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A Biographical Memoir by

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Clement L Markert

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BY GERALD M. KIDDER

CLEMENT L. MARKERT DIED on October 1, 1999, in Colorado Springs, Colorado, at the age of 82. He and his wife, Margaret, had been living there since his retirement from North Carolina State University in 1993. Markert was born in Las Animas, Colorado, and grew up in the area around Pueblo. He and Margaret returned to "their mountain" near Westcliffe, Colorado, each summer. It was in their beloved mountain wilderness that he was laid to rest. Margaret joined him in death the following year. They are survived by three children: Alan, Robert, and Samantha (Betsy) Schreck.

A MAN OF IDEALS AND ACTION

Clement Markert was a man of ideals whose devotion to social causes was evident from early in his career. His father had been a steel worker, and the family had suffered during the Great Depression, when the mines and steel mills were closing. This experience undoubtedly influenced the development of Markert's social conscience. Grateful for scholarships awarded for his academic achievements, he enrolled in the University of Colorado at Boulder to study biology. At the same time, however, he was concerned about events on the world stage, especially what he perceived to

be the failure of capitalistic economies to meet the needs of working-class people. He embraced socialism and even organized a communist group at the university. He was very soon presented with an opportunity to put his social ideals into more direct practice. Responding to the threat of fascist movements taking hold in Europe in 1938, he interrupted his studies and, along with his college roommate, rode freight trains to the East Coast, where the two men stowed away on a merchant ship bound for France. From there they joined the famous Abraham Lincoln Brigade, which was fighting the forces of Generalissimo Franco in Spain, hoping to prevent his toppling of the democratically elected government. Markert later explained that he had been one of the few members of his combat unit to survive the Spanish Civil War (his roommate was one of the casualties). In an obituary for Markert in *The New York Times* (October 10, 1999) he was quoted as having said in a 1986 interview, "I felt the most concrete thing I could do at the time was to destroy fascism, and Spain was the battleground on which to do that."

After the defeat of the anti-Franco forces Markert returned to the University of Colorado to complete his undergraduate studies. He was awarded a B.A. summa cum laude in 1940. In that same year he married Margaret Rempfer, who was to be his partner for life. The couple moved to California so that Markert could do graduate work at the University of California, Los Angeles, where he conducted research in vertebrate embryology; however, world events again intervened. The United States became involved in World War II, and Markert chose to reactivate his personal fight against fascism. He took a master's degree in 1942 to terminate his graduate education and tried to enlist in the U.S. Army. Not surprisingly, given the political climate of the time, his previous associations with American

and Spanish communists, who had also been fighting against Franco, made him unacceptable for military service. In response to this setback he moved to San Diego to serve as a dockworker until being accepted into the merchant marine. He served out the war as a radio operator on a ship supplying U.S. forces in the Pacific.

When his war years were finally behind him, Markert enrolled in the doctoral program in biology at Johns Hopkins University, where he conducted research under the mentorship of one of the country's foremost developmental biologists at the time, Benjamin H. Willier. After earning the doctorate in 1948 he completed his research training as a Merck-NRC postdoctoral fellow at the California Institute of Technology. There he specialized in biochemical genetics under the influence of George W. Beadle, the foremost proponent of that emerging field.

A MAN OF INTEGRITY AND COURAGE

Markert's first independent academic appointment was at the University of Michigan in Ann Arbor, where he accepted an assistant professorship in the Zoology Department in 1950. He became the intellectual leader of a group of junior faculty who were in tune with the recent advances in biochemistry and genetics that led in 1953 to Watson and Crick's publication of the structure of DNA. The Markert family, which by this time included all three children, settled into the pleasant life of the Ann Arbor academic community, and it seemed that Markert's earlier life as a social activist was a thing of the past.

