Michael Potter
1924–2013

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES
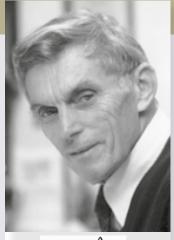
MICHAEL **POTTER**

February 27, 1924–June 18, 2013

Elected to the NAS, 1981

With the passing of Michael Potter on June 18, 2013, the scientific community lost one of the most outstanding cancer immuno-biologists of the last sixty years. Mike died at home at the age of eighty-nine after battling acute myeloid leukemia for several years. Those who have known Mike will uniformly remember him not only as a truly exceptional scientist and an unforgettable individual, but as one of the most generous and kind human beings ever to be encountered anywhere in life.

Early life

Michael was born on February 27, 1924, in East Orange, New Jersey. The first son of Thomas and Mavis Potter, he would later be joined by a younger brother and an adopted sister. When he was about eight years old, the family moved to the seaside town of Seagirt, where Mike spent his early adolescent years. As related by Mike and

By Stuart Rudikoff and J. Frederic Mushinski

his daughter, Melissa, he enjoyed a rather whimsical childhood with seemingly Tom Sawyer-like overtones. He was encouraged to explore things "of interest" and enjoyed a great deal of freedom to pursue his own agenda.

It was during this period that Mike developed a true love of the seashore and nature. He learned to fish and scavenge the beaches, activities that would remain two of the great joys in his life. He was fascinated by animals and was known to occasionally get into trouble when caught examining "road kill" as his early training in biology.

His father was a great influence in his life and strongly encouraged his approach to self-education. They spent much time together and the special relationship with his father extended to many discussions about life, which profoundly influenced Mike's future. For example, Thomas was, at the time, a practicing lawyer and involved in a case seeking compensation for women workers who painted radium dials on watches and

later developed cancer. Cancer and its incurable nature were subjects the two discussed at some length, perhaps as part of Thomas's desire to have Mike think about biology and medicine. The esoteric nature of Mike's early education is noted by the fact that he did not enter a structured educational system until the fourth grade. This, apparently, presented no problems for him as he was already an avid reader and had competent tutoring at home.

In 1938 the family moved to Princeton, New Jersey, where Mike spent the remainder of his youth. He often remarked what a memorable period in history this was and how events and people made such great impressions on him. As examples, he was particularly taken by major happenings like the burning of the Hindenburg zeppelin (which he had previously seen flying over New Jersey) and the Lindbergh kidnapping. He almost seemed to transport himself back in time when he spoke about living among awe-inspiring people in the "small town of Princeton," including the Russian pianist/composer Sergei Rachmaninoff and the German violinist/theoretical physicist Albert Einstein. These exposures, without doubt, contributed significantly to the development of Mike's lifelong love of classical music.

Following high school, Mike entered Princeton University as a sophomore and graduated three years later in 1945. His continuing interest in biology led him to attend the University of Virginia (UVA) Medical School, from which he graduated in 1949. He served both an internship and residency at UVA, during which time he met his future wife, Jeanne Ann Phalen, a nursing student. Mike was called into service in 1951 and spent about two years in the US Army as a medical officer in Korea. He returned to UVA Medical School in 1952 as a research assistant and shortly thereafter married Jeanne Ann. The Potters subsequently had two children: a son, Michael, and a daughter, Melissa.

During his assistantship, Mike came to the conclusion that research was where he wanted to focus and that cancer was a primary interest. In discussions with his mentors at UVA, he was basically told if he wanted to pursue cancer research, he should go to the National Cancer Institute (NCI) and join Lloyd Law, who was doing exciting things in leukemia research. Mike interviewed with Law and was offered a position as a biologist, resulting in the move of the Potter family to Bethesda in 1954 and the beginning of a brilliant career that would endure for nearly sixty years.

The science

A. Plasma cell tumors

The NCI was an exciting place for biomedical science in the 1950s. Wilton Earle and colleagues were developing methods for culturing tumor cells in liquid medium. James Holland, Emil Frei, and Emil Freireich were making groundbreaking advances in the treatment of childhood leukemia, and Lloyd Law was playing a key role in elucidating the biology that formed the basis for the clinical breakthroughs. Mike was, indeed, fortunate to have had Lloyd Law as his mentor at the NCI. Lloyd's approach to mentorship was a "laid-back" one, mainly allowing his young associates to define their own goals and then supporting and encouraging them along their chosen paths. This method was adopted by Mike when he ran his own lab, and it was reflected in the generous treatment of everyone who subsequently joined his group.

