Samuel Natelson: Genius, Heretic, Savior

By Amadeo J. Pesce, PhD

Ay, soon upon the stage of life,
Sweet, happy children, you will rise,
To mingle in its care and strife,
Or early find the peaceful skies.
Then be it yours, while you pursue
The golden moments, quick to haste
Some noble work of love to do,
Nor suffer one bright hour to waste.

"School is out" by Daniel Clement Colesworthy. (1810-1893)

Preface

Sam Natelson was larger than life. It is difficult to describe in simple terms his influence on the field of clinical chemistry and the issues that beset geniuses such as he. Although he was probably the greatest analytical chemist to enter our field in our lifetime, he felt that these contributions were not as important as his contributions to the understanding of the biochemistry of health and disease. His two greatest contributions, the development of microchemistry and its application to the understanding of electrolyte balance of the immature infant, have saved the lives of hundreds of thousands, if not millions, of infants.

Pediatricians have never appropriately recognized his great contribution to the management of the hydration status and electrolyte balance of the premature infant. In fact, his landmark study, "Correlation of Clinical and Chemical Observations in the Immature Infant" was judged as heretical by the 1950's medical establishment and he was henceforth banned from publishing in pediatric journals. Ironically, a careful review of the literature would easily demonstrate that Sam and his pediatrician colleagues at Rockford Memorial Hospital pioneered the effective treatment of these infants. These scientists learned to hydrate the premature infants, giving them salt and keep them from developing metabolic acidosis. Their results, although controversial, were so impressive that the State of Illinois published their methods of therapy and analysis, which subsequently changed the field of neonatology. (3)

I first met Dr. Samuel R. Natelson in 1967 when I was Director of Biochemical Research for the Renal Division of Chicago's Michael Reese Hospital. He was then Director of the Chemistry Laboratory, just two floors above me. Over the next three decades, he remained my mentor and friend. In later years, even when his failing health slowed him down he would telephone me from his home in Knoxville to discuss his research findings. Because I was aware of his great contributions to medicine, clinical chemistry, organic chemistry, and analytical chemistry, Sam gave me a summary of his scientific works so I could make certain his biography and his achievements would be formally recognized. The Ohio Valley Section of the AACC videotaped his lectures about his role in changing the care and survival of the newborn. The Forward of his three volume set of life works reads:

It is the intent of this report, presented in three volumes, to summarize my scientific contributions from 1930 to the present (1992). Volume I is to contain my curriculum vitae, a summary of the contributions documented in Volume I, a list of publications while at various institutions, from 1930 to 1957, and two articles written about me by others, neither of which is very complimentary. Volume II is to contain my U.S. patents obtained during my entire career. Volume III is to contain my scientific contributions from 1958 to the present (1992). This includes my stay at the St. Vincent and Roosevelt Hospitals in New York, the Michael Reese Hospital in Chicago and the University of Tennessee Veterinary Medical Center in Knoxville. --Samuel Natelson, Ph.D."

To further enrich this biography, I enlisted the aid of Sam's son, Dr. Ethan Natelson, whose recollections of his father have been of immense help. In addition, two short descriptions of Sam Natelson's life and work which were published in *Clinical Chemistry* (1) and in *Chemtech Magazine* (2) are also excerpted in this work

In order to add more to the biography one reviewer, Dr. Samuel Meites, insisted that it have more pictures. These have been placed on an accompanying CD-ROM. Also on the CD is a copy of the booklet *The Immature Infant*, and a copy of Sam's children's stories.

In following Sam's final wishes, this work will be a review of his major scientific contributions. I'd also like to take this opportunity, however, to describe Sam Natelson's life in more detail, to show how his genius so impacted the field of medicine that despite his pariah status in the eyes of his contemporaries, Sam's legacy continues on in the work of his students and their students, and in the lives of the millions of children that he saved.

It is this last fact that inspired my adding this word to the title. In the Christian world this most often refers to Jesus Christ, but in its true definition it means: One who saves, preserves, or delivers from destruction or danger. I think his life's work makes him worthy of that title.

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Chapter 1: Early Years

By Ethan Natelson

Origins

My father, Samuel R. Natelson, was born in Brooklyn, New York, February 28th, 1909, his parents were Russian immigrants, Mendel Notes and his second wife Bashe Henne Melnick Notes. The name was changed to Natelson for uncertain reasons. My father's eldest brother Ben claimed the immigration service did it because his name sounded foreign. My father claimed Mendel Notes, himself, did it to Americanize the name.

My Father had no middle name, only the initial R. on his birth certificate. His sister, Jane, nicknamed him Samuel Rudolph, which he hated. He never used his middle initial and for some reason, resented it. I am sure he would prefer that you left it out.

Mendel was very retiring and mellow and worked as a tailor. His second wife, Bashe Henne (Betty-Anne), had a much more aggressive personality (later reflected in Sam), and was very well educated schoolteacher. I am not sure that poverty played a major role in his upbringing; although there were many children and finances were tight, they lived in a large brownstone house.

The only other family of Natelsons in the United States had emigrated here from the same area of Russia about 30 years earlier. They may or may not be relatives and Mendel may or may not have taken their name. My brother was never able to prove the link between the two families but my father was convinced there was one.

My father was the sixth of ten children. The eldest child, Benjamin, was his half-brother, his mother (Liebe Rosenfeld) having died in childbirth in Russia. His second brother, Herman, was born in Russia to Mendel's second wife. Benjamin and Herman emigrated to the United States with their parents when they were about 10 and 4 years of age, respectively. Ben had to enter the workforce at a young age to help support the family in New York and did not attend college. He eventually managed a pest extermination firm and would entertain his young nephews with tales of how he trapped rats and other pests. He died at age 83. Herman obtained a PhD in education, becoming a high school principal and an education administrator in New York. He lived to age 100.

