Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

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Between Novembers: Demerec, Cold Spring Harbor and the Gene

EXACTLY fifty years ago my father-in-law, Milislav Demerec, coauthored a Genetics paper on X-ray-induced chromosomal breaks in Drosophila (Bauer, Demerec and Kaufmann 1938). Then, exactly 25 years ago, he authored a paper on bacterial genetics Demerec (1963), again in the November issue of Genetics. Why this migration from eukaryote to prokaryote, the opposite of present-day trends? What happened during those intervening 25 years? This is mainly the story of a man deeply involved in a search for the structure of the gene and who, at the same time, quietly developed two institutions at Cold Spring Harbor that emerged under his leadership as a hub of what is now known as molecular genetics. It is also the story of a man whose name is misspelled in at least two histories of genetics and whose last name is more often than not mispronounced ("Demer-etts" comes close to the Croatian).

Profiles of Demerec have appeared elsewhere [Glass (1971); five profiles are reprinted in Caspari (1971)] and Glass (1971) has compiled a list of his publications. That list is an underestimate because Demerec encouraged younger collaborators to publish as sole authors, thus encouraging their independence (*e.g.*, seven of nine papers in Demerec *et al.* 1956). Some 5000 items of Demerec correspondence and 56 volumes of research notes are housed at the American Philosophical Society Library in Philadelphia, along with the files of other prominent geneticists (Glass 1988). It is amazing to me to find such a paper trail because most of Demerec's communications were either in person or over the phone. As Alexander Hollaender said to me, "It's faster, and they can't say no."

Shortly after immigrating to the United States from Yugoslavia, Demerec studied for his Ph.D. at Cornell and completed his work in 1923. He was one of a number of young geneticists, destined to become well known, who were associated with the maize genetics group of R. A. Emerson (Sturtevant 1965). He then joined C. W. Metz, A. F. Blakeslee, E. G. Anderson (another Cornell graduate) and others at Cold Spring Harbor in 1923. There he continued with the genetics of maize, at the same time initiating pioneering studies of unstable genes in Drosophila (Demerec 1935). At that time a gene was defined by three operational criteria: it affected a particular phenotype, it was recombinationally indivisible but could recombine with other genes, and it could suddenly and permanently change, *i.e.*, mutate. Demerec focused on the last, believing that studies of the mutational process would ultimately lead to an understanding of gene structure. In fact, his work on mutable loci led him to infer that a gene was a linear array containing "different structural components of a molecule" (Demerec 1938). Earlier he had used DNA as an example of such a molecule (Demerec 1933) but the then general belief was that DNA was a monotonous series of tetranucleotides.

Besides studying mutable genes in Drosophila and in the plant Delphinium, Demerec added an additional approach, one that was almost universally popular at the time (Delbrück 1970). He took up the observations of Herman J. Muller (1927) and used X-rays to induce mutations in Drosophila. One outgrowth of the Drosophila work predominating in Demerec's laboratory was the founding, with Calvin B. Bridges in 1934, of *Drosophila Information Service.* This was an innovation in its day and still is a valuable mode of communication. Demerec continued as editor of the increasingly popular *DIS* through the 33rd issue in 1960, a full decade after his own laboratory had abandoned Drosophila. By then, the *DIS* directory listed 989 workers and the issue contained short communications from 191 laboratories in 29 countries (Demerec 1942–1960).

While involved with this and numerous other outside endeavors, Demerec became increasingly concerned with the operations of the laboratory itself. He took active roles in an attempt in 1932 and again in 1936 to attract to Cold Spring Harbor the young plant and Drosophila geneticist George W. Beadle (Miller 1978). Beadle declined the offers and went on to share the Nobel Prize in 1958; one can only

conjecture whether the same result would have ensued had BEADLE accepted one of DEMEREC's invitations and proceeded through approaches different from those used in his actual career.

DEMEREC became formally involved with the administration of the Department of Genetics of the Carnegie Institution of Washington (located, despite its name, in Cold Spring Harbor) when, in 1935, A. F. BLAKESLEE was appointed Director (previously Acting Director) and DEMEREC's appointment was changed from Investigator to Assistant Director. During this transition period, DEMEREC also served as secretary-treasurer (1935–1938), vice president (1938) and president (1939) of the Genetics Society of America.

B. P. KAUFMANN joined the Carnegie staff in 1937, rounding out the collaboration on that November 1938 paper (BAUER, DEMEREC and KAUFMANN 1938). Some 1038 induced breaks were located in euchromatic regions of Drosophila chromosomes. BAUER, one of numerous guest investigators to migrate through Cold Spring Harbor, did most or all of the described work on-site. An illustrious array of visiting researchers was to continue passing through Cold Spring Harbor (recorded in DEMEREC 1941–1960).