Lloyd's basic advice to Mike had been: "There is our animal room, down the hall. Go learn about mice and tumors." Needing no further encouragement, Mike proceeded to do just that.

It was an exciting time in murine tumor biology because, through the efforts of investigators such as C. C. Little, L. C. Strong, and others, inbred strains of mice were becoming available. These genetically identical populations were ideal for induction of a variety of murine neoplasms and, most importantly, they provided an invariant genetic background that allowed for continuous propagation of tumors by serial transplantation.

Mike proceeded to generate a variety of chemically induced tumors that he subsequently transplanted and carefully characterized as to cell type, in collaboration with Thelma Dunn, whom Mike considered the "authority" on mouse pathology. One of these tumors, P815, became the first transplantable mast cell tumor to be described. Many lymphocytic tumors were derived, transplanted, and characterized during this period, but Mike noted that none of these were of plasma cell origin. He had already realized that the availability of plasma cell tumors might provide an experimentally manipulable counterpart to human multiple myeloma, a neoplasm in which homogeneous immuno-globulins (Igs) or various constituent protein chains, were produced. The possible identification or generation of transplantable murine tumors that secreted homogeneous Ig would be an incredibly valuable source of materials to study antibody structure, function, and genetics.

The path leading to Mike's seminal discovery of the induction of transplantable plasma cell tumors was, as frequently happens in science, rather serendipitous, but it also reflects the keenly intuitive nature of his thought process. In 1956 Thelma Dunn received tissue sections of two unusual lymphomas from Ira Pilgrim at the University of California. Dunn determined that the tumors were plasma cell tumors and asked that they be sent to Mike for protein analysis. Mike had recently obtained a new-to-the-scientific-market, "state of the art" (as he laughingly described it in later years) paper electrophoresis apparatus. Using this technology, he was able to demonstrate that electrophoresis of serum from an animal that bore one of these tumors revealed a very thick band that remained at the origin and was, in fact, a myeloma protein. The second tumor also produced a homogeneous Ig spike, but with a different electrophoretic mobility. The latter was subsequently characterized, in collaboration with John Fahey, as an IgA myeloma protein. Thus, two transplantable, Ig-secreting plasma cell tumors had been identified, and this discovery focused Mike's efforts to expand the great potential he saw in research with these types of tumors.

During this same period, Glenn Algire and Ruth Merwin were conducting a series of experiments at the NCI to assess whether mammary tumor cells from one strain of inbred mice could survive in a second strain of a different histocompatability type which would normally reject the tumor cells. Their approach was to place the tumor cells (from C3H mice) in Millipore diffusion chambers and implant the chambers in the peritoneal cavities of BALB/c mice. After six months, the mice began developing abdominal tumors around the plastic chambers, which, in contrast with the mammary tumors inside the chambers, were characterized by Dunn as plasma cell tumors. Mike performed electrophoresis on serum from mice bearing these tumors and found that they were, indeed, producing myeloma proteins. In retrospect, it is extremely fortunate that Algire and Merwin chose BALB/c as the recipient strain in their experiments, as almost all other inbred strains were subsequently shown to be resistant to plasma cell tumor induction.

Mike originally thought that the plasma cell tumors were arising due to prolonged immunization from antigens secreted from the cells in the Millipore chambers. However, immunization of BALB/c mice for long periods with a variety of antigens failed to induce tumors. To amplify the immunization, he included in the protocol a modified Freund's adjuvant containing staphylococcal antigens that were developed by Rose Lieberman at the National Institute of Allergy and Infectious Diseases (NIAID), and subsequently, he observed that some of these mice did develop plasma cell tumors. With Charlotte Robinson Boyce, Mike then tested each of the components in the adjuvant

and discovered that the mineral oil component alone was sufficient to induce plasma cell tumors that could be serially transplanted. These results were published in the somewhat obscure *Journal of the National Cancer Institute* and were probably quite under-appreciated at the time.