The next child, Jane, became an expert in Braille and worked with blind children. She held a master's degree in education despite her father's disfavor of education for women. She had to work to help with the family finances. Her husband ran a coffee company, which is how my father became involved in developing a freeze-drying process for coffee. Jane is now 101 years old. Her sister Fannie, a school teacher, died at age 93.

Morris was the next brother, world-class in math, who attended two colleges simultaneously to obtain his degree faster. He was one of the original partners in Lehman Brothers. My father always lamented Morris' failure to enter the sciences. Morris provided financial support for many of my father's research projects.

His next brother was Henry who was very laid back and ran a very large fine china and dry goods business. Both Morris and Henry were heavy smokers and died in their 60's from cancer. Henry's son Michael and Michael's son are both nuclear physicists, the younger, Doug, now a professor at Rice University. [They obviously inherited the math genes I lack but my brother has (he was a Fulbright scholar in math and studied in Germany for a year prior to entering medical school).]

The next sibling was Sydney, who is very much like my father in looks and personality. Sydney developed osteomyelitis as a child after having been kicked in the leg by a horse pulling a milk cart. His mother took him home from the hospital when the doctors wanted to amputate and remarkably, the wound finally healed leaving a large scar and a muscle defect. My father became his protector in many fights on the New York streets and perhaps this contributed to his aggressive nature. My father was fearless in any situation of personal or professional aggression, regardless of the odds. Sydney became a catcher when my father was a semi-pro pitcher in the early 1930's. He was in general practice in New Jersey for many years. At this writing (2003), my Uncle Sydney is still living. He must be about 93 now. He is in a nursing home in Montana where his two sons live. Both his sons are physicians.

The next child was Tillie, still living, at age 90. She was a housewife, married to a CPA. Then came Florence, the youngest, an artist. She was also a heavy smoker and died in her sixties. Her son is a computer wizard.

Marriage and Family

On April 4, 1935, my father married my mother, Ethel Doris Nathan, in Brooklyn, New York. My mother was born on Dec. 4, 1913, in New York City. Her father was a painting contractor who died young of lead poisoning from his favorite Dutch Boy lead-based paint. Her mother was a homemaker. She had several brothers and one sister. Her oldest brother had a law degree, the next brother was a war hero and one of Chennault's Flying Tigers. He later taught high school science. They are both deceased. The next brother owned a metal works (sort of a lathe factory) and had no higher education. Her younger brother is a retired psychiatrist; my father tutored him through Rockford College and he was able to graduate from medical school in Switzerland. He practiced in the New York area. Her sister, who was younger, died of rheumatic heart disease in her forties.

My mother had a master's degree in languages from Hunter College, in New York, and won a New York City competition in French, for which she received a medal and a free trip to Paris (her parents would not let her go, since they did not believe in education for women). She was an expert in Latin and also German. She taught school for several years before she was married. She taught English to Dr. Kihachiro Takahara's children among others. [Dr. Takahara was a visiting research scientist from Japan who collaborated with Sam on a number of projects for several years] She loved to read, and was a regular at the library in Knoxville, which was only about three blocks from her home. She liked to speak French with the librarian there. She was an expert on crossword puzzles and at scrabble. My mother died in Knoxville, on Feb. 10, 1998.

My brother, Stephen, is a neurosurgeon in Knoxville, Tennessee. He was a child prodigy in music, giving flute concerts when he was 5 or 6 years old. He was a mathematics major and Phi Beta Kappa graduate of Carleton College and won a Fulbright scholarship in math, doing post graduate studies in Germany before entering the University of Rochester Medical School. I graduated from Haverford College and Baylor Medical School and am a hematologist in Houston, Texas. My sister, Elissa, has a BA from Rochester, a MA from U. of Pittsburgh, a MPA (Masters in Public Administration) from American University and a PhD in linguistics from Georgetown University. She recently retired from the CIA after more than 30 years of service. The youngest, Nina, attended William Smith College and did masters work at New York University. She is the creator and executive director of CHAI, an animal rights foundation in Washington, D.C.

Personality

My father was raised in a neighborhood that would be described as "tough". When kids went into another neighborhood they would get beaten up. My father held his own. This made him fearless in physical confrontations. One unverified story that I remember was that as a young man, apparently he wanted to get some money, I think for his brother Morris. He learned about a challenge issued by one of the local prizefighter promoters offering a purse of $100 if a person could stay in the ring for 3 minutes or three rounds. Sam took the challenge and boxed defensively, effectively avoiding the prizefighter. Needless to say he collected the $100 prize. In another episode, he and I were playing tennis at a public court in New York with one of my uncles. Three unpleasant large men tried to get us off the court so they could play. They kept insulting my father and finally came out on the court and pushed him. I was on the opposite court. Before I could get to the other side, he had knocked all three to the ground and given one a bloody nose. They ran off when a police car arrived.

Did my father really play semi-pro baseball? In terms of the baseball league, I doubt anyone would recall the teams and we have no literature about this. He claimed that the players would get $10 to $50 dollars per game (substantial in the 1920-30s). He was once given a car by several of his teammates after pitching a shutout, only to find out two days later, that they had stolen it. He quietly parked it in the street and slipped away. He said that gamblers often bet on these games, which was a source of some of the money. He was offered a contract to pitch by the Philadelphia Phillies, but they wanted to send him to the minor leagues first, presumably because he was a 'curve ball, sinker and slider' type pitcher and they were only interested in 'fast ballers.' His brothers Sydney and Morris, who were a catcher and an outfielder respectively, said that numerous scouts followed my father for his power hitting and great speed (he at one time held New York high school records in the 100 yard dash). They had no doubt he would have been a quality major league player. He and I played softball for the Roosevelt Hospital in a league in New York when I was on summer vacation at college. Even at age 56, he could still out-hit any of us.