This notion was shattered in 1954 when Markert and two colleagues were called before a subcommittee of the House Un-American Activities Committee meeting in East Lansing, Michigan. The subcommittee, chaired by Michigan Representative Kit Clardy, was mandated to identify

and root out communists from academia. Those who were targeted by the committee were threatened with being exposed as communists unless they named their former associates who might be considered communists or sympathizers. The three men declined to cooperate, refusing to name anyone. As a consequence all three were suspended from their positions with the university, which set up review committees at various levels to examine their cases. Markert was the only one of the three who was reinstated. According to David Nanney, a departmental colleague of Markert's at the time, Markert survived the ordeal because of support from his academic colleagues, who were convinced of his personal integrity, as well as scientists elsewhere (including George Beadle) who were impressed with Markert's scientific acumen and wrote letters on his behalf. Markert would later relate this experience to his students to emphasize the importance of standing up for one's convictions, whether scientific or political, regardless of the cost. Years later the university invited the three men back to Ann Arbor to receive an apology for the way they had been treated.

The controversy surrounding Markert's youthful socialist activism did not end there. In 1957 he applied for the position in developmental biology at Johns Hopkins that was being vacated by his retiring mentor, Professor Willier. When the search committee recommended Markert's appointment, administrative resistance developed. Markert had made no secret of his past; indeed, he was proud of it! The impasse was resolved when, after interviewing Markert himself, the president of the university, Milton Eisenhower (brother of the President), recommended Markert's appointment as a full professor and threatened to resign if the appointment was not confirmed. Markert accepted the position and remained at Hopkins until moving to Yale University in 1965 to become chair of the Department of Biol-

ogy. Once again Markert took pains to ensure that Yale's president at the time, Kingman Brewster, was fully aware of his past and his intention to remain involved in social causes. During the late 1960s Markert was an outspoken opponent of the government's continuing involvement in the Vietnam conflict and took an active role in public protests. Other causes that received his outspoken support included affirmative action to promote women in academia and the "Zero Population Growth" campaign (his car license plate for a time was ZPG). Through this entire advocacy, as always, Margaret was by his side. Indeed, Markert attributed much of his confidence during those difficult times in Michigan to the knowledge that his wife would be able to cope with whatever hardship his political activism brought upon them.

MOST NOTABLE SCIENTIFIC CONTRIBUTIONS

Throughout his career Markert aimed high: He wanted to tackle the big questions in biological science, questions like how genes control development and how the genome of an organism can be manipulated to bring about genetic improvement. In many cases answering such questions required the development of new research techniques. His scientific contributions covered a wide range from biochemistry through developmental and reproductive genetics.

Markert was best known early in his career for elucidating the importance and structural basis of isozymes, multiple molecular forms of enzymes. The stage was set for that work when in 1957 Markert and his University of Michigan colleague, Robert L. Hunter, combined enzyme histochemistry with the starch gel electrophoresis technique newly developed by Oliver Smithies to show that there are more than 10 separable forms of esterases in mouse liver (Hunter and Markert, 1957). Using different substrates or inhibitors

in the histochemical staining reaction, they obtained evidence that the different esterase bands in the gel were enzymatically distinct. The same technique but using different histochemical reagents also revealed multiple forms of other enzymes, demonstrating that this phenomenon is not limited to esterases. The investigators termed their stained gel, showing multiple bands representing the same enzymatic function, a zymogram. In a subsequent paper communicated to *Proceedings of the National Academy of Sciences* by Benjamin Willier, Markert and Freddy Møller used the zymogram technique to show that the number of molecular forms of lactate dehydrogenase (LDH) in mammalian tissues is greater than had been appreciated and proposed the term isozyme to denote these forms (Markert and Møller, 1959). They also showed that tissues differ in the number of LDH isozymes they contain and their relative proportions. Most importantly, their data made it clear that the isozyme patterns of embryonic tissues change through ontogeny until the tissue-appropriate adult pattern is achieved, a phenomenon that was interpreted as indicating changes in gene expression related to cell differentiation. This insight into the utility of isozyme studies for understanding developmental mechanisms was to influence Markert's research for years to come. Møller, a Dane who had been trained in veterinary medicine before joining Markert's lab (by then at Hopkins), later credited the excitement of those days with his decision to make research his career. Markert's insights into the importance of differential gene activation during development provided a new way of looking at abnormal development as well, and he was one of the first to point out that diseases such as cancer can be viewed as cell differentiation gone awry (Markert, 1968).

