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ROBERT KEITH CANNAN

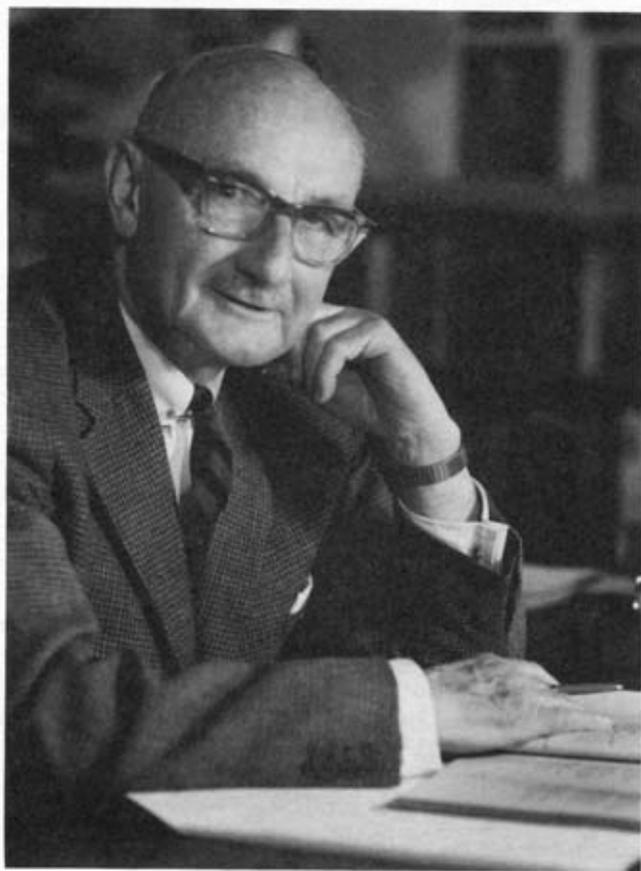
1894—1971

A Biographical Memoir by
JOHN T. EDSALL

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Biographical Memoir

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P. Keith Canman

ROBERT KEITH CANNAN

April 18, 1894–May 24, 1971

BY JOHN T. EDSALL

THE VARIED LIFE OF ROBERT KEITH CANNAN involved four years of front-line service in the British army during the first World War, a decade of research and teaching at University College, London; more than twenty years as head of the Biochemistry Department at New York University Medical School; and a final period of some fifteen years in Washington, as chairman of the Division of Medical Sciences of the National Research Council.

He was the son of a physician, David Cannan, and was named after an ancestor, one Bishop Keith, brother of Field Marshal F. J. E. Keith, the foremost general of Frederick the Great. His maternal grandfather was Robert Cunningham. Records extending back to the seventeenth century show that his ancestors were Scottish on both sides, though his parents lived in or near London. In 1890 David Cannan, his wife Mary, and son Horatius James, moved to start a new life, and settled in Fowler, California. There, after a sister Marjorie, Robert Keith Cannan—always called Keith—was born in 1894. In 1896, having decided to leave California, the family spent several months in Asheville, North Carolina, where David Cannan hoped to establish a practice. Apparently, however, too many doctors were already well established there, and in 1897 the family returned to London. Thus Keith grew up a British subject.

He received his early education in Forest Gate (London) and then attended the Coopers Company School in Bow, London, a school established by one of the wealthy City Companies of the City of London. In 1911 he entered East London College (later renamed Queen Mary College) of the University of London, completing the honors course in chemistry and receiving the B.Sc. degree in 1914.

SERVICE IN WORLD WAR I

When war broke out in August 1914, Keith Cannan was among the first to respond to the call for volunteers. He joined the London Scottish Regiment, but shortly obtained the King's Commission as an officer (second lieutenant) in the East Lancashire Regiment. The regiment proceeded to France in February 1915. Keith Cannan was badly wounded in one of the major battles of May 1915, was sent home, and returned to active service five months later. Soon thereafter he was transferred to take command of a Trench Mortar Battery, was promoted to captain in the Special Reserve in 1916, and became Trench Mortar Officer of the 66th Division. He fought in the Battle of Ypres and in other major campaigns of the British Expeditionary Force. He was twice "mentioned in despatches" from Field Marshall Sir Douglas Haig "for gallant and distinguished service in the field," and a later certificate added, "I have it in command from the King to record his Majesty's high appreciation of the services rendered" (Signed by Winston S. Churchill, Secretary of State for War, March 1919). He was finally demobilized in 1919, after four years of distinguished service.