Once my father learned an equation or a chemical synthesis, he had total recall for it. Almost like opening a book. I once saw him do this on a consulting project regarding the physics of certain gasses. Although he had not worked with these formulae for perhaps 40 years, he wrote them out just as they appeared in the texts. He also had the power of complete concentration, which was very annoying to me as a child. If he were reading or working on a project, you could “scream in his ear” and he would not be aware you were in the room.

He also had complete confidence that he could obtain the desired result, whether it was in the laboratory, or any other aspect of life. His energy level was remarkable. In Rockford, in his "spare" time, he completely re-wired our house, which was built in 1905, He also replaced most of the plumbing and the coal burning furnace with gas heat. Often his work was not pretty, but it was always durable and functional.

Recently, I was researching the life of a Belgian chemist, Jean-Baptiste Van Mons, who died in 1842. This man was a pharmacist, physicist, and innovative scientist and relatively late in life, also became a physician. In his spare time he grew 80,000 pear seedlings and was the developer of the Bosc pear, among others. His life had a number of parallels to my father's, in particular his broad range of scientific interests, mastery of several languages, interest in politics, drive for knowledge, and generosity to his students and colleagues. However, I doubt he played baseball.

Chapter 2: Organic Chemist and Inventor

Education

Sam received his B.S. in Chemistry in 1928 from the College of the City of New York. In 1930, he received his Sc.M.(Master's of Science) in Chemistry from the New York University, and in 1931 his Ph.D. in Chemistry from the New York University.

His doctoral thesis advisor, J.B. Niederl was a student of world-renowned Fritz Pregl of Gras, Austria, who had been awarded the Nobel Prize in 1923 for his contributions to organic microanalysis. Sam was thus well grounded in microtechniques.

While still a doctoral candidate at NYU, he invented a process to make octyl phenol in an inexpensive manner, a discovery that could have netted him millions of dollars. He tells the story in his own words,

> This invention came about as follows. Leo Baekland, the inventor of Bakelite, was invited to give a talk to a freshman chemistry course at the College of the City of New York where Natelson was an under graduate student. He said in his lecture that if an oil soluble Bakelite could be developed it would serve to paint the walls with a permanent coat, which could be renewed by merely wiping with a wet rag. I asked if amyl phenol (which was available at that time) could serve the purpose if polymerized with formaldehyde. He pointed out that it was too expensive.
>
> I wanted to study this problem at NYU for my Masters Thesis but Professor Ritter who was my mentor said that it was too commercial in nature. After I finished my Master's studies I approached [my doctoral advisor Professor] Niederl with the project. I proposed to condense diisobutylene (octylene at 6 cents/gallon) with phenol (selling for 10 cents/lb., at that time), using H_2SO_4 as the condensing agent, to form octyl phenyl sulfate. He accepted the project. On hydrolysis octyl phenol is formed. If these sulfates are neutralized with NaOH, detergents are formed. Thus detergents like "Tide" are based on octyl phenol.
>
> Because of its low cost, octyl phenol is used in many applications as an inexpensive high molecular weight alcohol. For example if condensed with polyethylene glycol it affords a non-ionic detergent.
>
> My Doctorate thesis resulted in the production of octyl phenol by the Rohm and Haas Co. It was made by condensation of diisobutylene (6 cents/gallon) and phenol (10 cents/lb. at that time). Yield was almost quantitative. Thus an inexpensive long chain hydroxy compound was formed suitable for the preparation of detergents, emulsifying agents and numerous other uses. Octyl phenol is one of the largest: volume bulk

chemicals produced today, (2, 4)

> Phenyl ethyl alcohol (Rose Oil), Patent # 2, was prepared by condensation of ethylene oxide with benzene, both inexpensive intermediates. This was published (6).
>
> Patent # 2 (above) was filed jointly by Natelson and Niederl. Subsequently, Niederl told the Patent Attorney that he wished to change attorneys. This was done without informing Natelson. With the attorney the application was allowed to lapse and a new application was filed in Niederl's name solely.
>
> Natelson found an attorney who would take his case on consignment. He was a novice and advised that Natelson also file an application of invention and go into interference with Niederl's patent. Niederl had committed fraud against the U.S. Government laws.
>
> Niederl assigned the invention to Rohm and Haas Co., and had infinite financial support. After four years of litigation, Natelson settled for a small sum of money in order to pay the attorney. [But] There was another reason. The way the patent attorney set it up, if Natelson won, the patent would be in the public domain since Natelson had filed more than a year after publication in the *American Chemical Society Journal*.
>
> It was later reported in *Coronet Magazine* that Niederl had received the highest royalty check in the nation's history. Niederl fled to Argentina to savor the loot and avoid criminal prosecution.

Ever the inventor, while at NYU Sam also studied the behavior of liquids in irregular capillaries. This resulted eventually in 1936 in the design of an instrument for the determination of surface tension on microquantities. The instrument was featured in some instrument catalogues. (5,7,14).

The bad experience with Niederl, however, ended any hopes of an academic career. Years later, Sam told me that because he had sued his doctoral thesis advisor, he never could obtain a position at an academic institution. Instead, he had to find work in industry. As he states,

> In 1931, I earned a certificate, a Ph.D. from New York University. But that's what it was, an unemployment certificate. It meant that I ceased to be a teaching fellow, at which I had been employed since 1928 and so I had to go look for a job. So, I went to the New York testing labs and I became a consultant in the chemistry industry. They gave me space because they had no business and they said, "Go find business." Well, one of my clients was a person who wanted a plastic with high electrical resistance. A process was worked out for the preparation of styrene and

styrene resins. The Naugatuck Chemical Company rejected the product since styrene cold flowed under pressure. I then published the results of the study in *Industrial and Engineering Chemistry Journal*. Subsequently, at the end of World War II, the Dow Chemical Co. wrote in the News Edition of the *Industrial and Engineering Chemistry Journal* that the "Classical paper of Natelson" permitted them to get into the production of Styrene resins within one year so as to help the war effort. The patent for the preparation of styrene resins was never filed due to lack of funds.