Two years later, Potter and Boyce published a definitive paper in *Nature* that described the induction of transplantable plasma cell tumors by mineral oil and mineral oil adjuvants. In subsequent studies, it would be shown that foreign bodies such as empty Millipore chambers or even plastic shavings, as well as a variety of mineral oils including Esso Bayol F Oil obtained from a local gas station, were capable of inducing plasma cell tumors in the peritoneal cavity, but only in the BALB/c strain of mice. Analysis of these tumors revealed that, although they produced a homogeneous Ig, each tumor's Ig was unique and different from that produced by any of the other tumors. Furthermore, when the tumors were transplanted, the myeloma protein produced afterward was always identical in electrophoretic mobility to that found in the original tumor-bearing animal.

These findings had marked implications in two important areas. They clearly supported the premise that tumors of this nature were clonal in origin and arose from a single cell. Additionally, they provided direct evidence that confirmed Sir McFarlane Burnett's theory of clonal selection, which proposed that a single lymphocyte produced only one molecular form of Ig molecule. This system would provide the field of immunology with tools subsequently used for decades to solve many of its most compelling questions.

B. Antibody structure/function

By the mid-1960s, considerable evidence had accumulated to establish the general structure of Igs, largely from studies of human myeloma proteins and homogeneous antibodies isolated from the serum of hyper-immunized rabbits. The basic subunit of the antibody molecule was shown to be composed of two identical, covalently linked light polypeptide chains (~23 kDa) and two identical, covalently linked heavy polypeptide chains (~50 kDa). These subunits could be proteolytically cleaved into two fragments. One, termed Fab, contained the antigen-binding site and the second, termed Fc, was responsible for effector functions such as complement binding and polymerization, and also determined the antibody isotype or class (IgG, IgA, IgM, etc.).

Realizing the enormous potential for the use of homogeneous murine Igs in studies of the antibody molecule, Mike immediately involved his lab in efforts to assess the primary structure of these proteins. Very early protein sequencing and peptide mapping studies,

in collaboration with Richard Parham, David McKean, Claude Bennett, William Dryer, and Leroy Hood, revealed that light chains from the murine plasma cell tumors shared a carboxy-terminal sequence similar to human kappa light chains. However, the chains differed considerably at their amino terminal (termed "variable") ends. These findings had profound implications for theories of antibody formation, in that the presence of multiple variable region sequences originating in genetically identical animals would, presumably, require multiple variable region genes to encode the corresponding protein structures. The studies further suggested that multiple variable region sequences might, by genetic recombination, become associated with a single or limited number of, constant (kappa) region sequences. This postulate was subsequently experimentally proven by Susumu Tonegawa, who was awarded a Nobel Prize in 1987 for his studies on Ig gene rearrangement.
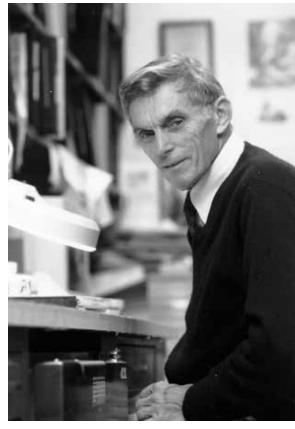
The results of multiple, different variable regions associated with a single kappa constant region conflicted with the seminal studies of Martin Weigert and Melvin Cohn, who determined the amino acid sequences of a second group of murine light chains, termed "lambda," which expressed a very different constant region. In the case of lambda light chains, the variable regions differed by only a few amino acids, leading to the proposal that very few genes were necessary to encode the variable regions of lambda chains and that most of the sequence differences could be explained by a process of somatic mutation. The debate as to the existence of many variable region genes encoding different antibody specificities versus the presence of only a very few genes that would diversify by somatic mutation persisted for years.

In thinking about the origins of cells that eventually become plasma cell tumors, Mike was convinced that they derived, for the most part, from normal participants in immune responses. He reasoned that many of these Igs would be involved in responses to pathogens such as bacteria and viruses. He therefore decided to screen the myeloma proteins for antigen-binding activity with the defined goal of generating appropriate models for structure/function studies.

An eclectic collection of antigens including carbohydrates, proteins, and hapten conjugates was assembled, and, with Elizabeth Mushinski, Mike began screening the myeloma collection. These efforts were rewarded with the identification, in 1968, of a nitrophenol-binding myeloma protein from plasma cell tumor MOPC 315 and three others that reacted with pneumococcal C polysaccharide. These proteins comprised the first collection of myeloma Igs with defined antigen-binding specificities. MOPC 315 would

become one of Mike's most widely known tumors and would eventually be used in hundreds of other studies. The MOPC 315 protein became a model for some of the earliest studies probing the structural nature of the antibody-combining site. Affinity labeling experiments with Henry Metzger and fluorescence quenching analysis with Herman Eisen were among the first reports to define specific amino acids involved in hapten/antigen binding and to begin a map for the actual antibody-binding site.