IN UNIVERSITY COLLEGE, 1919-1930

For about a year after demobilization, he pursued the medical course at St. Bartholemew's Hospital and University College, London; but having been appointed assistant in

biochemistry at University College, he decided to devote himself to biochemistry instead. He received a Beit Memorial Fellowship in 1921, and became senior assistant in physiology and biochemistry at University College after receiving the M.Sc. in 1923. During these years he worked with Professor J. C. Drummond in dietary studies on fat metabolism, and with Professor G. V. Anrep on sugar metabolism in the submaxillary gland, as well as lactic acid in the blood during experimental alkalemia and acidemia.

Crucial for his future career was his appointment as a traveling fellow of the Rockefeller Foundation in 1924. This brought him to the laboratory of William Mansfield Clark,¹ which was then part of the United States Public Health Service in Washington. Clark was in the full tide of his pioneer researches on the oxidation-reduction potentials of organic substances. Cannan joined in the work, obviously with enthusiasm, and this experience determined the direction of his own research for the next seven years. He was coauthor of two papers from the laboratory, along with Clark and Barnett Cohen, one on dichloro substitution products of phenol-indophenol and one on reduction potentials in cell suspensions (1926). Cannan's name stood first on the latter.

After returning to London, he carried out a study of the reduction potentials of hermidin, the chromogen of the green plant *Mercurialis perennis* (1926) and a similar study of echinochrome (1927) from the sea urchin *Arbacia punctulata*. Two other studies involved thiol-disulfide systems: one with B. C. J. G. Knight on dissociation constants of cysteine, cystine, and related compounds (1927) and one with G. M.

¹ H. B. Vickery "William Mansfield Clark, 1884–1964," *Biographical Memoirs of the National Academy of Sciences*, vol. 39 (Washington, D.C.: National Academy of Sciences, 1967), pp. 1–36.

Richardson (1929) on the complexes of thiol acids with iron. The latter in particular required a detailed analysis of complex equilibria. Both studies pointed the way to Cannan's later work on the physical chemistry of proteins and amino acids, as did his work with Agnes Shore (1928) on the creatine-creatinine equilibrium. R. A. Kekwick, who was later to become professor of biophysics at the University of London, and head of the Biophysics Department at the Lister Institute, started research with Cannan in 1929, and completed it later in New York after Cannan had moved there.

AN IMPORTANT BUT UNPUBLISHED DISCOVERY

These studies were significant contributions to biochemistry, and they fitted well into the existing pattern of understanding. Cannan's most important discovery in the field of oxidation-reduction, however, was never published. It would have required revision of some ideas that were then generally accepted—a process that necessarily followed when others published essentially the same findings. The essence of the story may be reconstructed from Cannan's correspondence with Clark and Cohen, and a few much later references in print. The story is told here, not with any intention of claiming priority for Cannan, which he never claimed himself, but as an illustration of his character and attitude and as an example of multiple independent discoveries of the same phenomenon.

Oxidation-reduction potentials had been studied in inorganic systems from the late nineteenth century on. When these processes came to be formulated in terms of electron transfer, it was apparent that some processes—such as the reversible oxidation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) iron—involved the transfer of a single electron. Others involved the simultaneous transfer of two electrons. For organic

compounds, however, as Clark and Cohen noted at an early stage in their work: "In all the recent and more exact electrode measurements of the reduction of *organic* compounds, the value of n [the number of electrons transferred] is apparently 2. Other values have yet to be revealed experimentally."² In the view of some workers, this concept of two-electron transfer was for a time almost a dogma.

Cannan was perhaps the first worker to study a system in which this dogma no longer held. At the end of a long letter to Clark, dated March 23 (probably 1927; certainly not later), in which he had been discussing the cysteine-cystine system, he wrote briefly of his work on pyocyanine, a pigment from *Bacillus pyocyaneus*. In neutral and alkaline solutions it gave a reversible potential, with a single color change on reduction, and with $n = 2$ like other compounds previously studied. In acid solution, however, below pH 5, there was a double color change, in two steps, from colorless to green and then to red as the titration proceeded. Correspondingly the potential of the system on titration changed in two distinct steps, for each of which n was 1, not 2. Around pH 5, and above, the two steps merged into one; also the pK value of the basic dissociation of the fully oxidized form was approximately 5. As Cannan put it: "I think there is no doubt that we have found a two electron jump becoming unstuck."

Some months later, probably in January 1928, Cannan sent Clark a copy of a manuscript. On January 20, Clark sent it on to Cohen with a note: "Enclosed is the Christmas letter and a paper on pyocyanine from Keith. I can see no hitch in Keith's data. Apparently his one equivalent jump is real and I think very important."³ A week later Cohen wrote to

² W. M. Clark and B. Cohen, *Studies on Oxidation-Reduction*, III, U.S. Hyg. Lab. Bull., 151(1928): 31-56 [See p. 40].

