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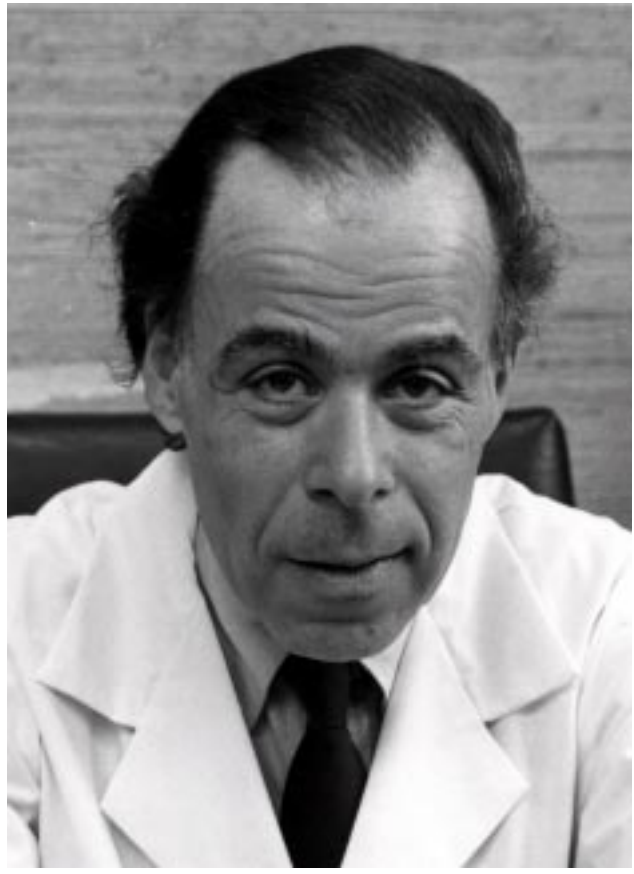

Photograph by Stan Willard, New York, N.Y.

Edward Teller

EDWARD C. FRANKLIN

April 14, 1928–February 20, 1982

BY HENRY METZGER

EDWARD C. FRANKLIN, was an outstanding example of a physician-scientist. By applying the new tools for analyzing protein structure he made significant contributions both to clarifying the fundamental structure of antibodies and to our understanding of particular clinical syndromes. Although his specialty training was in rheumatology, his career would today be characterized as encompassing clinical immunology. In addition to his achievements in research he was a dedicated clinical teacher and contributed actively to professional societies in his discipline. He died of a brain tumor at the height of his career just prior to his fifty-fourth birthday.

Franklin, the only child of a prosperous attorney and his wife, was born in Berlin, Germany, on April 14, 1928. The family did not flee Germany until late 1938, likely reflecting the ambivalence well-assimilated German Jews felt about leaving their homeland. After an enforced fifteen-month sojourn in Cuba, they were finally able to emigrate to New York City in 1940.

Franklin's native intelligence, his excellent scholarly preparation in Germany, and hard work allowed him to graduate from Townsend Harris High School at the age of fifteen. He went on a full scholarship to Harvard University, from

which, despite working part time, he graduated magna cum laude as a biochemistry major at the age of eighteen.

In the late 1940s most medical schools in the United States still enrolled few members of minorities and women, and despite his outstanding credentials, he was admitted only to New York University, from which he graduated in 1950. A year each of internship at New York's Beth Israel Hospital and residency in internal medicine at Montefiore Hospital were followed by two unremarkable years of military duty and then the completion of his residency at the Bronx Veterans Administration Hospital.

Biomedical research and the expanding support for physician-scientists in the United States got their jump-start in the decade of the 1950s, and ultimately, because of Henry G. Kunkel's investigations of liver disease, Franklin was drawn to Kunkel's laboratory at the Rockefeller Institute for Medical Research. Kunkel's enthusiasm for newly initiated studies on antibodies and multiple myeloma persuaded Franklin to work in those areas. He later reminisced that the laboratory was a "cauldron of excitement" with "endless stimulating discussions at all hours of the day or night." It is hard to think of a single laboratory whose influence was as profound in the training particularly of those leaders in immunology who would so fruitfully shuttle between the laboratory and the bedside. Hans Müller-Eberhard, who would become one of the world leaders in the field of complement, was already there; Gerald Edelman (Nobel prize, 1972), one year junior to Franklin at Harvard, became a graduate student with Kunkel during Franklin's tenure at the Rockefeller, and remained a longtime friend of the Franklins.