As important as it was, Markert and Møller's 1959 paper

left unexplained the molecular basis of isozymes. There was little appreciation at the time of the existence of gene families, evolutionarily related genes encoding proteins of similar or overlapping function. Yet Markert and Møller did offer that as one explanation, citing the multiplicity of genes encoding fetal and adult hemoglobins. They also suggested that a single gene might somehow encode an array of isozymes differing in "structural variations," a concept that seems to presage our current understanding of alternative mRNA splicing and post-translational protein modification. It was several years later, through the efforts of Ettore Appella, an Italian postdoc, that the Markert laboratory finally came to a clear understanding of the molecular basis of LDH isozymes. By treating the enzyme with denaturing agents it was learned that LDH is a tetramer of two types of polypeptide chains (Appella and Markert, 1961). Thus the multiple-gene hypothesis was partially correct: Two different LDH subunits, each encoded by a distinct gene, re-sort themselves in various tetrameric combinations to give rise to five different isozymes (Markert, 1963). During the succeeding years Markert and his students and postdocs continued to study the molecular basis and biological significance of isozymes and showed how the study of isozymes could contribute to our understanding of the biochemical variation that underlies cell differentiation and evolution. The culmination of this work was the new perspective presented in a *Science* paper (Markert et al., 1975) entitled "Evolution of a Gene," coauthored with former graduate students James B. Shaklee and Gregory S. Whitt. Markert took particular pride in his role in elucidating the isozyme concept, not least because this was a case of a developmental biologist teaching something about biochemistry to the biochemists. For several years he served as editor or coeditor of the multivolume

series "Isozymes" that emanated from the annual International Congress on Isozymes.

Markert's predilection for tackling the big questions sometimes caused problems for the person in his laboratory who was taking the lead on a project. For example, one idea that was tested during Markert's Hopkins years was that the program of gene expression within a cell is dictated by the constellation of nuclear proteins interacting with its DNA. If so, then it was hypothesized that introducing nuclear proteins from another source should reprogram a cell's genetic machinery. This was tested by injecting liver nuclear proteins into fertilized frog eggs with the expectation that the embryos would develop characteristics of liver cells. Instead the embryos arrested their development, and little was learned from the experiment despite exhaustive attempts to analyze the embryos using the techniques of the day. Markert was later criticized for investing resources and student time in such a simple-minded approach to a very complex problem, but if the experiment had worked at least partially, it would have been a major step forward.

Shortly after moving to Yale, Markert's laboratory became involved in a new research topic that was to have an impact at least as important as that of the isozyme concept. Yoshio Masui, a young scientist from Konan University in Japan, arrived at Yale in 1966 on sabbatical leave to study biochemical aspects of cell differentiation and development. Masui had become intrigued by Markert's view of development as emanating from differential gene activation and wanted to contribute to the elucidation of that concept. He began working on LDH isozymes in penguin embryos, characterizing their changing expression patterns during development. After less than a year, however, Masui came to the conclusion that the complexity of regulation of even a single enzymatic function during development was too great to be

elucidated by the technology available in the 1960s. He wanted a more tractable problem to work on. Markert encouraged him to choose a project of his own interest, one that he could continue working on after returning to Japan.

Masui decided that to understand cell differentiation it would be advantageous to study an unambiguous cell change induced by a well-defined external signal. Remembering the classical experiment by Heilbrunn et al. (1939) in which oocytes were induced to be released from frog ovaries treated in vitro with a pituitary gland suspension, Masui reasoned that this must be an example of a developmental induction evoked by a hormone. He was impressed that a hormone could act directly on its target tissue in vitro. Furthermore, Masui realized that hormonal induction of meiotic maturation and ovulation of the frog oocyte could provide a highly advantageous system for studying the control of cell cycle events: It would allow the investigator to use distinct stimuli to induce oocyte maturation (response to the hormone) and egg activation (cleavage in response to fertilization), thus separating the signals that drive the cell cycle from G2 to M phase and from M to G1 phase, respectively. He hoped in this way to develop a research program in nucleocytoplasmic interactions that he could continue in Japan, where research resources were not as plentiful at the time, taking advantage of the ability to obtain large numbers of synchronous frog oocytes for biochemical analysis. For his part Markert was enthusiastic about that line of investigation, because he had often mused about the possibility of suppressing meiosis in oocytes as a route to parthenogenesis. Masui's proposed experiments were seen as an early step along that road, since they could reveal how meiosis is controlled (Masui, 2001).