³ In W. M. Clark, *Oxidation-Reduction Potentials of Organic Systems* (Baltimore: Williams and Wilkins, 1960), p. 37.

Cannan: "Your manuscript on pyocyanine is returned herewith. . . . Your findings on pyocyanine are surprising, and the dissociation of the two electron jump is a discovery. I am wondering if you obtained identical results when the concentration of pigment was varied. You see, of course, what I had in mind." (Cohen was clearly thinking of the possible formation of an oxidant-reductant complex, sometimes called a meriquinone, which would dissociate reversibly on dilution. Studied at only a single concentration, such a system might give data resembling those that Cannan had obtained, but the form of the curve would shift when the concentration of pigment was altered.)

Clark was a searching critic, with a keen eye for flaws in thinking or experiment. His approval of the manuscript was thus in fact high praise. Cannan, however, apparently made no move to publish. Three years later, in 1931, two papers appeared, one by Friedheim and Michaelis⁴ from the Rockefeller Institute, the other from Elema⁵ in the Netherlands. Both laboratories, by a strange coincidence, had worked, like Cannan, on pyocyanine; and both reported essentially the same phenomena that he had observed but had not published.

On April 18, 1931 Cohen wrote to Cannan, upbraiding him: "Michaelis has published on Pyocyanine and now the fat's in the fire! To scold for having so long delayed publication of your own work is of no use now. Perhaps this is your reward. . . . Intrinsically the damage done by Michaelis' hurried publication is negligible because the work has all the earmarks of superficiality. I see no reason why you should be deterred from giving a full and complete report of your own more substantial findings."

⁴ E. Friedheim and L. Michaelis, *Journal of Biological Chemistry*, 91(1931): 355-68.

⁵ B. Elema, *Recueil des Travaux Chimiques des Pays-Bas*, 50(1931): 807-26; see also p. 1004.

Cannan replied from New York two days later: "Many thanks for your letter. My humble acceptance of your scolding. I presume I thoroughly deserve it, though I confess that I am not greatly perturbed at the situation that has resulted, because I do not feel that I have missed any important object. . . . I will write Michaelis when I am ready with my manuscript, and I am glad you agree that his superficial paper should be supplemented."

Cannan, however, never published his findings. Michaelis, although his first published paper with Friedheim was indeed rather superficial, soon gave a much more comprehensive theoretical treatment of reversible two-step oxidations; he extended his experimental studies to several other systems, demonstrated by magnetic measurements the existence of paramagnetic free radicals as intermediates in these systems, and christened these free radicals as semiquinones.⁶ He emerged as the undisputed master of the field, and Cannan evidently decided that publication of his own manuscript would be superfluous. The reasons for Cannan's long delay in seeking publication remain obscure. He was surely aware that his findings were likely to be challenged by reviewers; the idea that all oxidations and reductions in organic systems involved the simultaneous transfer of two electrons was firmly implanted in the minds of most workers in the field. It was later well known that Michaelis had great difficulties with reviewers when he first attempted to publish his findings on semiquinones, and more than one journal apparently refused his early manuscripts on this subject. Cannan, a most scrupulous and self-critical worker, undoubtedly wanted to meet all possible objections before

⁶ L. Michaelis, *Biographical Memoirs of the National Academy of Sciences*, vol. 31 (New York: Columbia University, 1958), 282–321. Author's Note: This is an autobiographic sketch, with brief additions by D. A. MacInnes and S. Granick. A more comprehensive study of the work of Michaelis is badly needed.

attempting to publish. At the same time he was working to complete his thesis for the D.Sc. degree, a far more demanding job than a Ph.D. thesis; this may well have delayed the pyocyanine work. He never publicly alluded to this work, and turned his research interests to a very different field—the physical chemistry of proteins.

A TRANSATLANTIC MOVE

PROFESSOR AT NEW YORK UNIVERSITY MEDICAL COLLEGE

Although this notable work on pyocyanine remained unknown, Cannan's achievements were attracting recognition. He had for several years been senior lecturer at University College, and was awarded the Sc.D. degree in 1930. In the same year he received, and accepted, an important offer from overseas.

In March 1930 he received a letter from Homer W. Smith, Professor of Physiology at New York University and Bellevue Hospital Medical College, inquiring whether he would consider nomination for the professorship of biochemistry there, which had been vacant since the death of Dr. John Mandel in 1928. There would be a professor, serving as executive head, an associate professor, an assistant professor, two or three instructors, and some technical assistants. The professorial salary would be \$10,000 a year; the associate professor would possibly earn \$6,000.