Franklin embarked on the field of immunology at one of its most exciting phases, namely, the development of the subdiscipline of molecular immunology. Specifically, his scientific career of about twenty-five years spanned the pivotal

period during which the structures of antibodies and the unusual genetic organization that codes for them were elucidated by the group of molecularly oriented immunologists of which he became an active member.

The advent of powerful new tools for separating proteins such as the ultracentrifuge and free electrophoresis made it possible to determine some of the physical characteristics of antibodies in the late 1930s. It was not until two decades later that the techniques of cellulose-based ion exchange chromatography, molecular sieve chromatography, and zone electrophoresis on starch blocks and in polyacrylamide gels spectacularly extended the preparative and analytic options. Likewise, the transfer of the classical precipitin reaction between antibodies and antigens from solution in test tubes to two-dimensional gels—later coupled with electrophoresis—added incisive tools. Finally, just as Franklin was beginning his career, the initial productive use of proteolytic enzymes to dissect the structure of antigens and antibodies validated the belief that the bewildering phenomenology of the immune response could yield to the reductionist approach. Ed Franklin was among the earliest of those who saw the opportunities these methods provided.

Franklin's special contribution was his perceptiveness in recognizing those "accidents of nature" occurring in the clinic that could provide insight into normal structure and function and in pursuing these with thoroughness and rigor. Some of his most important contributions relate to the abnormal proteins that piqued his curiosity. While some of the most influential immunochemists of his day looked askance at the so-called paraproteins as freaks, the investigation of which was more likely to mislead than to inform, others (among them Kunkel and Frank W. Putnam) recognized that the homogeneity of these proteins offered a unique opportunity for revealing canonical aspects of antibody struc-

ture that were shrouded by the confusing heterogeneity typical of "normal" antibody preparations. Franklin's contributions testify to the validity of the more optimistic assessment.

Franklin's bibliography reflects his constant interest in exploring the structure of the γ-globulins, or as they would ultimately be dubbed the immunoglobulins, and almost a third of his publications dealt with various aspects of their structure and relationship to each other. His early work in Kunkel's laboratory involved the relationship between the high molecular weight (19S) and low molecular weight (7S) antibodies and the nature of the autoantibody-like factor seen in patients with rheumatoid arthritis (rheumatoid factor). Other notable investigations after he became independent dealt with the relationship of various myeloma proteins to normal antibodies, characterizations of the disulfide linkages in various antibody classes, structural differences between the closely related human IgA1 and IgA2, and the unusual hinge region of IgG3. He became especially prominent because of his achievements in three particular areas: heavy chain disease, essential mixed cryoglobulinemia, and amyloid.

Franklin described the discovery of the heavy chain diseases as his major scientific contribution in a short autobiography he prepared in September 1980 in connection with his election to the National Academy of Sciences; it was also this subject that he chose for his lecture to the Harvey Society. (Franklin had been diagnosed as having a glioblastoma at the end of 1980, and on the day scheduled for the lecture, November 19, 1981, he was already so incapacitated that his talk had to be read by his wife, Dorothea Zucker-Franklin,[1] with Franklin in attendance. He died three months later.)

His discovery, described in that lecture, began character-

istically with the observation of a grossly abnormal electrophoretic pattern of the serum of a patient. Mr. Cra, a Bellevue employee, had been followed for some months because of unexplained fever and lymphadenopathy. Compared to an earlier sample of his serum, the recent one showed a virtual disappearance of the normal globulin fraction. It was replaced by a newly prominent peak of intermediate mobility that was likewise observed in the urine. Its plentiful supply from this source (1g / L!) aided its initial characterization, and within days that December of 1962, Franklin submitted an abstract describing his studies for the meeting of the American Association of Immunologists scheduled for Atlantic City four months later.

