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NATHAN ORAM KAPLAN

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A Biographical Memoir by
W. D. MCELROY

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Nathan O. Kaplan

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BY W. D. MCELROY

NATHAN ORAM KAPLAN was born in New York City on June 25, 1917. When he was two years old his family moved to Los Angeles where, after attending primary and secondary schools, he entered UCLA to major in chemistry. After graduating from UCLA he went to Berkeley for graduate studies. Until this time, Nate's main interests were in baseball and track. He ran the quarter mile and was a member of the track team at UCLA. However, he was also interested in the history of science writing, for which he received an award from the city of Los Angeles.

At Berkeley, Nate's latent talents in research were uncovered and he virtually exploded into recognition. Working in Professor David M. Greenberg's laboratory, he used radioactive phosphate, produced by Martin D. Kamen (a lifetime friend and colleague) with the cyclotron at the Radiation Laboratory, to study phosphate metabolism in rat liver. As he developed experience with radioactive phosphate, he established a collaboration with M. Doudoroff and W. Z. Hassid, two young bacteriologists who were studying phosphate-dependent sucrose degradation by an enzyme from *Pseudomonas sacchraphilia.* With Nate's help, they established that the enzyme transferred the glucosyl moiety

of sucrose to radioactive phosphate. Since this was the first demonstration of a sugar transfer reaction, Doudoroff and Hassid were recipients of the Sugar Research Award, the monetary part of which they shared with Nate.

World War II interrupted Nate's research career in biochemistry. From 1942 until 1945 he worked as a research chemist on the Manhattan Project. In 1945, when Nate attended an American Chemical Society meeting in New York, one of his relatives arranged a blind date for him and the couple met on the steps of the 42nd Street library. This was the first meeting of Nate and Goldie. Soon afterward Nate joined Fritz Lipmann's laboratory at the Massachusetts General Hospital. Every other weekend Nate would travel from Boston to New York to see Goldie and over the Thanksgiving weekend of 1947, Goldie agreed to marry him. This worried Lipmann, who thought that Goldie might be a "wild New Yorker."

Nate's research career flourished under the influence of Lipmann. During his time at Mass General he isolated coenzyme A, was instrumental in determining its structure, and helped establish the universality of coenzyme A in "two-carbon" metabolism. For this and earlier work that led to the discovery of coenzyme A, Lipmann shared the Nobel Prize in Physiology and Medicine in 1953. For his contributions to the work on coenzyme A, Nate shared the Nutrition Award in 1948 and received the Eli Lily Award in Biochemistry in 1953.

Nate left Lipmann's laboratory in 1950 to become assistant professor of biochemistry at the University of Illinois Medical School in Chicago, primarily because Sidney Colowick, who had just left the Cori laboratory at Washington University in St. Louis, was there. Problems developed for Colowick and Kaplan at Illinois and they were both hired

(by W. D. McElroy) as assistant professors at the McCollum-Pratt Institute of the Department of Biology of Johns Hopkins University. At Hopkins, Nate and Sidney developed a successful and productive collaboration studying the chemistry of the pyridine nucleotide coenzymes and the enzymes that are involved with them. This collaboration led to the founding in 1955 of the classic series, Colowick and Kaplan's *Methods in Enzymology*, which now has more than 140 volumes with more in press.

In 1957 Nate left Johns Hopkins University to become founding chairman of the Graduate Department of Biochemistry at Brandeis University. To establish the new department he, in association with Martin Kamen who joined him at Brandeis, hired about a dozen carefully selected young assistant professors and brought them to a campus where very little space was available for them for at least a year. Under these conditions and with Nate as catalyst, an uncommon camaraderie developed between faculty, postdoctoral fellows, graduate students, and staff that led to scientific productivity of such caliber that his fledgling department gained international recognition in a very short time. By recognition for his department, Nate Kaplan played a major role in establishing Brandeis, which had only been founded in 1948, as a major, research oriented university in the sciences in the 1960s. His research at Brandeis was primarily concerned with the structure-function relationships of dehydrogenases, which led him into the areas of enzyme evolution and isoenzymes. He was one of the first to recognize the potential of using isoenzyme analysis in clinical diagnosis and for this reason developed methods for detecting lactate dehydrogenase isoenzymes in human serum.

In 1968, pulled by the urgings of Martin Kamen who

had already come to USD, and pushed by circumstances of campus politics at Brandeis, Nate joined the Chemistry Department. His appointment and laboratories were in the School of Medicine. He was drawn to the medical school environment by his earlier association with Fritz Lipmann at Massachusetts General Hospital and his collaboration with Abraham Goldin of the National Institutes of Health in cancer chemotherapy, which dated back to his years at Johns Hopkins in the 1950s. In the 1970s, he and Gordon Sato established a successful colony of athymic mice. The mice were used to examine anti-cancer agents making this facility an important component of the UCSD Cancer Center. Nate's laboratory also made important contributions in more traditional areas of biochemical research at UCSD. Using NMR, his students and postdoctoral fellows established the conformations of the pyridine nucleotide coenzymes and other nucleotides in aqueous solution. Other important contributions were on the development of matrices for affinity chromatography of enzymes, immobilization of enzymes, and immobilization of ligands for membrane receptors.