Cannan did decide to accept the offer, to the obvious regret of his British colleagues. Sir Walter Fletcher, secretary of the Medical Research Council, the most influential man in Great Britain in providing research support in the biomedical sciences, wrote to Cannan on July 11, 1930, with "our warmest good wishes" but added:

I am really very sorry indeed that no similar post has been available for you here up to the present; I had been hoping that the new developments at Cambridge, especially in the field of biophysics, which are now assured financially there, might have given you good opportunity. I think that the

U.S.A. ought to breed their own men instead of stealing our best. . . . Certainly I shall look forward to your coming back to this country as soon as you can.

Professor Kekwick adds in a recent personal note: "In my view this departure was a great setback to the development of physical biochemistry in England—at that time he was the leading and almost the only senior person interested in this field." In fact Cannan never did return to Britain, except to visit there; his entire professional life thereafter was in the United States. In the latter months of 1930 he plunged into his new responsibilities.

We learned something of his problems in those early days from letters to his friend Professor A. C. Chibnall, then at Imperial College, London. On October 30, 1930, Cannan wrote:

I arrived to find the department without a single member of either staff or laboratory assistants. This with classes for 130 students looming 3 weeks ahead. So into chaos we plunged. We are, but now, struggling to the surface for a breath of air. On the whole, things have not gone too badly. [Isidor] Greenwald has taken over most of the organization of the laboratory teaching and has done very well. Miss [Agnes] Shore has proved of invaluable assistance. She is an eminently sane person, a sound teacher, a well-balanced head—and some imagination. . . . There is quite a good field for developing a graduate school. I have already, 3 Ph.D. students with sound chemical foundations. But, for ourselves, thoughts of our own work are not yet.

Later letters to Chibnall, along with personal and family news, deal chiefly with their common interests in protein chemistry, with amino acid analysis, with the disputed question of the existence of asparagine and glutamine residues in proteins, and other related matters.

The organization of what was essentially a new department, with much teaching and administration, was a very demanding business. As he wrote to Chibnall on December 10, 1933: "Much of my time is teaching—or rather reorgani-

zation of teaching, and work proceeds slowly and sloppily. For my sins I am cursed with the bug of an urge to improve curricula, exams and Gods knows what. I am a source of irritation to the Faculty for that reason—and the laboratory suffers.” In fact, however, he was making steady progress on his research concerning the physical chemistry of proteins, as the letters to Chibnall show. His first major contribution to protein chemistry, with R. A. Kekwick, appeared in 1936, and was the fruit of studies of acid-base equilibria on five different preparations of egg albumin. The experiments, originally begun in London, were largely completed by 1933, when Kekwick returned to England, but the need for some further experiments delayed publication. All their electro-metric titrations were done on rocking hydrogen electrodes; this was one of the last extensive studies done by this technique, before the far more convenient glass electrode came into general use. They found a maximum proton combining capacity of 31 equivalents per mole of albumin, taking its molecular weight as 35,000 (later revised to 43,000, raising the binding of H^+ to 38 equivalents). This figure should correspond to the sum of the histidine, arginine, and lysine residues, plus any free α -amino groups that might be present. They also determined the number of amino groups by titrations with formaldehyde and by reaction with nitrous acid, which gave closely concordant results, indicating 18 or 19 amino groups per 35 kg protein. Milton Levy, in Cannan’s laboratory, had recently published several papers that established quantitatively the nature of the interactions between formaldehyde and the amino groups of proteins. This was of importance for the protein studies with this reagent.

In this connection it is to be noted that Cannan regularly invited one or two promising medical students to spend a year in his laboratory, before resuming their medical studies. One of these students was Jonas Salk, who worked with

Cannan on the inactivation of viruses by formaldehyde; work that served in fact as a prelude to Salk's later development of the first successful vaccine against poliomyelitis.

Cannan, with Hildegard Wilson, did an important study (1937) on the reversible equilibrium between glutamic acid and its anhydride, pyrrolidone carboxylic acid (pyroglutamic acid). The rates of hydration and dehydration were both accurately first order. The equilibrium constant $K = (\text{pyroglutamic})/(\text{glutamic})$ was very large near pH 7, but the reaction rates were very low under these conditions. At very high or low pH, there was almost no anhydride. This was probably the most thorough study ever done of this reaction, which is important for protein and amino acid chemistry, and it involved a careful determination of the ionization constants of both the amino acid and the anhydride.