On the other hand, I published it, therefore, in *Industrial Engineering Chemistry*. In 1950 I received an award from the ACS as one of the most significant papers in the first 50 years. So you can see I was a pretty well known organic chemist. See references 11 and 12.

Chapter 3: Beginnings in Clinical Chemistry

Sam describes how he became a clinical chemist in 1932, when he was working at the New York Testing Laboratories.

> Along came a man by the name of Benjamin Kramer. Benjamin Kramer was an interesting person because he had a Master's Degree from University of Indiana in Chemistry and he was appointed the first clinical chemist at Johns Hopkins University to run the laboratory. And what was the laboratory doing mostly? Looking for methods to do calcium determination, because the floors were loaded with kids with the English disease. The English disease was rickets. I researched that two of my brothers at the age of two, a pair of twins, died of rickets.*

[*Footnote by Ethan Natelson: the twins he is referring to were his half brothers, born to his father's first wife who died in childbirth or shortly thereafter. When my brother Stephen visited Russia a few years ago, he discovered records indicating that my grandfather's second wife also had her first child die at an early age before the survival of my father's oldest full sibling, Herman. This death certificate cited nutritional disease as the cause of death. The fact that these children were born and died in Russia was never mentioned to my father or any of his brothers and sisters during their childhood and this came as quite a shock to them when they found out years later.]

> When Benjamin Kramer came into my laboratory, he had a problem. He had developed a technique of giving strontium to children with deformities from rickets and that decalcified them. Then he straightened out their bones and then he gave them calcium. The only trouble was he couldn't get the calcium into them. He had to give it intramuscularly or intravenously because he was using calcium gluconate. Calcium carbonate wouldn't dissolve, and calcium phosphate wouldn't go into them. Dr. Kramer was famous for the Kramer-Tisdall method for calcium. Tisdall was also a chemist. Later on this became the Clark Collip method. The Kramer method used 1 cc of serum and Clark used 2 cc of serum, which was the modification. But the interesting thing is Kramer showed me a letter, which said there is no way in which he could possibly do that with the small serum volume and therefore the paper should be rejected. So, he framed that and hung it up on his wall. And of course, that is why he came to me. He had heard that I had gotten my Ph.D. with a student of Pregl who had taught me microchemistry. And I had published several papers on microchemical organic analysis and that is how he came to me. Finally, he offered me space at The Jewish Hospital in Brooklyn, New York. He gave me 5,000 sq. ft. in which I did my consulting work without pay from him and I was consultant to the Department of Pediatrics.

> My first job was to find a way to get calcium into these kids. I remembered I'd had a client for whom I had made adenosine triphosphate. He sold it under the name of Mybden. He sold it as a proprietary for pepping people up, and it is an interesting report because when I was at Rockford, I had a man on IV fluids for 54 days and he wouldn't wake up. So I started shooting him with Mybden because I measured his red cells ATP level and it was very low and when I raised his ATP level and he aroused. But anyway, in making ATP you got a precipitate, which turned out to be calcium fructose diphosphate. If you put these, let's say, if you phosphorylate the glucose and convert it to calcium fructose diphosphate then [because of aldolase it is] split it in the middle. You can stop that splitting in the middle by adding a little bit of iodoacetic acid. This is an inhibitor for aldolase and then [if you make fructose diphosphate and add calcium]… you get a huge precipitate and you have it by the gallon or by the pound. So I took the calcium fructose and I reasoned it this way. Since calcium could be absorbed through milk, it was absorbed as a phosphate attached to a polypeptide and to find that calcium phosphate polypeptide out of milk was a tough job. I figured I would try to give calcium with calcium fructose diphosphate.
>
> Now, at that point, when I worked with the milks, Dr. Kramer gave me a project. He would come in and sit down and we would decide on a project. That was what the clinical chemist was doing. This was my main job. The job is now technical analysis. Today the clinical chemist does the analysis. Now, Dr. Kramer said that a number of formulas have been proposed using lactose in milk sugars. They all failed. He says you've got foul smelling stools. Tell me what's in the stool. Well, I said well the lactose is in the stool and it is not being absorbed. At least 90% of it is [in the stools] and the urine is loaded with lactose too. I reasoned in this way. If you pasteurize your milk what you do is heat it until the phosphatase test is negative. Therefore an enzyme is being destroyed which hydrolyzes lactose.

Sam went on to show that starch hydrolysates were absorbed by the infants while lactose from pasteurized cow's milk was not. This lead to the use of hydrolyzed starch in infant formulas. It is on this basis that the Mead Johnson Company made a fortune. Lactose was out, and from then on, every formula had to have a dextrimaltose or carbose. Yet he received criticism from Mead Johnson. He asked them why. They said, "Because all the doctors whom we talk to are up in arms because you Natelson are publishing papers in medicine."

> "They didn't realize that publishing in medicine is the standard practice for chemists in Europe. In France, Pasteur was publishing papers in medicine. In Germany, a chemist by the name of Wieland * won the Nobel Prize for work he did on diabetes. In this country Van Slyke was

publishing papers in medicine. Somogyi was publishing papers on diabetes. That was the clinical chemist in those days."

[*Heinrich Otto Wieland, Donald Van Slyke, Michael Somogyi.]

Founding of the AACC.

Nathan Radin in his article on the founding of the AACC (Newsletter: History Division AACC Spring 1998 Volume 7 number 2 pages 3-7) noted that the field had developed rapidly and that there was only a loose collection of practicing hospital chemists in 1948. It must also be mentioned that the medical establishment was not happy that chemists were practicing medicine. However in 1923 the American Chemical Society obtained approval from the medical establishment, which allowed hospital based chemists to practice their profession.

The biographer wondered why the field of clinical chemistry was started in New York City. A corollary is why were so many of the starting members Jewish with Ph.D. degrees.