What transcends his scientific accomplishments was the warm and inspiring influence that Nate Kaplan had on those who worked with him. Young investigators from the world over were drawn to his laboratory, where they were accommodated with excellent research problems, excellent facilities, and the qualities of the man himself. These qualities were a combination of warmth, understanding, keen insight, and a contagious enthusiasm for biochemistry which permeated all of his professional activities. Throughout the years from 1945 on, Goldie was supportive, not only as a loving wife, but also as a companion who accompanied Nate to meetings the world over. She proofread and gave

finishing touches to the numerous manuscripts that crossed his desk. Nate shared with Goldie the many problems of a varied career and she responded with good advice for calm and reason in seasons of turbulence. Nate's interests in biochemistry were very broad and included biochemical anthropology, the topic of a popular course that he taught. In the late 1960s and 1970s, partly out of his enthusiasm to learn more about particular aspects of biochemical anthropology, many of his family vacation journeys with Goldie and their son Jerrie ended up in remote places where he could observe, firsthand, social practices that had evolved in response to biochemical defects in the food supply or in the human population itself.

During his career, Nate Kaplan had enormous impact on the field of biochemistry and profound influence on his many associates in this country and abroad. He is deeply missed.

Martin Kamen has written a brief account of Nate's stay at Berkeley. "At the Radiation Laboratory, led by the charismatic Ernest Laurence, the Cyclotron was pouring out an unprecedented flood of radioactive isotopes for use in biological research. Some of his prospective customers were concentrated in the western end of the campus—the Life Sciences Building. Among them were soil scientists (H. A. Barker and W. Z. Hassid), bacteriologists (notably M. Doudoroff), and other groups in biochemistry (under the aegis of David Greenberg) and physiology (led by I. Chaikoff)." This was where Martin first met Nate. In the meantime, Nate had moved from the Chemistry Department to Biochemistry, where he was working with Greenberg on phosphorous metabolism for his Ph.D. dissertation. Here he met Doudoroff, Hassid, and Barker. Barker has recalled these events. "Doudoroff had been studying the utiliza-

tion of various sugars by *Pseudomonas saccharaphila* so called because it oxidizes sucrose much more rapidly than the constituent monosaccharides, glucose and fructose. Suspensions of dried cells of the organism were found to decompose sucrose more rapidly in the presence than in the absence of inorganic phosphate." Doudoroff, Kaplan, and Hassid worked together to demonstrate that glucose-1-phosphate and fructose were the products of sucrose breakdown. These results were published in 1943 in the *Journal of Biological Chemistry*; the article was Nate's first scientific publication.

After Nate received his Ph.D., he went to work with Fritz Lipmann at the Massachusetts General Hospital. Mary Ellen Jones has recounted these events. "At the time Lipmann's laboratory was small, only three people, Lipmann, Kaplan and a technician/secretary, L. Constance Tuttle. Lipmann had recently shown that the acetylation of sulfanilamide by pigeon liver extracts required a heat-stable factor which was autolyzed when the extract stood for several hours at room temperature. Kaplan began to purify the factor, now known as coenzyme A, using the restoration of enzyme activity to aged extracts as a measure of the amount of cofactor present." Nate, working with G. David Novelli and Beverly Guirard, soon found that the cofactor contained pantothenic acid, and later Shuster and Kaplan found that a phosphate group was attached to the 3′-hydroxyl of the ribose ring of adenylic acid. In the meantime Kaplan and Lipmann found that most of the pantothenate in tissues was present in coenzyme A. The time Nate spent with Lipmann was a great learning experience and influenced Nate's outlook on scientific research for the rest of his life.

Nate Kaplan and I had been friends and colleagues since 1950. The nature of our meeting was very unusual. In

1947, Mr. John Lee Pratt had donated a sum of money to start a center for the study of trace metals in biological systems at the Johns Hopkins University. I was an assistant professor in biology at the time, but for some reason, Dr. E. V. McCollum convinced President I. Bowman that I should be given the charge to describe what this new center should do scientifically. At the time very little dynamic biochemistry was being taught, either in the graduate or medical schools in the United States. In other words, there was a large gap between European–English biochemistry and that of the United States. Only in 1941 when Lipmann and Kalckar published their famous reviews was ATP introduced widely in the U.S. biochemical literature. Phosphorus was a macronutrient! I was convinced that a new approach looking at the dynamic functions of metals in enzyme systems was the way to go, so I wrote up a four- or five-page outline of the program and gave it to Dr. McCollum. Six outstanding nutritional scientists from England, Australia, New Zealand, and the United States, and two enzymologists were invited to Hopkins to discuss this proposal. Interestingly enough, they agreed with the plan and, subsequently, I was asked to propose names for the directorship. I submitted the names of a number of outstanding enzymologists, including Dr. Sidney Colowick. Unfortunately, most were not interested in the function of trace elements in enzyme function and metabolic processes in general and, unfortunately, right after the war there were not many enzymologists looking for jobs, so we had no takers. After a year things appeared to be desperate, and Dr. McCollum, without consulting me, convinced President Bowman that I should be named director of the center, which we subsequently named the McCollum–Pratt Institute. Within a few weeks after I assumed the directorship, I had a call