The group of proteins that reacted with pneumococcal C polysaccharide would shortly be expanded to eight members, and later studies would identify the actual hapten determinant bound as phosphocholine. The myeloma-screening program subsequently identified two other large groups of proteins that bound carbohydrate antigens. The first of these reacted with beta 1-6 galactan and the second with inulin. These two groups, along with the phosphocholine-binding proteins, would become the focus of a major effort in Mike's lab to evaluate antibody structure/function relationships.

Mike Potter at the lab bench.
(Courtesy of NIH.)

It was in this same time frame that I (Stuart Rudikoff) joined Mike's lab with similar interests in antibody structure/function. Shortly thereafter, a paper was published in *Proceedings of the National Academy of Sciences* describing the crystallization of the antigen-binding fragment from MOPC 315. These crystals did not diffract sufficiently for x-ray analysis, but Mike immediately realized the potential of his myeloma collection in approaching this problem. A collaboration was initiated with David Davies' crystallography lab at the National Institute of Diabetes and Digestive and Kidney Diseases

(NIDDK), and we began preparation of antigen-binding fragments from the set of phosphocholine-binding myeloma proteins for similar crystallization attempts.

Crystals were, in fact, obtained from one of these, McPC 603, and they were suitable for x-ray diffraction analysis. Diffraction studies, in conjunction with the primary amino acid sequence determined in our lab, produced the first molecular elucidation of the binding site from a homogeneous Ig with a previously identified binding specificity.

A number of fundamental observations derived from these studies. The phosphocholine antigen moiety was quite small in relation to the size of the potential binding surface area of the antibody, and the binding was asymmetric, with nearly all of the specific interactions occurring between phosphocholine and amino acids of the McPC 603 heavy chain. In retrospect, this was probably not surprising, as subsequent sequence analysis of other members of the phosphocholine-binding group revealed that all had nearly identical heavy chain sequences, including each of the amino acids that actually contacted the phosphocholine moiety, whereas the light chains differed enormously throughout their entire variable region sequences. In this case, the binding specificity was almost completely determined by the heavy chain. Furthermore, Elvin Kabat and T. T. Wu had previously analyzed primary sequence data from Ig heavy and light chains and concluded that within variable regions there existed three small, widely spaced areas in each chain that exhibited "hypervariability" in sequence and which, they predicted, would be brought together three dimensionally by the folding of the two polypeptide chains to form the antigen-binding site. This prediction was completely borne out in the McPC 603 structure that showed the six hypervariable regions forming a pocket-like area in which phosphocholine was bound.

The encouraging results obtained with McPC 603 led to a similar approach using a second set of myeloma proteins with binding specificity for beta 1-6 galactan. Crystals suitable for diffraction analysis were obtained from the antigen-binding fragment of the myeloma protein from the J539 plasma cell tumor, and the structure was subsequently determined. J539 and its related galactan-binding proteins were particularly useful in this structure/function analysis, as studies in collaboration with Neil Glaudemans (NIDDK) using chemically synthesized galactan derivatives and related carbohydrates provided a detailed picture of the requirements and limits of the galactan-binding site. In contrast with phosphocholine binding by McPC 603, the galactan-binding site accommodated a much larger antigenic determinant and involved extensive contacts from both light and heavy polypeptide chains, which could be readily deduced from the x-ray crystallographic

structure and modeling using the synthetic derivatives. These two structures provided striking contrasts as to the potential requirements for an antigen to be bound in an antibody-combining site, and were landmark contributions to understanding the nature of antigen/antibody interactions.