When Cannan first arrived in New York, the chemistry department of New York University Medical College was on the corner of East 26th Street and Third Avenue. In late 1932 the Cornell Medical Center moved uptown to its present location at 68th Street and York Avenue. Cannan and his Department then moved two blocks uptown to the former Cornell Laboratories at East 28th Street and Third Avenue. Dr. Kekwick recollects the move as "... a fairly hilarious occasion, in which all members of Keith's Department participated, with the aid of a shuttle service provided by two furniture removal vans, and a team at either end."

Cannan's central concerns in research during those years were the understanding of proteins in terms of their acid-base equilibria (proton transfer reactions), in their interactions with ions other than protons, and in the relation of these phenomena to the amino acid composition and structure of the proteins. Those who are too young to have personal memories of that period may find it hard to realize that no complete amino acid analysis of a protein was

obtained until 1945, when Erwin Brand and his associates reported such an analysis, by microbiological assays, for β -lactoglobulin, a milk protein first isolated and crystallized by A. H. Palmer⁷ in Cannan's laboratory, and closely studied by Cannan and his associates. (Even then, some of Brand's figures required significant revision, when W. H. Stein and S. Moore developed what became the definitive method of analysis by ion-exchange chromatography). Amino acid analysis of protein hydrolyzates in those days was slow, cumbersome, relatively inaccurate, and required (by comparison with present techniques) huge amounts of material. Some of the activity in Cannan's laboratory, as we shall see, was devoted to improving these methods.

The work on acid-base equilibria of proteins, however, proceeded actively, and the technique was well developed. It focused on two proteins in particular: hen's egg albumin, which had been crystallized by Franz Hofmeister in 1889, and Palmer's β -lactoglobulin, a beautifully crystalline protein already mentioned as a product of Cannan's own laboratory. Both, by the available standards, were highly pure proteins that might be regarded as definite molecules;⁸ and both were relatively small proteins, with molecular weights near 40,000. Palmer and A. C. Kibrick were involved with Cannan in the studies on both proteins (1941, 1942). In 1942 Cannan also reviewed the subject comprehensively in *Chemical Reviews*. The analysis of the data was based on the protein model first proposed by Linderstrøm-Lang.⁹ The protein was consid-

⁷ A. H. Palmer, *Journal of Biological Chemistry*, 104(1934): 359.

⁸ Later research has shown that β -lactoglobulin, as usually prepared, was actually a mixture of two or more closely related components. This heterogeneity was of minor importance, in any case, for Cannan's work.

⁹ K. Linderstrøm-Lang, *Comptes Rendus des Travaux du Laboratoire Carlsberg*, 15(1924)(7).

ered as a sphere of radius b , with a variable electric charge, Z , distributed uniformly over its surface. The Z value of course changed as the titration proceeded. The electrical free energy (Gibbs energy G_e) of a protein ion of net charge Z proton units was given from the Debye-Hückel theory by equation (1), where ϵ is the proton charge, D the dielectric constant of the

$$G_e = \frac{Z^2 \epsilon^2}{2D} \left(\frac{1}{b} - \frac{\kappa}{1 + \kappa a} \right) = Z^2 k T w \quad (1)$$

medium, κ the reciprocal mean distance of the ion atmosphere around an ion taken as center, and a the "collision diameter" for contact between the protein and one of the small neighboring ions in the solution; k is Boltzmann's constant, T the absolute temperature, and w is an electrostatic parameter defined by the equation. The reciprocal length κ is proportional to the square root of the ionic strength.

The electrostatic free energy G_e is obviously zero, for this model, at the isoelectric point, and increases as Z^2 , whether Z is positive or negative. Thus each added increment in Z increases the work required to add another charge of the same sign to the protein. This electrostatic effect tends to flatten the slope of the titration curve, that is, the slope (dZ/dpH) is less than it would be if the electrostatic repulsion did not exist. If the ionic strength I increases, however, κ (proportional to $I^{1/2}$) also increases, and it is apparent that this will reduce the value of G_e , and of w , in (1). Thus, in a series of titrations at increasing ionic strengths, the titration curves will rotate around the isoelectric point, becoming steeper as I increases and w decreases. Taking D as the dielectric constant of water, and setting $a = b + 2$ (values in Ångstroms), it was possible to calculate the equivalent radius

of the protein (*b*) from the slopes of the titration curves near the isoelectric point, as a function of ionic strength. The resulting protein radii were close to the values expected from the molecular weights and diffusion coefficients—near 27 Å for egg albumin and 29.5 Å for β -lactoglobulin.