from Dr. Stanley Carson at the Oak Ridge National Laboratories indicating that Dr. Colowick might be available. I immediately called Sid and made him an offer. The next day he returned my call and said he was interested if he could bring a young associate named N. O. Kaplan. I invited both of them to visit Hopkins, and they arrived within two days. That was the first time I met Nate Kaplan. Within two weeks I had all the paperwork finished and approved by the Academic Senate, the dean, and the president. To this day it is the fastest appointment that I have ever made, and they readily accepted. It is interesting that there are no letters on file concerning the qualifications of Nate, only a phone call from Fritz Lipmann and Mike Doudoroff. What a wonderful way to make an appointment; they were two of the best I ever made.

The original members of the McCollum–Pratt, in addition to myself, were Kaplan, Colowick, the late Alvin Nason, Henry Little, and Robert Ballentine. We were housed in a greenhouse on the Homewood campus. There were two large laboratories on the first floor. Nate and Sid shared one, and the other three shared the second. My labs were in the Biology Department about two minutes from the greenhouse. It was not the best of arrangements as we know them today, but it turned out to be a very scientifically productive environment. Housed in the basement was Dr. Elmer V. McCollum, who had just retired as chairman of the Department of Biochemistry in the School of Hygiene at Johns Hopkins. He and Nate became very close friends. With Nate's interest in history, he spent hours in the basement learning all he could about the history of nutrition and biochemistry from Dr. McCollum. It is interesting that the year that Warburg discovered the requirement of Mg^{2+} for the triose phosphate dehydrogenase was

the same year that McCollum demonstrated it as an essential micronutrient in animals. In this environment, Nate was "all ears," and it had a great influence on his teaching of biochemistry in later years.

I never asked Nate or Sid to be concerned with trace metal biochemistry, but I was reasonably sure how it would work out, because when bright people work side by side, things happen. The plan was to bring young postdoctoral students from laboratories where nutritional trace element work was being performed. Dr. Alvin Nason and I agreed to work with them on enzymological problems. At the time, I had a number of nitrate mutants in *Neurospora* that could reduce nitrate to nitrite, but the latter would not be further metabolized. There were reasons to suspect that molybdenum might be involved in the nitrate reductase reaction, so we invited Dr. D. J. D. Nicholas from Long Ashton, England, to join us in this research; he was an expert on removing trace metals from proteins and growth medium. After about six months, we had drawn a blank. Then one day, while talking with Nate, he suggested trying FAD instead of FMN as an electron donor. Fortunately, Nate had some FAD in the deep freeze, and the first time we tried it, we found that TPNH (NADPH) would reduce the nitrate to nitrite. This, of course, led to the eventual discovery that reduced FAD was the immediate electron donor for the reduction of molybdenum and subsequently the reduction of nitrate. So Nate was into trace metal metabolism! Demonstrating that the proximity of two types of investigators often leads to an exchange of ideas, techniques, and materials that is of great mutual benefit.

This was one of Nate's great assets. He was willing to help anyone in need—graduate students, postdocs, faculty and visiting scientists, and an undergraduate looking for a

problem. It is interesting that Dr. David Greenberg recalls that when Nate worked with him on war research Nate "had no interest in mineral metabolism. He used ^{32}P to study various aspects of carbohydrate metabolism."

Molybedenum was not the only trace element problem that Nate worked on. At the time, Al Nason was working on tryptophan metabolism in the zinc-deferent *Neurospora.* Without going into detail, this led to the discovery of an interesting and potent DPNase, which increased dramatically in zinc-deficient mycelia. It turned out to be very stable and easy to purify, in contrast to the mammalalian DPNases.

Following the discovery of *Neurospora* DPNase, Nate and Sid continued their work together on various aspects of this and other enzymes concerned with DPN, particularly the exchange reactions involving ADP ribosyl enzyme and various nicotinamide derivatives. The best known of these was the acetylpyridine analog, which was very active as a coenzyme in many dehydrogenases. The ratio of the activity with DPN and the acetylpyridine analog was a very sensitive measure of the differences of various dehydrogenases in different species and in different organs. I believe this work was the basis for Nate becoming interested in evolution. He studied the isozymes of various dehydrogenases and noted their changes during development. Probably his best-known work in the area was concerned with the M and H isozymes of lactic dehydrogenase, this latter work leading to his interest in cancer metabolism. It was from this interesting work that Nate really became a biologist. Working on lactic dehydrogenases from various crabs, he found that the horseshoe crab (*Limmulus*) did not fit the general properties of other crabs. Fortunately his asso-

ciate, Margaret Ciotti, pointed out that *Limmulus* belonged to the spider group.

