wholly new and fruitful series of investigations in endocrinology, to which White devoted much of his subsequent research effort.

It should be realized that White's early studies in protein chemistry were performed in the era long before modern chromatographic methods of analysis and purification were developed. Similarly, studies on metabolism at that time were largely performed on the whole animal, the only method then available. Thus his career spanned the evolution of biochemistry from its "classical" approaches to its present state, the result of the introduction of new methods.

White began his postdoctoral studies with Vickery with the development of a method for the quantitative estimation of cysteine (and cystine). The cuprous mercaptide method was the first useful gravimetric method for determination of this amino acid, and it was successfully employed to estimate the cysteine plus cystine content in the hydrolysates of a number of proteins. Protein analysis continued to occupy him for some time, particularly in conjunction with his later studies on the nutritional role of various amino acids.

Interest in the sulfur-containing amino acids and the role of cysteine in detoxification had been inspired during White's doctoral investigations under H. B. Lewis. Later, it was shown that when compounds that became conjugated to cysteine were fed to animals, the supply of both cysteine and methionine available to the animal was depleted and growth

was inhibited. In studies with a number of collaborators, these effects were apparent after feeding rats such substances as bromobenzene, cholic acid, various carcinogens, iodoacetic acid, and benzoic acid derivatives. It was then conclusively demonstrated, with E. F. Beach, that rats could grow on a diet containing protein hydrolysates that were completely devoid of cysteine (removed by the cuprous mercaptide method), provided that sufficient methionine was present. (Cysteine or cystine had earlier been thought to be an essential amino acid.) Thus, the conversion of dietary methionine to cysteine was clearly shown. Further, it was demonstrated that methionine was an essential amino acid for the rat, a finding independently made by William C. Rose and his coworkers. White and Beach also discovered that homocystine could replace methionine in the diet and postulated the conversion of its reduced form, homocysteine, to methionine, a prediction that was convincingly established by the later work of others.

In 1937 White (with Catchpole and Long) reported the successful isolation of bovine prolactin, the lactogenic hormone, the first of the protein pituitary hormones to be obtained in pure crystalline form. Considerable effort was devoted in the next years to establishing the properties, homogeneity, and protein nature of the hormone—tasks that in those years were time-consuming and necessary because of the reluctance of some investigators to accept the view that important biological activity resided in intact, large protein molecules. It should be recalled that during this period similar efforts were made in other laboratories to prove the protein nature of insulin and the protein nature of crystalline enzymes.

In 1943, with George Sayers and Long, the isolation of a highly purified preparation of porcine adrenocorticotropic hormone (ACTH), essentially free of other known hormonal

activities of the pituitary gland, was described. The availability of this ACTH preparation permitted studies of the physiological properties of the hormone, its action on the adrenal cortex, and the effect of adrenal cortical activity on various cells and tissues. This research also marked the start of a fruitful collaboration, begun in 1942, with the late Thomas F. Dougherty, an experienced histologist, who was then a postdoctoral fellow in the Yale Department of Anatomy. This close association lasted until Dougherty left Yale in 1947.

Of the greatest significance was the discovery that administration of ACTH produced an involution of all lymphoid tissues and a pronounced lymphocytopenia effected by the dissolution of lymphocytes. That the result was produced by the action of ACTH on the adrenals was convincingly demonstrated by careful observations and controls. First, no effect on lymphoid tissue was observed when ACTH was injected into adrenalectomized animals. Second, the effects could also be elicited by administration of adrenal cortical extracts or of isolated cortical steroids to intact or adrenalectomized animals. It was recognized later that the effect is due solely to steroids possessing an 11-hydroxy group.

White and Dougherty then demonstrated that injection of ACTH (or steroids with adrenocortical activity) produced an increase in the concentration of serum proteins concomitantly with the involution of lymphoid tissue. The increase was shown to be due mainly to augmentation of the immune globulin fraction of serum. This was followed by observations that lymphoid cells contain γ-globulins, the antibody fraction of the serum proteins. It was also demonstrated (with J. H. Chase) that lymphoid cells of hyperimmunized animals synthesize and release the specific antibodies elicited by the injection of individual antigens. This was one of the first studies indicating the important role of lymphocytes in antibody synthesis.

In 1945 White and Dougherty concluded, "the findings emphasize a mode of the functioning of the lymphocyte in its hitherto unexplained role in resistance to infectious diseases, transplantation, and other conditions of stress. Thus, the role of the adrenal cortex in these circumstances is related to its controlling influence over lymphoid tissue."