At that time there was a considerable resistance for industrial firms to hire Jews. My only anecdotal testimony comes from a Jewish colleague now about 80 who graduated near the top of his class from Harvard in the 1940's. No industrial firm would hire him. He also became a clinical chemist.

The places where individuals with such training could find positions and practice their skills were hospitals. As stated elsewhere, many large hospitals had research programs making these jobs more attractive. As Sam Natelson was practicing his consulting business, and able to use hospital facilities for that work, in lieu of a salary, this was an ideal solution for him. What no one predicted was that the understanding of biochemistry would become critical in patient care and that these measurements would be integrated into medical practice.

Dr. Nathan Radin wrote Sam asking about his recollection about the forming of the AACC. This is the correspondence as published in the History Division Newsletter.

Clinical Chemistry Before the AACC: A letter from Samuel Natelson, Ph.D.

Editor's [Nathan Radin] Note: On December 15, 1948, Samuel Natelson was an active clinical chemist who was present at the meeting of the group that initiated the founding of the AACC. The letter below, in part, is a reply to my question about the status of clinical chemistry before the founding of the AACC.

This letter is in response to your inquiry.

Before December 15, 1948, there was no recognition of "clinical chemistry" as a distinct science. There were two classes of individuals involved. One was a well-trained Ph.D., preferably in organic chemistry, as exemplified by Harry Sobotka of Mount Sinai Hospital working on vitamin A chemistry. Usually these were foreign-trained individuals who had been invited to join a faculty at a well-organized hospital such as Mount Sinai of New York. Others who practiced at this level were the group from the University of Chicago, University of Illinois and the University of Iowa such as Victor Myers and Joseph Routh. None of these had started out as "clinical chemists". Columbia University in New York City had a group of experimenters who could be classified as clinical chemists. Most of these individuals had M.D. degrees.

At a lower level, were the professional "technicians" who did the few analyses that were called for such as sugar, urea, creatinine, etc. Those developing new methodology also were recruited from the Ph.D. programs at the universities. In addition, there were lesser-trained individuals trusted with carrying out the actual tests. Some of these individuals became wealthy by operating public laboratories for a fee per test. These were in the vast majority and were not concerned with the development of any research projects. They were in greater numbers and there were always conflicts between what a clinical chemist was – a research chemist or a servant of the medical staff. An example of the latter was Max Friedman who was sponsored by Harry Sobotka and was picked by Sobotka to be the first president of the AACC. An example of a professional chemist was John Reinhold. There were very few well-trained chemists to choose from but technicians were plentiful, most of whom were associated with private laboratories.

A meeting was called in 1948, by Sobotka. He invited Samuel Natelson and Albert E. Sobel to meet in his office. We agreed that we had to have our own society. The problem was what to call it. We considered "Medical Biochemistry" and other terms of that sort. Finally we settled on "Clinical Chemistry" as being bedside chemistry. At the next meeting, about nine individuals appeared and the society was organized in 1948. We agreed not to admit commercial chemists and the private laboratories established their own organization.

Very truly yours,

Samuel Natelson, Ph.D.

As described above, Sam and a group of chemists working in hospitals in New York City recognized the need to form a new association, which would recognize the hospital-based chemist. These 10 founding members drew up the constitution and by-laws for the association. They chose to name it The American Association of Clinical

Chemists. Membership required courses in chemistry and biochemistry. The association was comprised of both a national association and local chapters. This was along the same lines as the American Chemical Society. As part of its charter, the Association agreed to publish a journal as well as a set of accepted procedures of analyses for analytes.

Chapter 4: Pediatric Clinical Chemist

The Rockford Years, 1949-1957
From The Awards Lectureship of the Ohio Valley Section of the AACC, University of Cincinnati Hospital, Feb. 28, 1992.

> By the late 1940's, the clinical chemist considered his major function was to cooperate with the medical staff in applying chemistry to an understanding of the human condition in health and disease and to assist in the rational application of the chemical findings to the process of diagnosis and treatment of the patient. To carry out these objectives, the clinical chemist was engaged in a cooperative research effort with members of the medical staff.
>
> Having sixteen years of experience in a Pediatric Department and the recommendation of Benjamin Kramer, Sam Natelson was recruited by W. L. Crawford, Chief of Pediatrics at the Rockford Memorial Hospital, in Rockford Illinois to set up a pediatric research laboratory there. Natelson's title became Chairman of the Department of Biochemistry of the Rockford Memorial Hospital.
>
> With the stimulus, cooperation and support of a talented team of professionals including physicians W.L. Crawford, F.A. Munsey, and J.H. Barbour, and the medical staff at the Rockford Memorial Hospital, Natelson set about to improve the chances for survival of the premature infant.
>
> At that time, a premature infant weighing less than 4 lbs, and born late in the last trimester of pregnancy had only a 50% chance of survival in the most modern of medical institutions. (Metropolitan Life Ins. Co., 1952)
>
> Our investigations uncovered the following facts:
>
> 1. Over 70% of premature infants who came to autopsy showed no abnormalities and death was listed as, "Prematurity". (JAMA, March, 1950).
> 2. A low weight premature (about 800 g.) left untreated for 24 hours lost about 20% of its body weight and expired in dehydration and acidosis. At that time, the recommended procedure for the premature was not to begin feeding for at least 24 hours.
> 3. Fluids administered at eight hours after birth could be well absorbed by clysis even in the low weight premature.
> 4. Oral administration of fluids was practicable with the use of an indwelling polyethylene tube. However, stomach capacity was low; in one case, stomach capacity was 4 ml and emptying time was 3 ml/hr. It was found that by continuous flow, fluid requirements could be approached.