When Nate moved to Brandeis, he was very excited by the challenges of setting up a new department. He once wrote, "Johns Hopkins had been very good to me in allowing me to develop my potential." As W. P. Jencks recalls, "In 1957 Nate O. Kaplan and Martin Kamen founded the Graduate Department of Biochemistry at Brandeis. Louis Rosenstiel, who had been the head of the Schenley Corporation for many years, was interested at this time in supporting a research institute dedicated to research on a form of cancer. President Sachar, the founder of Brandeis, explained to him that the best way to learn about cancer was to study the broader problem, in particular to do basic research. It quickly became clear that the best way to do basic research was in an institute of biochemists, and the best institute of biochemists could be established in a small, new university. Such a group would function best with graduate students. Thus, it was inevitable that the Graduate Department of Biochemistry should be established. Mr. Rosenstiel was one of the most perspicacious donors anywhere, a rare individual who preferred to "buy brains, not bricks." He gave $1,000,000 to start the department and supplemented this later with additional support to the department and university. Kaplan and Kamen were able to turn this investment into a 2,300 percent profit from various sources, to provide a strong base of support for the department.

At that time, Brandeis University was less than ten years old. The administration was housed entirely in a small white house, the library was in the former stable of the Middlesex Veterinary School and the whole School of Science was in one large glass box, the Kalman Building. The

entire Biochemistry Department moved into two teaching laboratories in this building and started to do research. Nate and Martin immediately brought in a flock of productive graduate students, postdoctorals and physicians from all over the world to work with the younger as well as the older members of the department. These members consisted at this point of Mary Ellen Jones, Lawrence Levine, Larry Grossman, Morris Soodak, and William Jencks. In addition to the founders, Gordon Sato, Helen Van Vunakis, Thomas Hollocher, John Lowenstein, Robert Abeles, Gerry Fasman, Robert Schlief, Al Redfield, and a number of others joined the department later.

After a year and a half, the department moved into its own Friedland Building, where it rattled around actively, expecting to have space for its activities into perpetuity. But in a few years Friedland was full and bulging with activity. This happened in spite of the decision of the department to remain small and maintain the communication, collaboration, and cohesion that had contributed so much to its success. So the Kosow–Wolfson–Rosensweig building was built, with the expectation that it should provide enough space forever. But it also filled rapidly and some members of the department were housed later in the Rosenstiel Basic Medical Sciences Research Center building. Louis Rosenstiel had given another large gift to the university to establish this center, which contains faculty members from several of the science departments at Brandeis in addition to biochemistry.

Initially the department made idealistic plans for idealistic students who would know how to plan and build their careers in science. Basic research was encouraged in all ways and directions. Nate brought with him the laboratory rotation program from McCollum–Pratt and all first-year

students spent six-week rotations carrying out six different research projects in six different laboratories during their first year. Several courses were offered, but there were few requirements and examinations. It took several years for the inherent weaknesses of human beings to reveal themselves; then some examinations and requirements were reluctantly established. Still, the tradition of research-oriented department has been maintained successfully to the present.

In accomplishing all of this Nate Kaplan played a major role in establishing Brandeis as a high-level research-oriented university in the sciences. By action and example, he contributed in a major way to the buildup of the science faculty and facilities for all disciplines, so that the university is now recognized as one of the few leading universities that is both highly successful but small enough so that communication is easy and the bureaucracy is (relatively) small.

Nate's ability to lead, plan, negotiate, and raise money from many willing and generous sources made of all this possible. Most departmental business was conducted in the hall. It is hard to resist change or start theoretical-political arguments while standing in a hall, so that this worked very well. He demonstrated an uncanny ability to go in the right direction and to find out how to get there. Numerous crises arose as new research programs grew in a new university, but he found ways to deal with these successfully and build up an infrastructure that made productive research and teaching possible.

How did Nate make all this work so well? It would be hard to predict that it would. It rested on his ability to sense what needed to be done and how to do it, without ever seeming to plan or calculate. He built the support of

the entire department and in turn demonstrated unwavering support and loyalty to his students, postdoctorals, and faculty.

All of this time he somehow also led a large and diverse research group that studied the biochemistry of DPN (not NAD) and many other subjects. This included highly productive students at all levels, from high school to professors of medicine. The many scientific contributions of this group are well known and are too extensive to review here.

When he went to the University of California at San Diego (really La Jolla), he left a successful department that had passed through its adolescence and was able to continue successfully on its own. However, no one has ever replaced the leadership and support that he provided so well.

Morris Friedkin and William Allison recall Nate's return to the West Coast. "After having developed a world class Department of Biochemistry at Brandeis, Nate was drawn back to the West Coast, to the University of California, where he had begun his career. It wasn't easy to leave Brandeis where, together with Martin Kamen, he had been instrumental in helping a young school get its feet on the ground. In leaving Brandeis he would be giving up the day-by-day personal interactions of a small institution for the milieu of a large university."