The introduction to the 1938 paper tells exactly what each of the coauthors contributed and goes on to mention that some of the slides of 1765 pairs of salivary glands were prepared by Mr. HERSCHEL ROMAN who had been sent there by L. J. STADLER (ROMAN 1988) to learn a little about Drosophila. One very important aspect of the Cold Spring Harbor laboratories that was established in the DEMEREC years was a tradition of catering to bright and eager young minds.

Research on effects of X-rays and important studies on spreading of gene inactivation along the chromosome in variegated position effects (STURTEVANT 1965) kept DEMEREC occupied in the laboratory in the late 1930s. He also was active in many other areas. The first edition of DEMEREC and KAUFMANN's widely used *Drosophila Guide* appeared in 1940 and this collaboration continued through the sixth edition published in 1957. A selected set of Drosophila stocks useful in teaching was assembled and made available to high school and college biology and genetics teachers. As many as 1876 stocks were sent out per year in the late 1950s. Also, from about 1935 the laboratory maintained specialized Drosophila stocks for research workers, sending out about 300 cultures per year in the late 1940s and early 1950s (DEMEREC 1942–1960) and preserving a valuable resource used today in molecular studies. From 1939 to 1942 DEMEREC provided impetus in an attempt to secure an appointment for H. J. MULLER at the Carnegie, a move blocked by the trustees (PAUL 1988) just 4 years before MULLER was awarded a Nobel Prize.

The year 1941 saw DEMEREC, already Assistant Director at the Carnegie, become Director of the adjacent Biological Laboratory. This year also witnessed the arrival of BARBARA MCCLINTOCK to the Carnegie staff. (She was to serve as President of the Genetics Society of America in 1945. It was about this latter time when she commenced her crucial studies, initially appreciated by few, that won her a Nobel Prize in 1983.) In 1941 and extending to his retirement in 1960, DEMEREC also played a major role in organizing and supervising the Cold Spring Harbor Symposium on Quantitative Biology. For the 1941 (ninth) meeting, DEMEREC squeezed what previously had been 5-week marathons into a streamlined 2-week period so that "biologists, biophysicists and biochemists interested in the gene problem" would remain together and interact (DEMEREC 1941). Wide conjecture not only was allowed but was invited; it included physicist M. DELBRÜCK's thoughts on autocatalytic synthesis and chromosome reproduction. This and later symposia had broad visions and crossed disciplines, stimulating novel interactions and thoughts. The "CSHSQB" volumes of this era are notable for the way in which discussions were captured so that distant students might mull over the outstanding controversies. DELBRÜCK was not only invited to be a symposium speaker but also to spend the summer at Cold Spring Harbor (LURIA 1966). His driving interests, his conviction that bacteriophages were organisms of major importance in genetics (ELLIS and DELBRÜCK 1939) and his contacts with key phage workers were to have a major impact at Cold Spring Harbor.

In the latter part of 1941 DEMEREC became Acting Director and in 1943 Director of the Department of Genetics of the Carnegie, replacing A. F. BLAKESLEE who retired. This move consolidated activities of the two institutions at Cold Spring Harbor, much to the benefit of each. These two laboratories had not shared a common Director since 1923. The consolidation added to DEMEREC's duties because he quietly supervised everything from budgets to mowing the grass to maintaining aging laboratory buildings to arranging purchase of laboratory land along Bungtown Road. In those days the Director could not hire a new staff person to cover each new responsibility; he had to do much of it himself. There were also formal annual reports to be written and compiled, both for the Carnegie (DEMEREC 1942–1960) and for the Biological Laboratory (DEMEREC 1941–1960). Both reports required an introduction and synopsis as well as a résumé of ongoing research. DEMEREC's Carnegie research section includes the names of 62 people in the 19 years he was Carnegie Director; few people are listed more than 2 years in a row. This is an indication of the flow and vitality of the laboratory and the man.

He also engineered similar visits from both younger and more senior scientists through positions at the Biological Laboratory, being indirectly responsible for a high percentage of the research accomplishments of the temporary staff at Cold Spring Harbor (DEMEREC 1941–1960).

DEMEREC managed these jobs, participated in various international scientific activities (MILLER 1978) and ran a tightly supervised laboratory by carefully and systematically partitioning his day. Into the lab early, he completed a lot of scientific concentration before laboratory rounds began around 9 am, by which time everyone else was supposed to be in. As a postdoc I was asked by DEMEREC one morning why I wasn't in at 9 am. I explained that the previous day's experiments hadn't been completed until about 2 am, only to receive the reply, "*That's* no excuse!" While my story was true, I'm sure that DEMEREC had heard it before and was skeptical. And, besides, he was always excited by each new research result and was anxious to have a full and free discussion on the spot, a fine training exercise for younger scientists like me.