Studies of the group of galactan-binding immunoglobulins were extended to complete primary sequence analysis with the goal of comparing the structure of antibodies that exhibited the same specificity. In contrast with phosphocholine-binding proteins in which nearly identical heavy chains paired with very different light chains, in anti-galactan antibodies there were very few primary sequence differences among either the light or heavy chains. In retrospect, these results might have been anticipated, considering that the more extensive contact with antigen in the galactan-binding site suggested a strong need for conservation of amino acid sequences in both chains involved in antigen contact. However, a small amount of amino acid variation was clearly observed, suggesting that somatic mechanisms were also involved in generating the observed protein sequences. Similarly, inulin-binding myeloma proteins exhibited marked restriction in both light and heavy chain sequences. Collectively, these analyses revealed fundamental limitations in pairing for given light and heavy chains in determining antigen-binding specificity and the nature of sequence variation among antibodies with common reactivities. Taken together, these studies contributed enormously to our understanding of the structure of the antibody molecule, its interaction with antigen at the molecular level, and the nature of primary sequence variation among antibodies with the same antigen-binding specificity.

C. Ig genetics and idiotypes

Following the initial discovery of transplantable murine plasma cell tumors, a second major area to be rapidly developed by the Potter lab grew from a collaboration with Rose Lieberman that spanned more than fifteen years. This work produced multiple classic studies of the genetics of Ig inheritance and idiotypes.

Mike quickly saw the advantages in the murine system in this research, because appropriate antiserums to normal and plasma cell tumor-derived Igs could provide a unique set of reagents to study Ig inheritance and linkage. Antiserums prepared to normal or plasma cell tumor Ig in other animal species, or in other strains of inbred mice, generally fell into two categories. First, those prepared by immunizing other species, typically rabbits, recognized determinants in the Ig constant regions, termed "isotypes," which identified Ig classes and sub-classes (IgM, IgG_1, IgG_{2a}, IgG_{2b}, IgA, IgD, and IgE). Additionally,

such antiserums frequently recognized constant region antigenic determinants, termed allotypes, unique to the donor mouse strain of the Ig used as immunogen. Second, there were antiserums that recognized determinants in the Ig variable regions, termed "idiotypes." Such antiserums could only be prepared by immunizing other inbred strains with the BALB/c-derived myeloma proteins, taking advantage of the very small differences in Ig sequences between strains, which define idiotypes.

These immunizations and the characterization of the antiserums generated were laborious and time-consuming, but they became a hallmark of Lieberman's skills and determination. Coupled with the relatively short gestation period of mice and the availability of numerous inbred strains in the Potter collection, allotype- and idiotype-specific antiserums were generated and provided the necessary reagents for detailed genetic analysis of both constant and variable region genes.

In some of their earliest studies in collaboration with Sheldon Dray, Mike and Lieberman assessed the reactivity of antiserums raised against a battery of myeloma proteins and were able to identify antiserums that recognized two distinct sub-classes of IgG (IgG_1, IgG_2) in the BALB/c mouse. Furthermore, the antiserums recognized allotypic determinants in these molecules, permitting a distinction between BALB/c IgG_1 and IgG_2 versus these same sub-classes in other strains carrying different alleles. Using these reagents in what were among the first studies of this nature, they were able to demonstrate in classic genetic experiments that the genes encoding the IgG_1 and IgG_2 proteins were tightly linked and could not be separated in F2 progeny. Similar studies with appropriate antiserums also showed a close linkage between IgG and IgA constant regions, resulting in the emergence of the concept that a single genetic locus contained tightly linked genes encoding all of the Ig constant regions. The identification of two rare IgD-secreting tumors led to the development of cDNAs that enabled the first mapping of the IgD heavy chain constant region gene.

In contrast with the constant region, antigenic determinants in the variable region, the idiotypes, would turn out to be much more complex being determined by either the light or heavy chain or a combination of the two. In 1970 Mike and Lieberman made the striking discovery that five of eight of the phosphocholine-binding myeloma proteins expressed the exact same idiotype. This result suggested that in these five independently arising tumors, the same variable region genes had been expressed. Further studies demonstrated that the same idiotype was also expressed on naturally occurring antibodies in mice immunized with phosphocholine, clearly validating myeloma proteins

as authentic examples of normal antibodies. Using anti-idiotype reagents to phosphocholine-binding myeloma proteins, as well as similar reagents raised against galactan- and levan-binding myeloma proteins and hybridomas (immortalized cells resulting from the fusion of normal lymphocytes with a myeloma cell, see below), they were able to demonstrate that idiotypes were linked to constant region allotype determinants. These results, combined with similar studies from and in collaboration with other labs, led to the critical conceptual understanding that Igs were encoded by a large locus in which constant region genes were linked to variable region genes.