5. The low weight premature lost salt readily and showed the need for hormonal support (desoxycorticosterone was the only salt retaining hormone available at the time). This observation has been confirmed repeatedly in the literature, and was a major discovery of these studies. We referred to this phenomenon as "Adrenal Immaturity."
6. The course of the patient's well being could be followed readily with microtechniques, which made it practicable to perform the numerous tests required for monitoring the infant.
7. If the infant is given the support it needs, in many cases this adrenal immaturity will be remedied as the infant matures.

Milk Formulas

Sam refused to believe that the physicians of his day knew intrinsically what was best for the premature patient. He attacked problems facing infants and children as a well-trained chemist with an understanding of biochemical pathways, organic chemistry, analytical chemistry and physical chemistry. The best example of his problem-solving skills involved his examination of milk formulas.

> I had a pH meter and I measured the pH of these children on the high protein milks. They were in acidosis. I measured their urea levels. [They had] ureas of 30 and 40, while on breast milk they had urea levels of 6, 7, and 8.

Sam concluded that the high protein milk was causing an acidosis and putting a [nitrogen] load on the infant's metabolism that could not be eliminated.

> I went to Rockford and I went to the Dean Mill Company and talked them into spending $50,000 to build two formulas. One which was 60% albumin (and they call it non-casein) formula, and the rest 40% casein. The other was 11% albumin and 89% casein. Those were the two different formulas. Now, you will notice that these formulas naturally contain 3% protein. I made it 2%. Breast milk was only 1.42% in the first seven days. How did I get these numbers? I went around to the mothers and collected their milk and analyzed it. You don't see that data very often. The pediatricians would not do it. It took a chemist to do it.
>
> Now, when I fed these (formulas) to the babies, I found that breast milk was the ideal and the casein formula was producing [containing] more [too much] protein. This is more or less evidence that the albumin is a source of plasma protein and not casein.

Sam published his findings (70, 75).

> When that happened, I made an enemy. The main advocate of high protein milk was Charles Levine at Hopkins. He was the chief consultant to Similac and a number of other companies. I said that what he was making

> was garbage, and that, of course, didn't make him very friendly with me. He was the editor of the journal *Pediatrics* and I never got a paper published there again. As a matter of fact, my assistant tried to publish a paper there, saying that some of the work I had done indicated newborns have high hematocrit values. He [Charles Levine] wrote a letter which I read which said, "Natelson's work is unreliable. I will publish this if you don't make reference to Natelson."

Calcium Absorption

Sam worked on the calcium absorption problem and came up with a solution, feeding the children hexose phosphates. In part this was based on his knowledge of chemistry that chelates might be absorbed better than the usual calcium salt formulations. Calcium administration is now carried out exclusively with chelated calcium compounds, specifically with hexose phosphates.

Sam states "We published in *Journal of Clinical Investigation*. That is before I became an outlaw. "Change in serum levels [of calcium and phosphorous] after administration of 6 grams of calcium fructose diphosphate."

Sam did some of this work in human volunteers. He showed a large increase in serum phosphate, and a slight but significant increase in serum calcium. In the case of children with rickets he found that if the child had a calcium of 5 mg/dL and was given calcium hexose phosphate, the 5 increased to 10 mg/dL right away.

> You have to have a control. I needed something that was identical to what we were doing. Fortunately, The Ernst Bishop Company made this material [calcium fructose diphosphate] in two forms. They made a hydrate and they also made an anhydrate. The anhydrate was stable and the hydrate was not. So, I got from them, nine-month old hydrate, which was completely hydrolyzed. It had no calcium fructose diphosphate. It had calcium phosphate and fructose and it didn't work
>
> You have to have it chelated in order to absorb calcium and that is why it amuses [me]. You take Tums. All the Tums you take, the calcium carbonate appears in the stool. None of that is absorbed. You take ground bones. They sell that at $10 a bottle now at health stores. You take a pill of ground bones and supposed to help osteoporosis. I don't believe it, because it just doesn't absorb.

Because of the discovery of Vitamin D, Sam didn't see very much follow-up of this work. He states

> I forgot about it until about 20 years ago I got a call from a society stating that they had cited this paper as probably being one of the most important papers in calcium absorption; and all the preparations that have calcium, oral calcium, are hexophosphate today.

> Casein is a calcium carrier. Now, all the work that was being done by Charles Levine for example . . . I criticized him, and that is why he didn't like me. They took the first weight and they measured the rate of gain up to the, oh maybe, tenth day. In the study that cemented the idea that high protein milk was good for children, there were six cases, three girls and three boys. I averaged the weight of the three girls in the study and the weight of the three boys. The statistics were nonsense. When I published a paper with Benjamin Kramer's name on it, of course, I had to use Benjamin Kramer to protect me, Charles Levine was furious. He was just furious.

Acidosis

Sam's mind was that of an exact analytical chemist who knew both physical chemistry and analytical chemistry. One of the best examples of his understanding was in the treatment of acidosis. One must keep in mind that the foremost pediatricians of the day knew little if any physical chemistry. Thus the **Henderson-Hasselbach equation** (which relates the pH of a solution to the ratio of the ionized and unionized form of an acid by a logarithmic ratio) had no meaning. Sodium bicarbonate for the treatment of acidosis was not considered the best practice because too often patients ended up dying from alkalosis.

> Now, one of the things I discovered, Benjamin Kramer kept telling me alkalosis is a condition produced by [medical] residents [whenever something goes bad it is the resident that caused the problem, not the staff physician]. He said that if you give bicarbonate, you are sure to end in alkalosis because you can't control it. I learned how to control it by building a pH meter and plotting and then calculating the amount of sodium bicarbonate as if [it were a buffer solution].