These seminal observations on lymphoid dissolution and immunosuppression by White and Dougherty provided the basis for the later clinical use of adrenal steroids (or synthetic analogs) in the treatment of lymphoid neoplasms, such as lymphomas and chronic lymphatic leukemia. Their findings also led to the treatment of patients with natural or synthetic steroids prior to organ or tissue transplants to depress the immunity of the transplant recipients, and thus diminish the likelihood of rejection of the transplant because of the immune reaction of the host. Their discovery of the effect of cortical steroids in enhancing erythrocyte production has found application clinically in certain autoimmune hemolytic anemias.

White followed up these studies by further investigations of the enzymes involved in the metabolism of adrenal steroids, on the role of lymphoid tissue in immunity, and the nature of the pituitary control of the adrenal cortex. Particularly noteworthy were studies showing the role of adrenal cortical steroids (glucocorticoids) on the increased excretion of urea nitrogen resulting from enhanced mobilization of tissue and lymphoid protein under conditions of starvation or stress. The direct effect of adrenal steroids in enhancing protein breakdown and in increasing amino acid catabolism are still active fields of investigation.

Of the greatest significance for later research was the finding by Sidney Roberts and White in 1949 that a partially purified cell-free extract of bovine thymus glands will, on injection into rats, increase the number of circulating lym-

phocytes and the amount of lymphoid tissue. In view of the earlier findings that lymphoid tissue and lymphocytes synthesize and contain antibodies, and later observations by others of the important role of the thymus in antibody production, it was clear that the nature of the active principle in thymus extracts needed further investigation.

White took up the problem again in the 1960s, with Allan L. Goldstein and others. They succeeded in obtaining a highly purified preparation of the active material, which they named thymosin. This had become possible through the development, with J. J. Klein and Goldstein, of a novel assay based on the incorporation of tritiated thymidine into the DNA of lymphoid tissue. This permitted evaluation of the lymphocytopoietic activity of isolated fractions obtained from calf thymus tissue. White and Goldstein thus established that the thymus is an endocrine gland. Later, it became clear that thymosin activity is due to a family of peptides, and that the preparations obained from various laboratories seemed to differ somewhat in properties. White and Pamela Burton also demonstrated that thymosin activity is associated with the prealbumin (now termed transthyretin) fraction of human serum. The field has become very active not only because of the great interest in studying the development of immunological competence but also in having for clinical use materials that enhance immunity.

At the time of his death, White was actively engaged in studies of various materials with thymosin activity, applications of the active materials to the study of immunological behavior, and possible therapeutic use.

From the foregoing brief account, it is apparent that White's work, which began in classical biochemistry, has had a major impact in opening new and major developments in physiological endocrinology and immunology. The applications of his work in medicine and surgery have already borne

rich fruit. The discovery of thymosin holds great promise for future use in augmenting immunological resistance to disease.

WORK AS EDUCATOR

Throughout his scientific career, White was a devoted and conscientious teacher and was concerned with methods of improving medical education. His lectures were meticulously polished and greeted enthusiastically by generations of students. Even during the brief period from 1951 to 1953, when he held a position in industry, he continued to teach as a visiting lecturer at Columbia College of Physicians and Surgeons. After retirement from the Albert Einstein College of Medicine, when he moved to Syntex Research in Palo Alto, he enjoyed his teaching affiliation with the Biochemistry Department of Stanford Medical School.

White's interest in innovative medical education resulted in his leaving Yale to accept the chairmanship of the Department of Physiological Chemistry at the beginnings of the UCLA School of Medicine. Later he became one of the major figures in the organization of the Albert Einstein College of Medicine in New York. At first he was a consultant and then the initial faculty appointment as professor and chairman of the Department of Biochemistry. During the early years of the school, as associate dean, he devoted much time and effort to faculty recruitment, the creation of architectural plans, and the organization and development of the curriculum. The great success of the school in bringing together a distinguished faculty certainly owed much to his efforts. After several years of being involved almost full-time in administration, he was happy to devote his major efforts to research and teaching, as he had done in earlier years.

It was his interest in education and his recognition that there was no satisfactory modern textbook of biochemistry, particularly for medical students, that encouraged White to promote such an effort. So it was that in 1949 he brought together Philip Handler, DeWitt Stetten, Jr., and the author of this memoir to develop such a text. The first edition of *Principles of Biochemistry* was published in 1954; the work was revised, at intervals of approximately five years, under White's senior authorship through six editions. During the course of preparing the second edition, Stetten had to withdraw because of the assumption of other responsibilities, but White, Handler, and I continued alone through the fifth edition. For the sixth edition (1978) we were joined by Robert L. Hill and I. Robert Lehman. Plans had already been made for preparation of the seventh edition at the time of White's death. Unhappily, neither he nor Philip Handler, who died in December 1981, could participate in this effort. The success of *Principles* owed much to White's gentle but firm hand. The collaboration was characterized by an intimate and deep friendship among the original coauthors that endured for almost thirty years.