While the structural basis of idiotypes was potentially complex, the sets of myeloma proteins and hybridomas with the same antigen-binding specificity, especially the anti-galactan group, would prove highly appropriate for addressing this interesting question. Anti-idiotype antiserums prepared against multiple galactan-binding antibodies fell into two groups: 1) those recognizing only the immunizing myeloma or hybridoma protein, or 2) those reacting with the immunizing protein plus one or more other members of the same antigen-binding family. Studies in collaboration with the Glaudemans lab demonstrated that hybrid molecules formed by recombining light and heavy chains from different galactan-binding Igs resulted in the idiotype expressed in the immunizing Ig being associated with the donor heavy chain. Sequence analysis revealed that the light chain variable regions from all family members were essentially identical, whereas small variations were observed in the heavy chains, but largely confined to the third hypervariable region. By combining the results of the sequence analysis with the pattern of idiotypic reactivity among the group, it was possible to identify the molecular basis of both individual and shared idiotypes within the family. As predicted, all idiotypes could be assigned to the heavy chains. Using the crystal structure determined for the galactan-binding J-539 myeloma protein and molecular modeling, Potter and colleagues observed that the amino acids predicted from the sequence analysis to encode idiotypes were located on the Ig surface that was exposed to solvent, where they were likely candidates to be seen as antigenic determinants. This combination of sequence and three-dimensional analysis provided the first molecular characterization of idiotypes.

D. Tumorigenesis

Mike had a longstanding interest in cancer and its causes and felt that understanding the mechanisms leading to this disease in animals would provide important clues to likely similar events leading to human cancers. He was particularly interested in the reason that

BALB/c mice were the only strain that was routinely susceptible to experimental plasma cell tumor induction, as well as the nature of mechanisms that led to the development of these tumors. The identification of genes controlling susceptibility and resistance, undertaken in collaboration with Beverly Mock, would prove to be a complex problem, as tumor-induction studies in mice generated by crossing the susceptible BALB/c strain with resistant strains revealed that multiple BALB/c genetic loci contributed to susceptibility and resistance.

Early hints about the nature of the genetic events involved in plasma cell tumor formation came from a collaboration with Francis Weiner and George Klein beginning in 1979, during which chromosomal analysis revealed abnormalities in the immunoglobulin loci in plasma cell tumors. These abnormalities were eventually revealed to be chromosomal translocations involving one of the Ig loci and a second locus from a different chromosome. During this same period Mike, in collaboration with Marshall Sklar and Wallace Rowe, had been examining the effect of avian retroviruses on tumor induction. They observed that Abelson murine leukemia virus, a retrovirus that contained a portion of the abl gene embedded in the genome of the Moloney leukemia virus, greatly reduced the latent period of plasma cell tumor formation. Considerable efforts in a number of laboratories led to the understanding that the transforming elements in Abelson and other oncogenic retroviruses had normal mammalian homologues that appeared to be involved in the regulation of cell growth. When overexpressed or expressed in certain mutant forms, these "normal" genes frequently led to the development of cancers and were termed "oncogenes."

Mike intuitively deduced that oncogenes would be involved in plasma cell tumor formation. Subsequent studies demonstrated that mRNA levels of the *myc* cellular oncogene were elevated in plasma cell tumors and that infection of BALB/c mice with leukemia viruses that expressed *myc* led to generation of plasma cell tumors lacking chromosomal translocations. Involvement of the *myc* gene in tumor development was further confirmed by characterization of the chromosome translocation sites in the oil-induced tumors, demonstrating almost invariantly that the translocations involved juxtaposition of the *myc* locus to one of the Ig loci. This chromosomal rearrangement led to overexpression of *myc* owing to its up-regulation by active promoters and enhancers associated with the Ig genes. Although the translocation of *myc* into the Ig locus and its resulting activation was provocative in terms of identifying a possibly pivotal initiating event in plasma cell tumor generation, additional studies by the Potter group revealed that the same translocations could be observed in normal lymphocytes from both tumor-sus-

ceptible and tumor-resistant mouse strains. Thus, additional events would clearly be necessary to reach the state of complete neoplastic transformation.

Mike was an advocate of the premise that most cancers resulted from the accumulation of multiple genetic events that eventually led to complete transformation and loss of growth control. In parallel with the studies of chromosomal rearrangements, the lab was also attempting to define other requirements for tumor initiation and growth. Early stages of plasma cell tumor growth had proven particularly difficult to study, as primary tumor cells taken from animals could not be adapted to *in vitro* culture for propagation and analysis. It was only after primary tumors had been subjected to several serial passages in mice that they could successfully be grown in tissue culture.