Sam explained that, in the case of a child in severe acidosis, with a pH of 6.9 if given 20% of the calculated bicarbonate needed, there is no change in the pH of 6.9. When 40% of the calculated bicarbonate is administered the pH rises to pH 7.05. When 60% is given and the pH may remain at 7.05. At this point the doctor will call down and say, "You people don't know how to do pH's. I have given a huge amount of material and the pH has gone from 6.9 to 7.05". When 80% of the calculated bicarbonate is given, the child's pH increases to a pH of 7.25, which is still acidosis. But now if you give the remaining 20%, the child's pH increases disproportionately. The child becomes alkalotic and may die if this occurs. So all Sam did was to very carefully give 10% of the calculated bicarbonate and measure the pH. That is he titrated the last part of the pH curve.

> Sam was a true chemist, at a time when physicians knew little chemistry.

> I wasn't afraid of bicarbonate because I knew that lactate didn't work. How did I know that lactate didn't work? Because I had a piece of filter

> paper and I dipped it in the [sodium] lactate [solution] and it turned litmus paper red. I called the company and said, "How come your sodium lactate is lactic acid." [They said,] "Oh, we put in extra lactate acid as a preservative." So, they were using lactate [lactic acid] in the solutions. If a youngster cannot handle his own lactate, how could he burn up the lactate [lactic acid] that was in the sodium lactate? Why was lactate given? Sodium lactate was given in acidosis, on the theory that the lactate would be metabolized or excreted and the sodium would be introduced.
>
> There was only one hematocrit value for infants reported in the literature when I started this work, and that was very low one on a child that was about six months old. No one knew then that premature and newborns have very high hematocrit values; around 60% is normal for a newborn baby. Nobody had measured it.

Sam approached improving the survival of the newborn in a logical manner.

> Now, the first thing I did was I said, "I am going to do exactly what they say." Here is a child that weighs 754 g. That meant that 99 out of 100 would die. That's what it meant. It was a death sentence. So Dr. Crawford said, "You can have this kid. It's not going to survive". So, I put it on a scale, and periodically I took a reading of the weight. I found out in 24 hours (and you were supposed to leave it alone for 72 hours according to directions), it weighed 610g. It died at the end of 24 hours and it lost 20% of its body weight.
>
> I said, "Therefore, we've got the secret of how to manage a premature." Just keep them hydrated. How do you keep them hydrated? The way you do with adults. So I put a polyethylene tube in. At eight hours arbitrarily I said I am not going to wait 24 hours, I am going to start giving this youngster fluid at eight hours. This is the paradigm of the treatment.

Sam calculated the amount of fluid he needed to keep the premature hydrated. He first measured the amount of fluid that could be absorbed by the stomach of the premature. He found that the stomach capacity of that infant was 4 cc and that the exiting time was 3 cc per hour. He calculated the amount of fluid that would go into the infant through the stomach. This was about 70 cc in 24 hours. From his previous experience, Sam calculated that the premature needed about 150 [cc] for 24 hours. Because he could not get in enough fluid through the stomach, Sam set up a clysis. Clysis, more specifically, hypodermoclysis, is done by placing the iv needle in the subcutaneous tissue on the abdominal wall or forearm and outside a vein. When fluid is administered, it is absorbed slowly but completely. The arm may become swollen but this resolves promptly when the needle is withdrawn. This technique was still rarely used circa 1960, but with the better IV catheters and the use of long term subclavian venous catheters, it has become passe. Sam's clysis fluid was a saline and glucose mixture.

> To my amazement, the clysis fluids went in and were absorbed as though by a dry sponge. This premature survived. At 15 days the child got into trouble. I was sitting in my office, and his father came in and wanted to take the body because they had called him and told him the baby wasn't breathing. I had an anesthesiologist who comes in, and I said, "We don't give up." I got a sample of blood, and here's what I found. 115 meq chloride, 137 meq sodium, what does that mean? Acidosis. So we gave a little bicarbonate. The urea was 33 and he was drying out, so we increased everything.
>
> We started using breast milk, and what we did was put salt in the breast milk to try to hold him with the milk. [His serum concentrations were] 120meq sodium and 85meq chloride. We kept giving him salt in the breast milk and it [the sodium and chloride] kept dropping off. Therefore, we came to the conclusion that there was a salt-losing phenomenon in these kids. It seemed that the premature didn't have a mature adrenal system. In other words, what I was saying, they don't produce aldosterone.
>
> A little later, I made a very interesting discovery. We gave 5 ml of blood. The reason we gave 5 ml of blood was that we saw this dropping hematocrit, and I didn't know whether 41% was good or bad for a premature. So I said, let's give him 5 ml [of blood]. As soon as we gave him 5 ml of blood, we saw a sharp rise in chloride.
>
> Finally, we kept giving blood because he seemed to look better, and there was a sharp rise in the chloride. We didn't give him any more salt. We concluded there was a hormone in his blood that was holding the salt, so that was when we starting giving him deoxycorticosterone. By the time he was 61 days, we removed the polyethylene tube.

At this time, Sam found the infant had a good sucking reflex and could be fed orally. However, Sam did not allow the infant's mother to feed him directly.

> We took the breast milk, added 1 g of salt, mixed it up and fed it to him. He was getting about 150 cc to 200 cc of breast milk a day, and deoxycorticosterone. Finally this deoxycorticosterone was discontinued and we sent him home. Ten months later, he was perfectly normal. Then we realized we had made a discovery because we found this to be true in every low-weight premature. The secret to maintaining the weight was to give him two things: salt and hormone support. The best way to give him hormone support was to give a little blood.

As a result of the studies at Rockford, premature and full-term infants are routinely monitored for signs of dehydration and blood components, especially hematocrit values, electrolytes, and pH of blood. This real time monitoring of blood

chemistries resulted in a marked reduction in mortality rates, (Sam claimed that approximately 1.8 million people were alive today [1992] who would not have been alive had this technique not been developed). Today's standard pediatric floor anywhere in the world looks like the pediatric department Sam set up in Rockford. In addition, milk formulas are now designed to simulate the composition of breast milk.

Chapter 5: Heretic

The Booklet

The work at Rockford was published in a 1952 booklet entitled, *Correlation of Clinical and Chemical Observations in the Immature Infant*, authored by Samuel Natelson , W.L. Crawford, and F.A. Munsey.