THE MAN

The foregoing brief account of the work of Abraham White does not reveal the kind of person he was. Perhaps I can give an indication of the relationships that developed during the long association of White, Handler, and myself on the *Principles of Biochemistry* by quoting from my remarks at the memorial service for Abe White held at Stanford University on February 27th, 1980.

> In all ways, Abe was the inspiration and the leader that bound us together in this enterprise—one which gave us the great intellectual satisfaction of being able to review and describe the explosive changes in

biochemistry that have continued during this remarkable period. For the young, it may not be easy to appreciate how different biochemistry is now from what it was thirty years ago, and how much joy it gave us to chronicle the unfolding of our science as it developed.

During these past thirty years, we enjoyed an intimate and always harmonious relationship with the greatest mutual love and respect. Abe was always the leader—patient, tolerant, thorough and wise in his approaches—always the arbiter for those difficult decisions of expansion or deletion—always judicious and kind in dealing with our misjudgments and errors—and always with wit and wry humor.

But that was Abe. At no time in our friendship of more than forty years, did I ever hear a negative or caustic comment about any fellow scientist. He was the most tolerant and humane person I have ever known. His loyalty to people and his personal kindness, warmth, and generosity had no limits. Perhaps his only fault was his unlimited faith in all people. He expected others to be what he was himself. Each of us who was close to Abe became a better human being by absorbing something of his nature and wisdom.

Abraham White shared with Edna, his wife of more than forty years, not only his scientific and administrative life, but also an enthusiastic interest in and appreciation of art, music, literature, and the theater. They were constant companions in travel to many parts of the world. They were generous and warm hosts to a multitude of friends.

I AM GREATLY INDEBTED to Mrs. Edna White, the late Julius White, and to many others for their help in preparing this memoir. Several long-time friends and former associates of Abraham White were kind enough to offer helpful comments on this memoir including Joseph S. Fruton, Bernard Horecker, the late Henry S. Kaplan, Sidney Roberts, and Sam Seifter.

AWARDS, HONORS, AND DISTINCTIONS

CHRONOLOGY

1908	Born March 8, Cleveland, Ohio
1927	B.A., University of Denver
1928	M.A., University of Denver
1931	Ph.D., University of Michigan (Physiological Chemistry)
1931–1932	Sterling Fellow in Physiological Chemistry, School of Medicine, Yale University and Connecticut Agricultural Experiment Station (with Hubert B. Vickery)
1932–1933	Porter Fellow of the American Physiological Society at School of Medicine, Yale University (with Hubert B. Vickery)
1933–1937	Instructor, Physiological Chemistry, School of Medicine, Yale University
1937–1943	Assistant Professor, Physiological Chemistry, School of Medicine, Yale University
1943–1948	Associate Professor and Acting Chairman, Physiological Chemistry, School of Medicine, Yale University
1948–1951	Professor and Chairman, Physiological Chemistry, University of California School of Medicine at Los Angeles
1951–1953	Vice-President and Director of Research, Chemical Specialties Co., Inc., New York City (U.S. Division of Syntex, S.A., Mexico); Visiting Lecturer, Biochemistry, College of Physicians and Surgeons
1953–1972	Professor (later Dan Danciger Professor) and Chairman, Department of Biochemistry, and Associate Dean, Albert Einstein College of Medicine, Yeshiva University
1972–1980	Distinguished Scientist, Syntex Research and Consulting Professor of Biochemistry, Stanford University School of Medicine

MEMBERSHIPS (SELECTED)

National Academy of Sciences (elected 1970)
American Academy of Arts and Sciences (elected 1968)

American Society of Biological Chemists
Biochemical Society
American Chemical Society
American Society for Cell Biology
American Institute of Nutrition
Endocrine Society
Society for Experimental Biology and Medicine
American Association of Immunologists
History of Science Society
New York Academy of Sciences (Fellow)
Harvey Society (Council 1956–1959; Vice-President 1965–1966; President 1966–1967)
Laurentian Hormone Conferences (Cofounder and Member, Board of Directors and Program Committee)

HONORARY MEMBERSHIPS

Harvey Society (Lecture 1947)
Alpha Omega Alpha

AWARDS

1935	Traveling Fellowship, American Physiological Society, to attend XVth International Congress of Physiology (Leningrad and Moscow)
1938	Eli Lilly Prize in Biochemistry
1960	Distinguished Alumni Award, University of Denver
1967	Sesquicentennial Alumni Award, University of Michigan
1969	Borden Award, Association of American Medical Colleges

HONORARY DEGREES

1959	Doctor of Humane Letters, Yeshiva University
1975	Doctor of Science, University of Denver

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1935

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