In 1986, Richard Nordan, a graduate student in the Potter lab, made the observation that primary tumors could be adapted to culture if they were grown in the presence of supernatants obtained from cultured macrophages. Characterization of the factor in the macrophage supernatants required for plasma cell tumor cell growth resulted in its identification as interleukin-6, a member of a family of cytokines that would prove to be critical in lymphocyte growth and differentiation. Interleukin-6 would later be demonstrated to play a key role in growth and differentiation of normal B lymphocytes. Thus, primary tumor cells were not fully growth-independent, but required, at a minimum, interleukin-6 for survival until additional events led to growth factor independence.

 Mike was now able to meld the translocation and growth factor studies into a model in which the *myc* translocations were likely to be an early event in tumor development (since they could be found in normal cells), but complete neoplastic transformation occurred only in those cells with *myc*-activating translocations that survived in a growth factor (interleukin-6)-dependent manner until successive event(s) would lead to fully unregulated growth. Mike would continue to pursue his search for those additional events for the remainder of his career.

Personal observations

Both of us were fortunate to have had Mike as a mentor and a friend. When I (J. Frederick Mushinski) interviewed at NIH for a post-doctoral position in 1964, I found Michael Potter to be the most fascinating and engaging character I had ever met. Our interview was so engrossing that it lasted well past the allotted time, and I missed my next appointment. As I discovered at that initial meeting, Potter's charm and wide-ranging interests made him an unusually delightful conversationalist. We would

Mike preparing for a "lab meeting" on the Chesapeake Bay.
(Courtesy of Beverly Mock.)

frequently drive Mike to our lab retreats that were about two and a half hours away, and the conversations during these trips were always the highlight of the meetings for me. I later learned that he also had an interest in seeing that I had ample interactions with his new technician, Betty Bridges, subtly playing the role of matchmaker. He was quite successful and we were married in 1971.

When I (Stuart Rudikoff) interviewed with Mike in 1970, it was clear that we both had a deep interest in Ig structure and function, but we also discovered a shared attraction to the water and fishing. I believe Mike decided he could get a two-for-one deal with me, an eager young scientist and a fishing companion. So began a relationship that lasted more than forty years. It took me a while to get used to the sight of Mike arriving daily on his bicycle. The bicycle looked like it was claimed from a trash pile sometime in the 1950s, but that never fazed him. He would ride to and from work every day, regardless of the weather, unless it was so bad that Jeanne Ann said "no." There was no appeal from a "no" decision rendered by Jeanne Ann.

It took only a short time to realize what an incredibly generous person Mike was. He never refused a request for any materials his lab had generated, even if it was from someone doing the exact same type of studies that he was involved in. His attitude was that it was only advancing science that mattered and one could not be concerned with trying to limit access in any way to materials or reagents that would benefit experimental progress.

For a man of his accomplishments, Mike was one of the most unaffected and self-effacing individuals one could ever meet. It was almost impossible to get him to travel and promote his own work. He rarely attended meetings and would usually only do so at the request of friends and colleagues. He did take great pleasure in the workshops he organized beginning in 1969, which occurred almost yearly thereafter. These meetings originally focused on Ig structure and genetics, but subsequently expanded to related

topics including B cell development and B cell neoplasia.

In 1983 the workshops took on a rotating site format between the United States and Basel, Switzerland, due to the beginning of a long lasting friendship between Mike and Fritz Melchers, who, at the time, was director of the Basel Institute of Immunology. These meetings were unique in that there were usually no more than about fifty people invited and it was understood that only the latest and most exciting experimental findings would be presented and discussed. The workshops thus came to be focal points for exposure of much of the leading edge of B cell immunology/neoplasia research, and the invitation to attend these workshops was an acknowledged recognition of outstanding work in the field.

Mike with Fritz Melchers, his friend and co-organizer of the Ig/B-cell workshops. Taken at the symposium on the "Mechanisms of B-cell Neoplasia," which honored Mike's first fifty years at the NIH. (Courtesy of Edward Ramsey and Beverly Mock.)