Examination of breaks in the titration curves, and studies of temperature effects to obtain heats of ionization at various pH values, permitted estimates of the total number of free carboxyl groups (aspartic and glutamic acid residues), imidazole groups (histidine), amino groups (lysine and α -amino), and guanidinium groups of arginine (determined by difference from the maximum number of protons bound in acid solution, minus the sum of the amino and imidazole groups). Cannan compared these figures with the available data from amino acid analysis, with reasonably good agreement for arginine and histidine, some discrepancies for lysine (the analytical data gave lower values than those inferred from titration), and good agreement for aspartic plus glutamic acid from the very careful analyses that Chibnall was doing in England, keeping Cannan informed of his progress. The data also required correction for the presence of asparagine and glutamine residues in the protein, which would appear as aspartic and glutamic acids in the acid hydrolyzate, with release of ammonia. Later Cannan (1944) in a paper followed by one from Kibrick,¹⁰ confirmed Chibnall's results by a different analytical method.

Later (1946, 1949) Cannan, with Keston and Udenfriend, developed a method for microanalysis of amino acids in the form of isotopic derivatives. With M. E. Karsten (1952) he studied the ion exchange behavior of some neutral amino acids, and with W. R. Troll (1953) developed a modified ninhydrin method for amino acid analysis.

¹⁰ A. C. Kibrick, *Journal of Biological Chemistry*, 152(1944): 411–18.

Earlier (1942), with J. Redish, Cannan had developed a method for the large-scale production of crystalline human hemoglobin, and had made preliminary observations on the effects of its injection in man. This work was probably a result of the urgent interest in problems of blood transfusion that accompanied (and preceded) the involvement of the United States in the Second World War.

Later in the war years, from 1943 to 1945, he took a leave of absence to become director of the Toxicity Laboratory at the University of Chicago, under a contract with the Office of Scientific Research and Development. This laboratory made studies of the toxicity of chemical warfare agents.

THE DIVISION OF MEDICAL SCIENCES
OF THE NATIONAL RESEARCH COUNCIL

From about 1945 on, Keith Cannan's administrative talents caused him to be increasingly involved with the work of the National Research Council, the operating arm of the National Academy of Sciences. The Division of Medical Sciences of the Council was forming a Committee on Growth, in conjunction with the American Cancer Society, to develop and support a program of research related to cancer. Cannan started as chairman of the Panel on Proteins (1946). During the next four years he became chairman of the Chemistry Section and a member of the Executive Committee. In 1950 he became chairman of the entire Committee, devoting more and more of his time to this work, relinquishing this post only when he became vice chairman of the Division of Medical Sciences in 1953. He contributed immensely to the work of the Committee on Growth, and set a pattern for the support of research that was highly influential for research support in other areas. In his dealings with

the American Cancer Society, he insisted firmly on keeping the activities of the Committee on Growth directed to the support of fundamental scientific research, against strong pressure in favor of involvement with other aspects of the cancer problem.

During these years he also carried heavy responsibilities at the New York University–Bellevue Medical Center, serving as vice chairman for research (1948–1950) and assistant director of the Center (1950–1952). He played a key role in the organization of the center, made long-range plans for its operation, and played an important role in establishing policies for the coordination and handling of research problems.

He became a naturalized citizen of the United States in 1951. He thus acquired the unusual distinction of being both native-born and naturalized, to the confusion of the U.S. Passport Office.

In 1952 he was invited to become vice chairman of the Division of Medical Sciences of the National Research Council—a full-time post. To accept meant resigning his professorship at New York University. He did accept, and moved to Washington, D.C. A year later he became chairman of the Division on the retirement of his predecessor, Dr. Milton C. Winternitz. He continued in that position for fourteen strenuous years, until 1967. Even after that, as we shall see, he continued in active service to the National Academy of Sciences.

His leadership as chairman of the Division was universally recognized as outstanding. He was responsible for appointing some forty committees each year; most of their members, of course, continued to serve over periods of several years, but all appointments were reviewed each year. Some major committees, during those years, dealt with such subjects as anesthesia, drug dependence, drug safety, envi-

ronmental physiology, emergency medical services, the genitourinary system, naval medical research, blood plasma and plasma expanders, radiology, shock, the skeletal system, tissue transplantation, and trauma. He opened most of the meetings of these varied committees himself, outlining the problems that each was expected to consider and report on. This required many hours of work in advance of the meeting, so that he might master the details of the problems confronting each committee and frame brief opening remarks that would bring these problems to a focus, while leaving the committee to form its own independent judgment. As a member, and in some years chairman, of the Committee on Plasma and Plasma Expanders during the middle 1950s, I came to appreciate deeply his skill and wisdom in bringing us face to face with difficult and sometimes baffling problems, encouraging us, listening closely to the discussion, and asking searching questions from time to time before he was called away to attend to other pressing business.