In early 1967 Masui started research on oocyte matura-

tion by repeating Heilbrunn's classical experiment using *Rana pipiens*. His experiments eventually led him to conclude that pituitary gonadotropin acts on the follicle cells of the ovary to stimulate them to release a progesterone-like hormone that directly acts on the oocyte. Further work revealed that progesterone could have an effect only when it acted from the outside of the oocyte or on the cell surface, leading him to propose that the oocyte cytoplasm carries the hormonal signal to the oocyte nucleus to induce the first meiotic division. To test this hypothesis Masui injected the cytoplasm of oocytes induced to mature by progesterone into immature oocytes and found that these oocytes were induced to mature without hormone treatment. That was the now famous experiment that demonstrated the presence of a cytoplasmic factor, which Masui and Markert called *maturation promoting factor* (MPF), that caused oocyte maturation by triggering meiosis (Masui and Markert, 1971). Using the same bioassay it was shown that MPF appears before the oocyte enters M phase, but declines when the oocyte proceeds to G1 phase after fertilization. Masui also demonstrated that maturing oocytes contain another factor, named cytostatic factor (CSF), that is responsible for the arrest of oocyte meiosis until fertilization. The manuscript reporting these exciting results (Masui and Markert, 1971) was published shortly after Masui moved to the University of Toronto, where he is still working. It was the first significant step in understanding how cell division is controlled. That work was followed by research in other laboratories studying cell cycle regulation in yeasts, where the power of genetics was used to identify specific molecules having the properties of MPF and CSF. Today we know that MPF, more generally known as *M-phase promoting factor*, is a complex of cyclin B2, a regulatory protein that is synthesized and then destroyed in each cell cycle, and Cdc2, a

catalytic protein that promotes entry into M phase. CSF is a Mos protein-containing complex that acts to prevent cyclin B2 degradation, thus maintaining the cell in M phase (Duesbery and Vande Woude, 2002). The importance of Masui and Markert's 1971 paper was recognized in 1992 with the awarding of the prestigious Gairdner Award (<http://www.gairdner.org/>) to Masui along with Leland Hartwell and Paul Nurse, two of the scientists whose work in yeasts had identified genes involved in cell cycle regulation. In 1998 the Lasker Foundation (<http://www.laskerfoundation.org/>) recognized the same three scientists with the Lasker Award; but in 2001, when the Nobel Prize was awarded for contributions to understanding the cell cycle, the winners were Leland Hartwell, Paul Nurse, and Tim Hunt, the last of whom had discovered the cyclins in his work with rapidly dividing embryos. Many of Masui's students and colleagues, particularly those who had shared in the excitement of his discoveries while working alongside him in Markert's laboratory, were deeply disappointed at his being omitted from receiving the ultimate science prize.

In the final phase of his research career at Yale, Markert turned the attention of his laboratory to early mammalian development, a field that had lagged behind other areas of developmental biology until techniques were developed to allow experimentation with embryos developing outside the womb. He undertook an ambitious project that was ahead of its time for its sheer boldness: the production of a homozygous diploid mouse. His approach was to remove one pronucleus from a fertilized egg, a very delicate procedure, and then suppress the first mitotic division to restore the diploid condition in the remaining pronucleus. Markert saw homozygous diploidy as an indirect route to cloning, since the offspring of successive generations produced in the same way would theoretically be identical. Homozygous diploid

blastocysts were obtained by this procedure, but none survived to term after transfer to foster mothers (Markert and Petters, 1977). Soon afterward another team of researchers claimed to have succeeded with the same procedure (Hoppe and Illmensee, 1977). Those results have not been replicated. The current view, based on a large body of data, is that differential epigenetic modification of sperm and egg genomes precludes normal post-blastocyst development when the embryonic genome is derived from a single parent. Markert lived just long enough to see mammalian cloning, now performed by nuclear transfer into enucleated oocytes, become a reality (Wilmut et al., 1997).