Even before his presentation, Franklin generously allowed the patient and his serum and urine to be studied by Elliot F. Osserman at the Francis Delafield Hospital. Just three months later a patient with similar clinical and laboratory findings was referred to Osserman prompting him and his colleague K. Takasuki (still an active investigator at Kumamoto University in Japan) to review the 400 cases of monoclonal gammopathies Osserman had collected. One of these, examined four years earlier, proved to be the third case of what was clearly a plasma cell dyscrasia with clinical features distinct from those seen in multiple myeloma and with a unique γ-globulin-like serum component consisting of an incomplete heavy chain. It was they who designated the syndrome as heavy ($H^{\gamma 2}$) chain (Franklin's) disease.[2]

Franklin's first full description of his original patient appeared in 1964, and is his third most cited paper. The molecular defect in one instance of heavy chain disease was first fully elucidated in 1969 in the laboratory of Caesar Milstein (Nobel prize, 1984) by Franklin's future longtime colleague, Blas Frangione, and in 1971 Frangione and Franklin uncovered the abnormality in the original pro-

tein, CRA. By the time of his Harvey Lecture, Franklin had authored twenty additional research reports on this subject and seven reviews. Franklin recognized that these immunoglobulin sports gave insight into the genetic organization of immunoglobulin structure, a subject that excited not only some of the foremost immunologists of the day but geneticists more broadly.

The mixture of invariant and variable domains (a term popularized by Gerald Edelman) challenged the dogma of "one gene/one polypeptide chain." I remember well how in 1964 at a workshop in Warner Springs, California, Norbert Hilschman first showed (briefly!) his still unpublished sequences of the two Bence-Jones proteins he had analyzed in Lyman C. Craig's laboratory (also at the Rockefeller). The complete partitioning of the constant and variable regions of the two kappa light chains electrified the participants and provoked animated discussion and speculation. J. Claude Bennett and William J. Dryer, who had attended that meeting, were the first to clearly articulate the heretical hypothesis that eventually proved if anything an understatement: that in the case of immunoglobulins a single polypeptide was encoded by two discrete genes.[3] In analyzing the ever-increasing number of heavy chain disease proteins, Franklin extended this idea and was led to the notion that in heavy chains, the hinge and each domain might be coded for by separate gene segments. He took pride in having anticipated by many years the molecular genetic studies, for example those by Tasuku Honjo, which directly demonstrated the genetic discontinuities.

Franklin's discovery of γ heavy chain disease proved to be only the first example of such discordant synthesis of heavy chains. Maxime Seligman and his colleagues at the Hôpital St. Louis in Paris discovered α chain disease, a syndrome previously known as Mediterranean lymphoma character-

ized by intestinal infiltrates of plasma cells. Two years later, Franklin was a co-author of the publication describing the first patient with recognized μ chain disease.

In the mid-1960s Franklin spearheaded a systematic study of cryoglobulinemia, and the back-to-back articles in the prestigious *American Journal of Medicine* describing the results are the most cited works in Franklin's bibliography. Proteins that reversibly precipitate on cooling of blood had been described in cases of multiple myeloma and macroglobulinemia for some thirty years and had been implicated in the symptoms of peripheral vascular insufficiency that were induced or aggravated by cold in some of these patients. Franklin, Martin Meltzer, and their colleagues in the New York University Rheumatic Diseases Study Group exhaustively studied some twenty-nine consecutive patients they encountered in their clinic, and the first paper describes the clinical picture and the common and variable features of the abnormal proteins in those patients. The investigators were only partially successful in uncovering the molecular mechanisms by which the abnormal serum proteins induced the clinical consequences. They were unable to define any distinctive physical chemical characteristics of those proteins exhibiting cryoprecipitability, and they remained unclear about how the cryogammaglobulins produced the complex of symptoms and why these symptoms occurred at particular concentrations. They did note that the temperature at which precipitation of the proteins began, rather than the concentration of the cryoglobulin, appeared to be one of the more important factors that correlated positively with clinical severity.