One of his major accomplishments was the development of a "unified program" for the Atomic Bomb Casualty Commission (ABCC), which had operated in Japan for nearly ten years, but without a carefully considered total design for that immensely important study of the effects of the atomic bombs on the survivors at Hiroshima and Nagasaki. In 1955 he gathered a group of experts, led by the eminent epidemiologist Dr. Thomas Francis, Jr., and including others such as A. Baird Hastings and Alexander Langmuir, to visit Japan and advise with him. Thereafter he made arrangements with the medical schools of Yale and the University of California at Los Angeles that provided a continuing rotation of able physicians and pathologists who worked in Japan to maintain the effectiveness and continuity of the program. There have been other important develop-

ments since Cannan's time, but the reforms he brought about preserved and strengthened the work of the ABCC at a time when such intervention was urgently required.

Another notable accomplishment was the development of a satisfactory standard for hemoglobinometry. Cannan, in response to a request from the National Institutes of Health, established a panel of experts to work on the problem. Under his direction the panel selected, and carefully characterized, a solution of cyanmethemoglobin, which was tested in a number of laboratories in the United States and Canada. As a result a standard solution was proposed, commercial production of the standard was assured, and the College of American Pathologists agreed to serve as an independent certifying agency to maintain the uniformity of the standard (1958). European hematologists proposed some modifications in the standard; Cannan appointed a new panel to work with the Europeans on an international standard. At the meeting of the International Society of Hematology in 1967, the standard was accepted on a worldwide basis.

Probably the largest enterprise that Cannan guided during those years was the Drug Efficacy Study of the NAS-NRC. This resulted from the Kefauver-Harris amendments of 1962 to the Food, Drug and Cosmetic Act of 1938. The 1938 Act required that evidence of the safety of new drugs should be submitted to, and accepted by, the Food and Drug Administration (FDA), before the drugs could be placed on the market. The Kefauver-Harris amendment added the requirement that evidence for effectiveness, as well as safety, should also be submitted to, and accepted by, the FDA before the drug could be released. This imposed an immense new task on the FDA, and the newly appointed Commissioner, Dr. James Goddard, turned to the NAS-NRC for advice. As Cannan said, in a talk given in 1968, "we approached the

problem somewhat fearfully." The task was immense, and could be highly sensitive to powerful pressures from the drug industry. Cannan was the chief author of the resulting "Guidelines" for the study, for which he was able to enlist 180 experts, each being assigned to one of 30 panels, covering the main categories of disease. Over five years of effort, these panels, together with a staff of medical and lay personnel, carefully evaluated the therapeutic effectiveness of some 3600 drugs, and reported their conclusions to the FDA. Nothing like this had ever been done before; as Cannan said: "The Efficacy Study has been uniquely extensive in scope and uniquely intensive in time."

In 1967 Cannan retired from the chairmanship of the Division of Medical Sciences. On the occasion the Committee on Shock presented a tribute to him in a booklet, of which I quote a few words: "During your fifteen years as chairman you have guided the division quietly but most effectively, gently but firmly, and with a light touch that has extracted the best from your diverse committees and led to fruitful developments in the field of medicine." Many others who worked with him could have said the same.

Cannan, however, did not retire, but continued full-time activity as consultant to the new division chairman, unofficial adviser to the Drug Efficacy Study, and representative of the National Academy in several international organizations. He held the title of special assistant to the president, and in that capacity did much work in drawing up plans for reorganization of the NAS-NRC structure. This, of course, he did in constant consultation with President Philip Handler. The formation of the Academy's Institute of Medicine was one of the results of this work. He remained active until ill health forced his retirement in January 1971. A few months later, on May 24, he died of cancer in Washington. Two years

before, in April 1969, he had been elected a member of the National Academy—an honor that, to many of his friends, seemed long overdue.

PERSONAL LIFE AND CHARACTER

Early in his life Keith Cannan had faced an ordeal that few, if any, of his contemporaries in the National Academy had endured—four years of active military service in the First World War. He survived it as a profoundly civilized human being: sensitive, highly literate, humorous, and gentle in his relation to others, but capable of strong and decisive action when action was called for. Poetry meant much to him; indeed it had been a source of strength and comfort to him in his wartime service at the front in France. The number of his published scientific papers was not large, but his standards were exacting. He strove for the highest attainable accuracy in experimental work and, as Dr. Kekwick has written to me: “The clarity of his thinking was mirrored in the style in which he wrote his papers, with an economy of words yet with complete and unambiguous definition of his intended meaning.” As a teacher he was much admired for his lectures, which were brilliant, well organized, and lucid; but he was more concerned with establishing communication with individual students than with formal examinations.