In the mid-1960s, Nate vacillated between going to the San Francisco Medical Center or to La Jolla where a new campus and medical school were being developed. In 1968, he opted to join Martin Kamen in the Department of Chemistry at UCSD, where an innovative relationship between the basic departments of chemistry and biology and the medical school was envisaged. At UCSD, there would be no Department of Biochemistry. Colleagues with the same

scientific interest would be scattered through many buildings.

It wasn't surprising that when Nate wrestled with the complexities of the academic structure of UCSD, nostalgia of the good old days at Brandeis would well up. This explained Nate's great joy when he returned to Brandeis in 1982 to receive an honorary degree. At UCSD, Nate continued his studies on various lactate dehydrogenases. He sought for greater insight into the structure and properties of the pyridine nucleotides (Nate was never comfortable calling DPN by its newfangled name: NAD). With students and colleagues he utilized NMR with great ingenuity. These are but a few examples of the many directions Nate's fertile and lively imagination carried him.

Nate was attracted to a medical school environment because of his interest in chemotherapy dating back to the 1950s. Because of his findings with nicotinamide derivatives, he thought an analogue of NAD might interfere with the cellular metabolism of cancer cells. Although such compounds were found that were effective against experimental mouse tumors, they proved to be too toxic. However, Nate's objective to develop practical chemotherapeutic agents did not wane. Together with Gordon Sato, Nate established a very successful athymic mouse colony. A small building was designed not only to house the athymic mouse colony, but also to provide facilities for tissue culture work with many human cancer cell lines.

Nate departed from the basic arena of enzyme mechanisms to enter a new field in which a variety of techniques associated with the disciplines of immunology, virology, electron microscopy, and cellular biology were utilized. Nevertheless, he had an abiding love for biochemistry, believing strongly that biochemistry had become the language of bi-

ology. He wrote, "students should not lose sight of the eloquence of the experiments of Warburg because it is the same eloquence which is inherent in the isolation, characterization, and manipulation of genes."

Nate's broad experience was appreciated worldwide. Because of his unusual acumen and intuition, his advice was sought after by scientists at universities and industries worldwide.

Even when he knew his days were numbered, he threw himself into long-term projects. To the very last, he was fascinated with the dynamics of change, be it an enzymatic event, an evolutinary process, or the migration of people.

Nate had an enduring interest in the history of science, in biochemical anthropology, and in the communication of ideas. He has left a heritage of scholarship and of research into the chemical nature of life documented in hundreds of articles.

Upon reading Nate's contributions to science and reflecting on his outlook of those factors that influence the training and development of any scientist, it is apparent that he had high praise for the research teachers responsible for his education. In the early years, it was Fritz Lipmann who had a major impact on Nate's scientific perception. Nate learned how to keep an eye out for the unexpected and not hesitate to change the goals of a research problem to accommodate a new situation. In this way, Nate always has a number of incomplete problems which he gave to postdoctoral or graduate students. It was natural for him to do this—a main reason he was so well liked by students at all levels.

As a graduate student at Berkeley, Nate had the opportunity to learn about radioactive phosphate from Professor D. M. Greenberg. He studied the turnover of ATP and the influence of insulin and other factors on the acid soluble

phosphate in liver. He submitted these results for his Ph.D. dissertation in 1943.

Nate also had the fortunate opportunity to attend a microbial metabolism course given by H. A. Barker. From Nate's description, it must have been very much like Van Niel's course offered at the Hopkins Marine Station. While enrolled in this course, Lipmann's article on phosphate bond energy appeared in Volume 1 of *Advances in Enzymology* (1941). This article, along with Barker's course, had a tremendous influence on Nate and is probably the reason he decided to continue his career in biochemistry. He gave credit to Barker for getting him into Lipmann's laboratory after the war. While at Berkeley, Nate also became friends with W. Z. Hassid, Sam Ruben, Martin Kamen, and Michael Doudoroff. It was these interactions that led Nate to work on sucrose metabolism in *Pseudomonas sacchraphila.*

When Nate was associated with the Manhattan Project, he was sent to Detroit for several months to carry out a special assignment. He met Dr. Maurice Franks, who was an instructor in medicine at Wayne State Medical School. Dr. Franks was an internist with a special interest in diabetes, and he and Nate induced diabetes in rats by the use of alloxan. They were able to show that the diabetic state that developed was accompanied by a marked drop of ATP in the liver and an increase in inorganic phosphate. It was striking that a very large amount of phosphate was excreted. This suggested that it might be worthwhile to investigate phosphate levels in diabetic coma. Fortunately, Dr. Franks had access to human patients through the clinic at the emergency room in Detroit City Hospital. They learned that severely comatose patients exhibited a lower serum inorganic phosphate that coincided with an increase in urinary phosphate. They administered large doses of inor-

ganic phosphate to these patients and, in the presence of insulin, the phosphate levels approached normal and excretion decreased. They concluded that inorganic phosphate was helpful in the treatment of coma. Phosphate treatment has since proven to be of some value in comatose patients.