In part because they allowed the serum to incubate over many hours in the cold, they discovered a relatively high incidence of mixed cryoglobulins (in most, a complex of an IgM rheumatoid factor and IgG) compared to prior

studies, and it is the twelve patients with this phenomenon on which the second paper focuses. A careful clinical description of each patient in turn documents the characteristic clinical features in this group with essential mixed cryoglobulinemia: a female presenting with purpura involving principally the lower extremities, arthralgias generally without arthritis, moderate anemia, and hypergammaglobulinemia. Where data could be obtained, there was evidence for a diffuse glomerulonephritis as well as more widespread arteritis. The group concluded that they were likely dealing with a previously unrecognized type of connective tissue disease. Its similarities to experimental serum sickness suggested an aberrant response to some antigenic insult.

Their repeated observation of clinical or laboratory evidence of hepatic involvement in these patients suggested a hepatitis virus as a plausible culprit. They were also aware of the reports from the Rheumatology Service at the nearby Hospital for Special Surgery and by a group at Baylor University of extensive extra-hepatic manifestations in the absence of severe hepatic signs and symptoms in cases of hepatitis B viral infections. Assays for the hepatitis B surface antigen (or for antibodies to it) and electron microscopy of the cryoprecipitates strongly supported their suspicion. They proposed that the hepatitis B virus "plays a part in the pathogenesis of the syndrome of essential cryoglobulinemia in the majority of cases," and a subsequent more complete clinical analysis supported their hypothesis.

Franklin's last assessment of the pathogenesis of the syndrome he described appeared in 1980 in a report on the long-term follow-up of forty of their patients. He and his colleagues reiterated that the clinical features, the characteristics of the cryoglobulins, the usually depressed levels of complement during the active phase of the disease, and the deposition of immune complexes and complement in the

lesions together supported the notion that the cryoglobulins are immune complexes and that the disorder is an immune complex-type of vasculitis. They reviewed the circumstances leading to the proposal that the mixed cryoglobulins represented immune complexes, and then summarized the variety of antigen-antibody complexes likely responsible for the elicitation of the rheumatoid factors that formed the basis of the cryoglobulinemia. That cryoglobulins interacted with complement and the localization of IgM, IgG, and complement in the cutaneous and renal lesions was felt to be compelling evidence for the direct pathogenetic role of the cryocomplexes. Nevertheless, the underlying etiologic agents "remain[ed] ill defined," and they concluded that a variety of infectious agents and perhaps other stimuli might play a role. They proposed further that the different sex ratios in particular subsets of patients suggested a predisposition to an aberrant immune response in those with particular HLA genotypes or hormonal status. Over the succeeding twenty years only two features need to be added to their assessment: clinically, the greater appreciation of peripheral neuropathy as part of the symptom complex and pathogenetically the association of hepatitis C infection in ≥90% of the patients.

In 1968 Mordechai Pras, a newly arrived Fulbright fellow with an interest in amyloidosis, brought with him from Israel a frozen spleen from a patient with the idiopathic form of the disease. Franklin had never personally worked on amyloid, and had planned for Pras to work on one or another aspect of immunoglobulins. However, Pras had shown some of the sections to Dorothea Zucker-Franklin who was fascinated with amyloid's birefringent properties, and she convinced Ed that it would be fun to learn more about this substance.

Infiltrates of the material had been observed in a variety of tissues in an assortment of diseases. Four main types had been distinguished: primary, secondary (e.g., to chronic

inflammation), multiple myeloma-associated, and a variety of familial types. (Thirty years later, during his training at the National Institutes of Health under Daniel Kastner, Pras's son Elon was to be a principal in uncovering the gene for familial Mediterranean fever, one of the most common causes of such familial amyloid.) Despite the common structural features of the amyloid fibrils, differences in their binding of Congo red and certain metachromatic dyes had suggested that there might be differences among amyloids, but biochemical investigations had been hampered by the lack of a suitable solvent that could quantitatively extract the native material.