In addition to his love for science and its history, Mike had many other interests, among which fishing was near the very top. As soon as the blue fish began their annual migration into the Chesapeake Bay, his schedule became altered in order to accommodate "scientific retreats" in his little Boston whaler. Discussions on these outings covered everything from science, to politics, to the sad demise of the Washington Redskins. Mike had several unique approaches to fishing that were entirely in character for him. Fishhooks have barbs that prevent the hook from slipping out once a fish has taken the bait. Mike filed the barbs off in order to give the fish a better chance at getting away. He also took great pleasure in making lures out of anything he could find, such as pop tops from soda cans. He was always surprised when the fish ignored these prized creations. His attraction to the water was further embodied in an annual trip to Kitty Hawk, North Carolina, where the Potters and their various pets would spend a summer month. Jeanne Ann would read and Mike would surf fish and scavenge the beaches, much as he had in his childhood. Mike was also a devotee of classical music and actually built his own harpsichord. In his later years, he became an avid bird watcher and

Always the scavenger.
(Courtesy of Beverly Mock.)

frequently would travel the coastal areas of Maryland and Virginia in search of shore birds and waterfowl.

At the time we joined the lab, Mike was chief of the Immunochemistry Section in Lloyd Law's Laboratory of Cell Biology, a position he would hold until 1982. It was surprising when it quickly became apparent that he did not have an office, but just a lab desk like everyone else, where he could almost always be found examining specimens in his microscope. Mike always told us that a Section Chief in the NCI was the best job in science. According to him, your only responsibility was to do first-rate research and you even had a lab chief above you to deal with the institutional "crapola," as he termed administrative concerns.

Mike had a unique sense of humor as exemplified by the understated pleasure he seemed to get from sending everyone who entered the lab, from Harvard graduates to Maryland students, to the animal room where they would learn to collect urine from tumor-bearing mice by squeezing their little bladders.

As it became clear that Mike deserved additional resources to pursue his expanding interests, the Laboratory of Genetics was created in 1982, and he, somewhat reluctantly, became its chief. He still refused to have an office and continued to work from his lab desk. In 2003 Mike gave up his responsibilities as chief and returned to a senior investigator position that he held until retirement.

In 1976 Mike became an adjunct professor at the University of Maryland, where he taught courses in immunology. As a result of this association, a number of Maryland students would, over time, become PhD students in his lab at the NCI. In 1990 he was appointed to the position of research professor. He greatly enjoyed this arrangement with the University and took pleasure in having the opportunity to expose Maryland graduate and undergraduate students to the fields of immunology and cancer biology.

In 1981 Mike was elected to the National Academy of Sciences, an honor that he particularly cherished, as it constituted recognition of his contributions by his peers.

In 1983 Mike was awarded the Paul Ehrlich and Ludwig Darmstaedter Prize for outstanding contributions to medical research, and in 1984 he shared the Albert Lasker Medical Research Award with Cesar Milstein and Georges Kohler. It is somewhat ironic that Milstein and Kohler would go on to win the Nobel Prize for development of the technology used to fuse Mike's tumor cells with normal splenic lymphocytes, resulting in immortal-

Mike and his faithful companion, Mr. Cook.
(Courtesy of Mike's daughter, Melissa Adde.)

ization of the normal lymphocytye. Fused cells, or hybridomas, could be generated (and subsequently selected) with virtually any specificity desired by immunizing with defined antigens prior to fusion, resulting in the generation of clones (hybridomas) that secreted monoclonal antibodies with targeted reactivities. The use of monoclonal antibodies from such hybridomas in disease treatment, as diagnostic reagents in the clinic, and in research has been one the great breakthroughs in modern science. Mike had begged cell biologists to do exactly this experiment, but he was routinely told that it was a waste of time, as the fully differentiated plasma tumor cell would always shut off the functions of the normal lymphocyte, and, even if successful, it would be impossible to identify the few fused cells with the desired specificity among the vast array of cells with irrelevant specificities.

Mike was an avid student of the history of modern science and medicine. He read virtually everything he could find on the lives and works of the early giants in these fields, including such notables as Pasteur, Jenner, Koch, Ehrlich and Percival Potts, among many others. Mike seemed to have the same intuitive approach to medical and scientific problems that one would assume these eminent individuals employed. He was truly a renaissance man, and it almost seems as if he were born one hundred or so years too late, as he would surely have fit in perfectly with the innovative minds of that time. Those of us who knew and were associated with him were truly fortunate. He will be missed, but his scientific legacy is a monument that will live on.

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