Nate left Dr. Lipmann's laboratory to join the Department of Biochemistry at the University of Illinois Medical School in Chicago, where he became a colleague and very close friend of Sydney Colowick. His stay at Illinois was a brief one and not very productive. Both he and Sid left Illinois to come to the McCollum–Pratt Institute at Johns Hopkins University. Nate started a project at Hopkins involving the study of the mechanism of Coenzyme A action in pyruvate oxidation. There was conclusive evidence from work in Lipmann's laboratory that CoA was involved in the oxidation of keto acids, not only in microorganisms, but also in plant and animal tissues. During the course of these studies, Nate used cyanide to inhibit respiration. An excess of NAD was added in order to measure the reducing equivalents generated from pyruvate dehydrogenases under these conditions.

During the initial experiments, Nate observed NADH could be formed when pyruvate was oxidized but the same results were obtained when the enzyme preparation was omitted. In collaboration with Sydney Colowick it was determined that cyanide was adding to NAD to yield an adduct which has UV adsorption in the same region as NADH. They characterized the NAD cyanide compound and found it to be a good method for measuring oxidized pyridine nucleotides. NADP also could be determined by the cyanide reaction. They later learned from the literature that Meyerhof and his associates had also observed such a reaction.

The cyanide adduct was a good qualitative measurement of the quaternary pyridine ring. They used this method for determining the oxidized forms of the coenzyme in extracts of various organisms and tissues. During this time, Alan Nason was working on zinc deficient *Neurospora.* The deficient *Neurospora* showed very little glycolytic activity, and alcohol dehydrogenase was not present in the cells. Reduction of NAD could not be demonstrated even upon addition of known dehydrogenases to the extracts. Discussing the problem with Nason, Nate believed there was a possibility that NAD may be hydrolized and was unavailable for reactions in the deficient *Neurospora.* They used the cyanide method to measure NAD levels in the zinc-deficient *Neurospora* and found the amount was negligible when compared to controls. Adding exogenous NAD, they observed a rapid destruction of the coenzyme. They continued their work and detected an enzyme which could split NAD at the nicotinamide ribosidic linkage. Nate and Sid called it NAD adenase. This enzyme was later named NAD glycohydrolase. The enzyme was a very potent one and present in relatively large amounts in zinc-deficient *Neurospora.* The coincidence of Nason being present in the institute and working on deficient organisms, particularly of zinc, was an important beginning in Nate's lifetime interest in the pyridine nucleotides.

During these studies it was observed that NAD hydrolysis by the enzyme was not complete as measured by the cyanide reaction; however, when assayed enzymatically using alcohol dehydrogenase all the reactive coenzyme was destroyed. This indicated a possibility that a molecule was present in the preparations that had the nicotinamide ribose linkage but was not subject to attack by NADase. Large amounts of NAD were hydrolyzed with the *Neurospora* NADase

until all the biological activity had disappeared. They attempted the isolation and the purification of the compound, which was resistant to the action of the NADase but still maintained a reaction with cyanide. They were successful in isolating a compound that proved to be the alpha isomer of NAD. This material exhibited very low or no activity with most dehydrogenases. It was noted that most commercial preparations of NAD, at that time, contained approximately 15 percent of alpha NAD. They were also able to cleave NADP and obtain pure adenosinediphosphate ribose using the *Neurospora* NADase. When Nate and Sid studied NADase isolated from mammalian sources they found some extremely interesting differences. The animal enzyme was inhibited by nicotinamides whereas the *Neurospora* enzyme was quite insensitive to the free vitamin. Later Leonard Zatman observed that radioactive nicotinamide could be incorporated into NAD and demonstrated that an exchange reaction was occurring. This led Nate and Sid to study other pyridine compounds and conclude that many similar pyridines could undergo exchange reactions to form new derivatives of NAD. One of the more interesting reactions was the exchange of the isonicotinic acid hydrazide to form an isonicotinic acid hydrazide analog. Using the exchange reaction, Nate was able to prepare the acetyl pyridine derivative of NAD, which turned out to be extremely important as it was the compound used later by Nate to compare the biochemistry of various dehydrogenases. The reduced form of the acetyl pyridine NAD had an absorption maximum at 375 nm as compared to 340 nm for NADH. Thus, they could independently study various dehydrogenases. This, of course, eventually led to the important research on isozymes.