DEMEREC and his wife MARY constantly entertained the flow of visitors through the laboratories. But, if parties lasted too late, DEMEREC excused himself and went to bed in order to rise early the next morning. MARY and her sister VERA ZIEGLER always cordially carried on the gatherings with friends who took such a happening expectedly, or at least with good grace. MARY and VERA were teachers at a local grade school. MARY was a teacher of science who gained national recognition for her innovative, hands-on laboratory experiments in physics and in biology. I remember her excitement at obtaining beautifully colored mutant silkworm eggs. These were kindly supplied by Japanese scientists. The eggs had been pasted to white cardboard and formed letters in a striking poster at the Tenth International Congress of Genetics in Montreal. Silkworms love mulberry leaves. Thus, mulberry trees were always included among the fruit trees that were one of DEMEREC's hobbies. DEMEREC was a member of both the Organizing Committee and the Program Committee for that Tenth Congress in 1958. Much of the Congress paperwork was done at home at his card table, often set up in the middle of the living room where he could follow the day's comings and goings and visit with the family. He never seemed to be in a hurry.

The early 1940s witnessed a decided shift in DEMEREC's interests toward microorganisms as tools for genetic study. Partly this stemmed from contributions during World War II when his laboratory made a very important practical discovery: they obtained a derivative of Penicillium that would grow when submerged instead of only on the surface of liquid medium. This allowed greatly increased penicillin production in large vats (MILLER 1978). There were also ongoing collaborations with A. HOLLAENDER, then at the National Institutes of Health, on the induction of mutations in Neurospora with X-rays and ultraviolet light. DEMEREC studied mechanisms and patterns of bacterial mutations to antibiotic resistance. Also, following the classic LURIA and DELBRÜCK (1943) paper in a November issue of GENETICS, he took up studies of mutations to bacteriophage resistance. In 1945 DELBRÜCK was a temporary member of the Biological Laboratory and initiated the phage course, an instant success that was superbly taught for a number of years by MARK H. ADAMS. This course greatly enhanced interest among young people in the new genetic system and helped to move Cold Spring Harbor to the center of microbial genetics by the mid-1950s.

The year 1946 was crucial for the two laboratories. A long-range plan for future activities was prepared at the request of V. BUSH (DEMEREC 1942–1960). This plan paved the way for further consolidation of research focus, interlaboratory collaboration, and construction of new laboratories and a lecture hall beginning in 1951. The laboratory building was later to be named after DEMEREC following his retirement. The auditorium housed the annual Symposium and other meetings in the summers and was a center for seminars and badminton in winters. The old laboratory building was converted to a library which, by the time of DEMEREC's retirement in 1960, was to hold close to 20,000 bound books focusing on genetics (DEMEREC 1942–1960). The library has served as a quiet and useful workshop for staff and numerous summer visitors.

In 1947 the first issue of *Advances in Genetics* appeared with DEMEREC as editor. His editorship continued through volume 9 (1958), after which E. W. CASPARI and J. M. THODAY took over. The first volume of *Annual Review of Genetics* was not published until 1967. Thus, for 20 years *Advances* remained the lone, key American outlet for timely reviews in genetics.

The latter 1940s saw DEMEREC's interests shift from radiations to chemical mutagens. While some of the first work was done with Drosophila (DEMEREC 1948), there was a gradual shift toward emphasis on *Escherichia coli* so that, by 1950, the DEMEREC lab was almost exclusively working with this organism. *E. coli* genetics also was the center of interest in the laboratories of E. M. WITKIN, who received a full staff appointment at the Carnegie in 1949 after several years as a Fellow, and of V. BRYSON and W. SZYBALSKI of the Biological Laboratory. The next year saw the arrival of A. D. HERSHEY at the Carnegie where he initiated the studies on phages that were to lead to a share of the Nobel Prize with M. DELBRÜCK and S. E. LURIA in 1969. In the summer of 1950, the first

informal and highly successful summer course in bacterial genetics was established by DEMEREC, BRYSON and WITKIN. A short conference on bacteriophages was organized by DELBRÜCK. Also in 1950, *The Biology of Drosophila*, edited by DEMEREC, was published in its one and only edition. Supplemented more recently by various treatises, that classic still remains a valuable resource.