Persuaded by his wife, Franklin asked Pras to solubilize some of the protein. Pras's inexperience with protein physical chemistry came to the rescue! Instead of using buffered isotonic saline to extract the homogenate as a more sophisticated protein chemist might have, he used distilled water. Remarkably this worked and he was able to obtain in high yield a protein that had all the anticipated characteristics of amyloid. In that first paper, which is still cited more than thirty years later, Pras and his colleagues reported on the amyloid's solubility characteristics, physical properties, amino acid and carbohydrate composition, and stoichiometry of binding of Congo red (a useful quantitative assay). The electron microscopic characteristics of both the water-soluble and saline-precipitated material, chemically cross-linked with glutaraldehyde, were also detailed. Despite this considerable progress, they noted that many fundamental questions remained: the relationship of amyloids from different disease states and even its homogeneity in a single disease; the nature of amyloid's interaction with other tissue components; and the possibility of associated γ-globulins.

Earlier studies from Osserman's laboratory had noted the association of immunoglobulin proteins with amyloid deposits,

but it was not until 1971 that George G. Glenner and his colleagues at the National Institutes of Health showed that certain amyloids are themselves composed of the variable region of light chains. It soon became apparent that other amyloids were not, and the amino acid sequence determined by the New York University group on amyloid fibrils from a patient with familial Mediterranean fever revealed a protein that is still referred to as serum amyloid precursor or serum amyloid A (SAA).

Franklin and Zucker-Franklin were particularly intrigued with the mechanisms responsible for the cleavages leading to generation of amyloid from a variety of proteins, particularly SAA. They uncovered evidence that the proteases might be on the plasma membrane of mononuclear leukocytes rather than inside the cell, an idea for which there was virtually no precedence. It is a testimony to their prescience that not only has the general subject of surface proteases become an important one, but that the specific question of how amyloid is generated by proteases is now of intense interest, especially with respect to the amyloid associated with Alzheimer's disease and various spongiform encephalitides. It would also gratify Franklin that the whole subject of pathogenic fibrillization is now becoming intimately related to the most fundamental investigations of protein folding.

During the fifteen years after his first publication on amyloid, Franklin authored or co-authored some forty papers on amyloid—more than he wrote on any other single subject except for his papers on various aspects of immunoglobulin structures per se. Seven of his last ten papers, some published posthumously, were on amyloid, including the characterization of a prealbumin mutant as the lesion in a heredofamilial amyloidosis syndrome, the last paper in his bibliography of almost 250 publications.

Before reviewing some of Ed Franklin's other professional

activities and his approach to research, it is appropriate to consider Franklin as an individual. This aspect of Franklin is not easily apprehended. He was generally a quiet and private man lacking the more overt exuberance of his wife.

In his younger years, the Zucker and Franklin (then Freundlich) families lived across from each other in Berlin, but their paths parted upon emigration from Germany, with the Zuckers secreted away in the Netherlands throughout World War II. By extraordinary coincidence the parents met again while on vacation in Lake Placid in 1952 and discovered that they again lived virtually across from each other in Forest Hills, New York. Ed and Dotty's reacquaintance in New York was in the context of a blind date, which she remembers as "a bore." Nevertheless, a relationship developed, although Dorothea's friends were puzzled at her attraction to this taciturn individual, who was such a wallflower at parties. The mutual attachment blossomed and matured into a very close and lively marriage. Indeed they had to arrange separate offices for themselves in their home because when together their constant conversation prevented them from getting their work accomplished.

Comments of his former colleagues refer to Franklin's "extreme conscientiousness and hard work" and Dennis Stanworth, whose family became close to the Franklins, writes that coming from England he was bemused by Franklin's dynamism in his pursuit of both laboratory and clinical investigations. It wasn't only research that occupied Ed. He and Dorothea shared broad cultural interests, and he was a devoted father to his daughter, Deborah. In 1957 the Franklins purchased a farm in the Berkshires and his friends remember with fondness weekends spent there. The Franklins had an extensive apple orchard, and a gift of some of the fifty gallons of the cider they would produce annually was a cherished memory of the fortunate recipients.

The photograph that accompanies this memoir shows Franklin looking full-face into the camera. Perhaps having now familiarized myself somewhat more with this man, I read into that picture more than others might, but I think it admirably captures his high intelligence, sophistication, skepticism, and puckishness.