Markert and postdoc Robert Petters did succeed with another technically demanding experiment: the production of hexaparental chimeras, mice made up of cells from three different embryos having different genotypes (Markert and Petters, 1978). They then repeated the experiment with four different embryos, producing octaparental mice (Petters and Markert, 1980). This result proved that at least four embryonic stem cells of the early embryo give rise to the fetus. Pictures of those hexaparental mice are still featured in developmental biology textbooks. At the same time, a graduate student in Markert's laboratory, Vijay Thadani, was showing that rat oocytes can be fertilized by sperm of other mammalian species if the sperm are injected directly into the oocytes (Thadani, 1980). This experiment demonstrated that fertilization can occur without the normal processes of sperm activation, penetration of the zona pellucida, and sperm-oocyte binding, processes that are sometimes defective in infertile men; it presaged the now widely used technique of intracytoplasmic sperm injection (ICSI) as a treatment for male infertility.

Ever the adventurer, Markert was eager until the end of his active research career to tackle the most difficult and,

as he saw it, the most important biological questions. After retiring from Yale he finished his career as Distinguished University Research Professor in Animal Science and Genetics at North Carolina State University.

SERVICE TO SCIENCE

Markert believed that scientists have an obligation to do their share of administrative work and to serve on volunteer boards and committees for the good of the scientific enterprise. In addition to serving as chairman of the Department of Biology at Yale (1965-71) he was director of the Center for Reproductive Biology (1974-85). He was managing editor of *The Journal of Experimental Zoology* (1963-85) and coeditor (with John G. Scandalios) of *Developmental Genetics* (1979-92). He served terms as president of the American Institute of Biological Sciences (1966), American Society of Zoologists (1967), and the Society for Developmental Biology (1973-74). Agencies and institutions that benefited from Markert's advice as a board member included the Bermuda Biological Station (1959-83), President's Biomedical Research Panel (1975), American Cancer Society (1976-78), Bioscience Information Service (1976-81), La Jolla Cancer Research Fund (1977-86), National Research Council (1979-83), Jane Coffin Fund for Medical Research (1979-87), American Academy of Arts and Sciences (1981-84), and the Federation of American Societies for Experimental Biology (1987-93). As a member of the National Academy of Sciences he served on several committees and was elected to the Academy's governing board, the Council.

MARKERT AS TEACHER AND MENTOR

Markert was a superb teacher whose lectures were legendary among undergraduates. Like his research interests, his lectures emphasized the big questions. He taught a course

at Yale entitled "Biology of Reproduction" that covered, in addition to the important biological principles, hot-button issues of the time such as overpopulation and abortion rights. The course also presented cutting-edge reproductive technology, including actual production of chimeric mice. Markert returned to Yale for several years after his mandatory retirement to give lectures in the course that he had pioneered.

For many of us who trained with Clem Markert, our memories are as much about the culture of his laboratory as about the science that was done. Graduate students even more so than postdocs were given free reign to choose their own research topics and to pursue them more or less independently, the only requirement being that any project needed to fit within the broad scope of Markert's research interests, which was certainly not difficult. In the late 1960s, for example, research in the Markert laboratory ranged from LDH isozymes in various species through maturation and fertilization of frog and mouse oocytes to ribosomal gene redundancy and the molecular biology of molluscan development. Given the independence with which graduate students pursued their research, Markert usually declined to add his name to their publications; he did, however, receive explicit acknowledgement for financial support of the work and his mentorship. Despite his heavy administrative responsibilities he was often available to talk with individual trainees without prior appointment and, unless he was traveling, could be expected to sit down to a bag lunch with laboratory members on a daily basis. In addition to science, the conversations often focused on history (the American and Russian revolutions, for example), politics (a topic on which Markert was never hesitant to share his views), and even religion. An avowed atheist, Markert nonetheless was knowledgeable about and respected the beliefs of his trainees and colleagues. Whether his trainees agreed with him

or not they knew they were being mentored by a man of superior intellect and strong social convictions who was willing to put his life and career on the line for what he believed in. That, most of all, was Markert's legacy.

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