By 1951 DEMEREC's journey from maize and delphiniums to Drosophila to prokaryotes was complete; his scientific section of the annual reports (DEMEREC 1942–1960), which had always been entitled "The Gene," was changed in 1951 to "Bacterial Genetics." This is not to say that DEMEREC had suddenly become technique-oriented rather than problem-oriented. In fact, a final transition was to come, engendered once again by the search for the gene. Stimulated by ZINDER and LEDERBERG's (1952) description of transduction in Salmonella, DEMEREC suddenly converted his entire laboratory operation to this close cousin of *E. coli* with almost immediate success (CARLSON 1966). These studies satisfied DEMEREC's long-term goal of highly definitive analyses of gene structure. They critically complemented other work of that mini-era, studies performed with phages and fungi. Furthermore, they revealed the presence in bacteria of linkages among genes with related functions (DEMEREC *et al.* 1956). This finding was one important precursor of modern descriptions of gene function (JACOB and MONOD 1961). DEMEREC's jackpot spilled over so fast that he decided to produce a book (DEMEREC *et al.* 1956) where his work could be viewed collectively. However, a peak year of this work, 1955, saw V. BUSH, a firm backer during the DEMEREC years at Cold Spring Harbor, retire as President of the Carnegie Institution.

The mid-1950s work included contributions by several young Japanese guests, beginning with T. YURA and H. OZEKI, who were to found new schools of microbial genetics in Japan. Both F. J. RYAN at Columbia University and DEMEREC were interested in such a development. However, it is my understanding that RYAN trained bright individuals who had written to him directly and who, with the prominent exception of T. WATANABE, mostly stayed in the United States. In contrast, DEMEREC had firm contacts among more established Japanese geneticists and asked for their best students who were expected to return to their native land. DEMEREC used the same approach through the years with Yugoslavs, including D. KANAZIR, now President of the Serbian Academy of Science and Arts; unfortunately that country has not been able to mobilize and afford substantial molecular biology, although the nucleus and talent is in place.

In 1956 DEMEREC was a member of an important National Academy of Sciences Committee on the Biological Effects of Atomic Radiation. The committee, chaired by W. WEAVER, included such luminaries as G. W. BEADLE, J. F. CROW, H. B. GLASS, H. J. MULLER, A. H. STURTEVANT and S. WRIGHT. This group prepared the first major risk assessment for ionizing radiation, a prototype of more recent assessments for exposure to other agents such as chemical mutagens.

Over the next few years the DEMEREC laboratory continued to describe new bacterial genes and operons as well as to examine genetic homologies between Salmonella and *E. coli*. But at age 65, DEMEREC was facing obligatory retirement as Director in 1960, and there was no smooth transition in sight analogous to the DAVENPORT→BLAKESLEE→DEMEREC eras. Perhaps the absence of a younger leader, combined with financial constraints, led the post-BUSH Carnegie to the 1962 decision to phase out its presence at Cold Spring Harbor, supporting only those on-deck until their impending retirements. In any event, DEMEREC sought to carry on with grant support using space in the Biological Laboratory at Cold Spring Harbor. However, he was turned down at the last moment and moved to the Brookhaven National Laboratories where H. J. CURTIS was Chairman of the Department of Biology. For Cold Spring Harbor it was the end of the *zlatno doba*—the golden age—of DEMEREC.

An active laboratory immediately sprang up at Brookhaven where the Salmonella studies were continued. The second November GENETICS paper, published out of Brookhaven (DEMEREC 1963), summarizes and analyzes a wealth of data on "selfing." Selfing is the unexpected ability of transducing phage grown on particular mutants to convert the respective mutants to the wild type. Because some deletion mutants were found to be selfers, this is a phenomenon that should now be analyzed with the tools of molecular biology. Just as he had earlier helped to establish a Drosophila stock center at Cold Spring Harbor, DEMEREC now set up a similar Salmonella center at Brookhaven and initiated comprehensive reviews of Salmonella genetics (DEMEREC and SANDERSON 1965). Both ventures have been competently carried on to the present by K. E. SANDERSON. DEMEREC also set standards for nomenclature that now are almost universally used by bacterial geneticists (DEMEREC *et al.* 1956, 1966). This nomenclature is easy to understand and eliminates an almost infinite number of subscripts, superscripts, and Greek symbols.

When he reached 70 in 1965, DEMEREC again retired, only to open a new laboratory at C. W. Post College near his home in Laurel Hollow. Again an active laboratory was generated in a short amount of time, before DEMEREC quietly passed away. He died of a sudden heart attack while in his sleep in April 1966 after a full and productive day at work. At Post he had taken in three novice technicians and trained

them, without help, in the ways of science and the intricacies of the bacterial genome. All three went on to Ph.D. degrees and to successful careers in biology. HERSHEY (1966) has said, "When it came to decisions of importance to research, to the laboratory, or to science at large, he seemed to call on an infallible instinct." Perhaps that's because he had an infillable instinct about honest people, upon whom all the rest depends.

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