Returning to Franklin's professional achievements, after his apprenticeship in the Kunkel laboratory he was awarded a coveted senior investigatorship by the Arthritis Foundation in 1958, and he moved from Rockefeller to New York University, one of the world centers for biomedical research in general and probably at that time the premier center of immunological research. Under Currier McEwen, the director of the interdepartmental Rheumatic Diseases Study Group and the erudite Lewis Thomas, newly appointed chief of medicine, the young faculty were protected from excessive routine duties and assured ample time for research. Five years later, Franklin was appointed career scientist of the New York City Health Research Council and after another five years was a full professor of medicine, an attending physician at University Hospital, and had succeeded McEwen. In 1973 he was appointed director of Irvington House Institute, a privately endowed research enterprise originally focused on research and treatment of rheumatic fever. Franklin had an informal and non-interfering approach to management, and likely this contributed to his effectiveness as an administrator.

He noted in his autobiography that his participation in numerous editorial boards, study sections, and councils of the National Institutes of Health and advisory boards of several private research foundations "managed to occupy some of [his] few leisure hours." He also served with professional societies, and was elected to the Council of the

American Society for Clinical Investigation, and served as its president in 1972-73.

It might be supposed that Franklin's style of research would reflect his virtually Prussian early upbringing, tending towards the rigid and excessively formal. (His wife remembers Ed's mother as somewhat pedantic.) Perhaps in reaction, Franklin harmonized his approach more with the expressive, innovative aspect of German culture characteristic of that period of the twentieth century, particularly in the arts. His wife described it this way: "Our attitude vis-à-vis scientific research? Nothing was ever planned! Neither by Ed, nor by me. If data looked intriguing, they were pursued . . . Repetition of experiments and appropriate controls were kept to a minimum, their number being entirely dictated by the need for publication, if possible in prestigious journals."

In his presidential address at the sixty-sixth annual meeting of the American Society for Clinical Investigation in 1974, Franklin approvingly quoted Jaques Monod's comment that "rational intelligence is an instrument of knowledge especially designed for mastering inert matter but utterly incapable of apprehending life's phenomena." He added in his own words that "instinct and intuition serve as additional tools in our quest to answer questions in the realm of living matter. . . ."

These remarks were made in the context of his fears about the trends he saw towards centralized direction of federally funded biomedical research. He noted that those who had not had an opportunity to participate in research "do not always appreciate the crucial importance of the intangible factors. Straight-jacketed centrally directed programs would leave no room for these essential ingredients." He closed with a plea that we continue to support the individual as an

essential component in the researcher enterprise, "giving everyone the opportunity to evolve his own style."

In his autobiographical essay, referred to above, he reiterated similar concerns. "It is my hope that the pressures of fiscal restraints and the tendency to emphasize directed research will not inhibit investigator-initiated research in years to come. Freedom to choose a problem and follow up exciting leads is the surest way to success. No committee or administrator, no matter how wise, can anticipate important leads and approaches in biology."

I AM GRATEFUL TO Dorothea Zucker-Franklin for sharing some of her reminiscences with me, as well as for providing me with copies of several eulogies and obituaries, and for Lalezari Parviz's concise, detailed "In Memoriam for Edward C. Franklin" *(Montefiore Medicine* 7[1982]:78-81). Letters from several of Franklin's colleagues were also helpful. Candace Canto of the NIH library kindly performed a citation analysis of some of Franklin's most influential papers. Paul Plotz made helpful suggestions on a first draft.

NOTES

1. Dorothea Zucker-Franklin pioneered the application of electron microscopy in hematology and frequently collaborated with Franklin. Her early career (through the mid-1980s) is described in M. Wintrobe, *Hematology, the Blossoming of a Science,* pp. 468-69, Philadelphia: Lea & Febiger, 1985.

2. E. F. Osserman and K. Takatsuki. *Medicine* 42(1963):357-84.

3. W. J. Dryer and J. C. Bennett. *Proc. Natl. Acad. Sci. U. S. A.* 54(1965):864-69.

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