He was often in demand as a speaker; for instance, he delivered a memorable address on “The Educated Heart” to the graduating medical students of Baylor University in 1956. This was a notable expression of much of his philosophy, and its application to medicine. Though he himself was not a physician, he had spent most of his life in medical schools, and knew their students and their problems intimately.

Another address to a group of physicians, about 1955,

was entitled "A Biologist's View of Philosophers and Physicists." Here he remarked on his dismay at finding that "the impact of science on philosophy seems to have been mediated almost entirely by physicists and mathematicians. As a biologist I resent this." He remarked that "science is too important to be left to the physicists" and he indicted their on-sidedness on several counts.¹¹ All this he set forth with a rather light touch, but he had a serious and valid point to make—a point that has indeed been stated eloquently and at length by Ernst Mayr in his major book *The Growth of Biological Thought* (1982).

R. A. Kekwick writes: "When I first met him as a young student I found him rather reserved almost to austerity. I think at that time he was not infrequently experiencing pain from his war wounds and this caused him to retire into himself. He did not give his friendship readily but when he did it was wholeheartedly and his actions were full of unobtrusive kindnesses. He relished the occasional practical joke against himself with great good humour and usually retaliated with one better."

Frederick Seitz, who was president of the National Academy while Keith Cannan headed the Division of Medical Sciences, wrote of him: "His insights were creatively profound and his energies unbounded. Each day he set a standard which the rest of us were pleased to match occasionally. . . . Through it all, I do not remember a single occasion in which he lost either his sense of balance or his good humor. It was a rare privilege to be associated with him."

He was a member of the Chemical Society and the Biochemical Society of Great Britain, the American Chemi-

¹¹ Much of this address, and of several others, is reprinted in the memoir by Hildegard Cannan (see acknowledgment paragraph at end of text).

cal Society and the American Society of Biological Chemists, the New York Academy of Sciences, and the Harvey Society, which he served as president from 1934 to 1936.

He was elected to the National Academy of Sciences in 1969.

He received a medal "For Distinguished Service" on the twentieth anniversary of the Atomic Bomb Casualty Commission, in 1969, from the Commission and from the Japanese National Institute of Health. Earlier, in 1961, he received a medal of the University of Hiroshima. In 1962 he was awarded a medal by the Armed Forces Institute of Pathology of the United States.

He was twice married, first in 1920 to Catherine Ann Smith, by whom he had one daughter, Dr. Cecily Cannan Selby (now Mrs. James S. Coles). He was divorced from his first wife in 1953. In August 1953 he married Hildegard Newcomb Wilson. He had three grandsons: Norman, William, and Russell Selby.

DR. CANNAN'S WIDOW, HILDEGARD CANNAN, prepared a memoir concerning him that was distributed to a number of his friends. This has proved of immense value in the preparation of the present memoir; it gives much information concerning his career, and also concerning his character and philosophical outlook, with illuminating passages from speeches, notes, and verses composed for convivial occasions. His daughter, Dr. Cecily Cannan Selby, has also been a source of valuable information. She has supplied copies of some of his characteristic talks to students and to scientific societies, and has made available some important letters, including those from Homer W. Smith and Sir Walter Fletcher, from which I have quoted. Dr. A. C. Chibnall has kindly provided me with copies of the letters that Keith Cannan wrote to him from New York (1930-33); these have provided valuable background and I have quoted some passages from them. Professor R. A. Kekwick's personal recollections of Cannan, whom he considers his scientific "father," have been of great value, and I have quoted them in

several places. Material supplied by the National Research Council has been indispensable for my discussion of Cannan's service there. The discussion of his unpublished work on pyocyanine is based on letters between him and William Mansfield Clark and Barnett Cohen. These are from the W. M. Clark Papers, now in the Library of the American Philosophical Society in Philadelphia, the gift of Miss Miriam Clark. My work on these papers was in connection with the Survey of Sources for the History of Biochemistry and Molecular Biology, supported by NSF grant SOC76-11194 and NEH grant RT-25201-76-759. I also acknowledge support from NSF grant SOC7912543.

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* These reports were signed by Robert Keith Cannan as chairman of the Division of Medical Sciences of the NRC. Dr. George Cartwright was actually the chairman of the Committee that prepared the final report.