It was during this same time period that Nate and Sid

decided to begin studies on oxidative phosphorylations in the microbe *Pseudomonas aeruginosa,* a well-known bacteria with a very high oxidative capacity. Kornberg had previously shown that extracts of these organisms contained an NADP-isocitric dehydrogenase as well as a second dehydrogenase that used NAD as the electron acceptor. Sid and Nate made the interesting discovery that a transfer of hydrogen from the NADPH to NAD was occurring when both pyridine nucleotides were present in the reaction mixture. It was this discovery that led to many efforts to characterize the transhydrogenase that was obviously present in the system. They were able to demonstrate that this was a direct hydride transfer. Here again the various analogs of NAD were used extensively, particularly the thionicotinamide analog. This compound had an absorption maximum around 400 nm, was actually quite yellowish, and could be observed without the spectrophotometer. The work on NAD and NADP and the analogs, which they were able to make by the exchange reaction, formed the basis for an intense collaboration between Nate and Colowick concerning the function of these coenzymes in various dehydrogenases.

When Nate moved to Brandeis he began extensive work on isozymes. He was able to show that the heart and muscle lactate dehydrogenase of a given species were quite different using NAD analogs. Nate found that the heart enzyme of one species was much more closely related to the heart enzyme of another species as compared to the muscle enzyme of the same species. This led, in collaboration with a number of workers, to the study of changes in lactate dehydrogenase during development in chickens. He began to investigate the type of LDH that occurred in the embryonic chick breast muscles and was surprised to find that the enzyme isolated from muscle was actually the heart

type LDH, as determined by immunological methods. He observed that during development the genes for the M types were being expressed at an increased rate and it became the principal LDH type at the time of hatching. Immediately after hatching, there was a great increase in the LDH, so that the breast muscle of the chicken is largely M4 enzyme with traces of H4 present. In contrast, the embryonic chick heart contained pure H4 enzyme. A connection was made to an observation that Markert had reported with regard to the fact that LDH was actually a tetramer. Their results supported the view that there were five forms of LDH consisting of the two parent types, occurring as H4 and M4, with three intermediate hybrid types, which migrated predictably inbetween H and M forms on polyacrylamide gels.

At this time, a young postdoc by the name of Alan Wilson joined Nate's laboratory. He was interested in molecular evolution and saw the potential of studying the LDH system. From these studies many interesting taxonomic and enzymatic relationships were observed. For example, the flatfish, halibut, flounder, and sole have only the anaerobic type of LDH(M4) in their tissues as adults. Since they bury themselves in the sand and live in an anaerobic environment, one can see why the M enzymer is present in the heart of these fish. When the flatfish larvae hatch they are free-living forms. They have one eye on each side, but at the time when one of the eyes move from one side to the other there is also a change in the lactic acid dehydrogenase. The young fish have the H type present in heart and other tissues and at the time of the eye movement there is a change to the M form. When Nate and Alan examined a number of invertebrates, they found that the arthropods, particularly the lobsters and crabs, had a very unusual LDH.

The rate of enzymatic lactate oxidatin with NAD was very slow, but this group of arthropods had high activity with the acetal pyridine analog of NAD. It was at this same time that studies on the LDH's in horseshoe crab (*Limmulus*) were started. They thought this organism was a crab and, upon examination, found to their dismay that this LDH reacted very well with the natural coenzyme in contrast to other crabs. Margaret Ciotti was working with him and had some knowledge of elementary zoology. She indicated to Nate that *Limmulus* was not a crab but belonged to the spider family. An examination of spiders, scorpions, and tarantulas revealed that all had enzymes similar to horseshoe crab. It soon became apparent to Nate that the horseshoe crab was related to the spider species and not to the lobster-crab group. It was very surprising to Nate that he would be able to classify an organism using enzymological techniques which agreed with the taxonomic classification. Another interesting aspect of this work was that the *Limmulus* enzyme would not work with pure L-lactate. The enzyme was actually isolated and purified using a DL mixture to assay the activity. It was found that pure L-lactate was not a good substrate but that D-lactate was very effective. It turned out that the LDH for *Limmulus* was D-LDH. This was surprising, because almost all animal LDH's are of the L-configuration and are tetrameric.

An interesting sidelight to these studies occurred when they were working with LDH's from haddock and cod. Nate received a telephone call from the Bureau of Fisheries in Boston inquiring if they could distinguish between haddock and cod using their techniques. There was a suspicion that the filets being sold in the market were not haddock but mostly cod. Since haddock sold at four times the cost of cod, the Bureau of Fisheries was pressured to find

out what was going on. As it turned out, when the two biochemists investigated the frozen filets, most of them contained almost exclusively cod muscle LDH. This led the Food and Drug Administration to obtain an injunction and confiscate all the frozen filets. Today all the filets of haddock are tested for the presence of cod. It is interesting that these observations were put into the *Congressional Record* as an indication and illustration of how molecular biology could be of value to the average consumer.

Following these extensive studies on lactic dehydrogenase, Nate turned his attention to many other enzymes including creatinekinase, malate dehydrogenase, transaminases, and glyceryl phosphate dehydrogenase. He continually looked for enzymatic problems that would help in understanding the molecular evolution of isozymes. These problems necessitated new techniques in protein structure, and many physical approaches were explored such as fluorescence, circular dichroism, and nuclear magnetic resonance.

At UCSD Nate's interest continued on the characterization of various enzymes and was particularly concerned with their evolution. Exposure to Professor Ephraim Katzir at the Weizmann Institute in Israel and Dr. Klaus Mosbach stimulated great interest in immobilized enzymes, particularly how these could be used to study the action of chemotherapeutic agents.

In studying the function of immobilized hormones and chemotherapeutic agents, they turned their attention to the use of tissue cultures. Nate renewed his collaboration with Dr. Gordon Sato, who had just moved to La Jolla from Brandeis. Sato had obtained several athymic mice and was planning studies on these animals. Since these mice lacked a thymus, human tumors were not rejected and tumor xenografts could be grown in the animals. This impressed Nate as a potential for studying chemotherapy in animals

as well as investigating the metabolism of the human tumor. These experiments led to some interesting results but not much of any practical interest. He soon came to the conclusion that although the athymic mouse colony was important in a number of studies, they didn't seem to lend themselves to the treatment of human cancer.

Nate was still working in the broad area of immobilized enzymes, athymic mice, and chemotherapeutic agents at the time of his death.

THE QUOTATIONS BY William Allison, Morris Friedkin, Martin Kamen, H. A. Barker, David Greenberg, Mary Ellen Jones, and W. P. Jencks were taken from a memorial publication dedicated to Nate, and appeared in *Analytical Biochemistry* 161:229–44, 1987.

HONORS AND DISTINCTIONS

PROFESSIONAL (ACADEMIC) POSITIONS

1940–42	Assistant Biochemist, University of California, Berkeley
1942–45	Research Chemist, Manhattan Project
1945–50	Associate Research Biochemist, Massachusetts General Hospital, Harvard Medical School
1950–52	Assistant Professor of Biology, McCollum–Pratt Institute, The Johns Hopkins University
1952–56	Associate Professor, The Johns Hopkins University
1956–57	Professor, The Johns Hopkins University
1957–68	Professor of Biochemistry and Chair, Department of Biochemistry, Brandeis University, Waltham, Massachusetts
1968–86	Professor of Chemistry, University of California, San Diego

HONORS AND AWARDS

1946	Sugar Research Award
1948	Nutrition Research Award
1952	National Science Foundation Travel Fellowship
1953	Eli Lilly Award in *Biochemistry*

1960	Commonwealth Travel Fellow
1964–65	John Simon Guggenheim Fellowship
1970	National Academy of Science
1971	Honorary Fellow Harvey Society
1971	American Academy of Arts and Sciences
1975	John Simon Guggenheim Fellowship
1976	American Association for Clinical Chemistry Award
1982	D.Sc (Hon.), Brandeis University
1983	Fogarty Scholar 1984 in Residence

SOCIETIES

American Association of University Professors
American Chemical Society
American Society of Biological Chemists
American Society of Cell Biology
American Society of Microbiology
American Society for Cancer Research
American Cancer Society
American Institute of Nutrition
Biophysical Society

Biochemical Society
Sigma Xi

EDITORIAL ACTIVITIES

Editor in Chief, *Methods in Enzymology*, 132 volumes
Editorial Advisory Board:
- Molecular Pharmacology
- Biochemical Genetics
- Biochemical Medicine
- Chemico–Biol Interactions
- Bio–Organic Chemistry
- Journal of Insoluble Matrices
- Journal of Solid–Phase Biochemistry
- Analytical Biochemistry
- Journal of Applied Biochemistry

OTHER PROFESSIONAL ACTIVITIES

Member, National Academy of Science Committee for the Overview of the National Institutes of Health
Chairman, the University of Chicago Biomedical Sciences Advisory Committee
Special Senior Consultant to the National Cancer Institute
Member, the American Cancer Society Council Executive Committee
Member, the Oak Ridge National Laboratory Advisory Committee
Member, the Advisory Committee of the Rockefeller Foundation
Member, Review Committee, University of California, Berkeley
Member, Review Committee, Wichita State University
Chairman, National Research Council Advisory Committee to American Biochemical Journals
Member, United Nations Energy Council
Scientific Advisory Committee on Biochemistry and Chemical Carcinogenesis
Member, Publications Committee, American Society of Biological Chemists
Honorary Member, Consejo Superior de Investigaciones Cientificas (Spain)
Member, Scientific Affairs Committee, W. Alton Jones Cell Science Center
Member, Advisory Committee, Rockefeller Foundation
Member, Advisory Committee, Massachusetts Institute of Technology
Member, Advisory Committee, University of Pennsylvania
Member of Council, U.S. National Committee for the International Union of Biochemistry
Honorary Editor, *Journal of Applied Biochemistry*
Honorary Editor, *Bioorganic Chemistry*
Co–Chairman, Editorial Committee, *Analytical Biochemistry*
Member, Investigational Review Committee of Scripps Memorial Hospital
Adjunct Professor and Consultant to Mt. Sinai School of Medicine
Member, Advisory Committee, the Massachusetts General Hospital

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1950

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