> It was proposed…that the expression, "immature infant", should replace the commonly-used term "premature infant," since both the premature and full term infants could show immaturity in the development of some system of control, such as for calcium metabolism, the erythropoietic system, or the Na and Cl control system.

In this booklet, techniques were described for carrying out the chemical studies done at Rockford. These procedures were described in greater detail in a book published by Charles C. Thomas entitled, *Microtechniques of Clinical Chemistry*. This work subsequently gained world-wide acceptance, resulting in a major improvement in mortality statistics for all infants. Abbott Company later featured these techniques in its newsletter, "What's New, all over the World. "

The Rockford studies, however, revealed that mid-20th century pediatricians had continued to practice medicine just the way they had in medieval days. Sam states, "they never measured anything. They got the impression that something would work." Unfortunately, physicians did not take kindly to such constructive criticism.

> My pediatric studies ended in 1958 when I left Rockford. After that I was blackballed by all the physicians…[The publication] …caused an explosion in the United States. A meeting was held of the leading pediatricians in the country and they had a symposium in the *Quarterly Review of Pediatrics*. Each one saying vile things. Saying that salt is the worst thing for premature, and they were led by Clarence Smith and also by a guy by the name of Bertrum, and also by Charles Levine. They ripped me apart. I have here the name of 12 famous institutions with somebody there writing a criticism. The criticisms were all fruitless. [reading] "If you give salt, they'll get retrolentalfibroplasia, [blindness now thought to be caused by excessive pure oxygen administration] and of course retrolentalfibroplasia has nothing [to do with it].
>
> For the next 20 years, the papers from the Mayo Clinic …. and Hopkins came out and everyone said the same thing: 'It is remarkable the way premature are able to tolerate salt and how they lose it so easily,' but nobody referred to Natelson. In the summary of *Pediatric Currents* in February 1979, [reading] 'these data suggests that the daily sodium requirement of immature sick infants-- and notice he uses the word I used, "immature" instead of premature-- may be much higher than what's

> previously thought. In such infants the investigators say urinary sodium should be monitored and sodium intake adjusted to prevent hyponatremia in the first days of life' and they refer to the *Journal of Pediatrics*. I said that in 1951 and this is [now] 1979. In the interim there were at least 20 or 30 papers and not one of them referred to the work which we had done [at Rockford].
>
> Again I'll say this. Premature and full-term infants are now monitored for signs of dehydration. Just go up to the pediatric floor.…One of the people who rebuked in this criticism said "I would hate to see every kid with a polyethylene tube in his nose". Well I can tell you this. Every kid in your pediatric center has a polyethylene tube in his nose. As a result of marked reduction in mortality statistics, I pointed out the fact that this was a greater benefit. I don't know of any invention, including penicillin that had a greater impact on the mortality statistics than this.
>
> Many years later, one of the physicians said to me, "Natelson, everybody knows that you somehow or other have to do with the survival of premature. But when I look in the literature for a reference I can't find any." I can't find any either. They won't publish my papers.

Quarterly Review of Pediatrics Rebuttal

It is hard to believe that a number of prominent pediatricians would get together and have a meeting specifically to discredit the Rockford publication, but that is in fact what happened. The contents of that meeting were published in the *Quarterly Review of Pediatrics*, volume 8 no. 2, May, 1953. The rebuttal was entitled, "Forum: Does the Premature Infant Need Adrenal Cortical (DOC) Support? A Critical Evaluation of the Rockford Program."

Sam had quoted some of their rebuttal in his 1992 lecture to the Ohio Valley Section of the AACC. I include more excerpts from that rebuttal. Only years later would these leading pediatricians of the day be proven wrong. In the meantime tens of thousands of infants died needlessly.

It begins,

> A report by Natelson, Crawford and Munsey has recently been widely disseminated. This propounds that many if not most premature infants (and also some full-term infants) are born with a functional immaturity of the outer or glomerulosa zone of the adrenal cortex, and that the outlook for such infants is much improved if they are supported by DCA and sodium chloride therapy begun soon after birth. **The radical and highly debatable character of this so-called Rockford program** [bold by biographer] has prompted us to prepare the following abstract (approved

> by Natelson), along with a number of comments solicited from experts in the fields of premature physiology and premature care.

After a brief description of the Rockford observations, a series of comments attacking the work are made by the following individuals:

Jonathan T. Lanman, New York University-Bellevue Medical Center, New York, New York.

> The authors present such data, finding in many instances low Na and Cl levels, elevated K, and extreme acidosis. The methods employed used finger-prick blood. Since these authors are much more intimately familiar than I with the vagaries of ultra-microtechnics, they will understand a certain hesitation to accept their unusual findings until confirmed elsewhere. This is particularly so since their findings are at variance with other studies in both newborn and premature infants by Bruch and McCune, Graham et al., Svendsen, and others, none of whom demonstrated the changes described in spite of the fact that signs of adrenal insufficiency were specifically sought by some of the above investigators.

These comments are simply wrong. The analytical methods were valid. The work cited was incorrect. The premature does require hormone support.

Henry F. Lee, Philadelphia Lying-in Hospital, Philadelphia, PA.

> Most of the physiologic handicaps of the premature can be met by proper formulas with sufficiently light solute loads – viz; diluted cow's milk mixtures with added carbohydrate; vitamins; oxygen; heat; and, for the smaller infants, supersaturated humidities.
>
> Since the adoption of the use of super saturation of air with water droplets (mists) for the management of the smaller infants, the problem of dehydration and significant acidosis has virtually dropped out of sight.
>
> In the past year, on a service involving 272 premature infants, no parenteral injection of fluids has been required except small transfusions of packed cells for the correction of anemia.
>
> The information derived from the study may be valuable but before adopting such a complex regime with all its injections of fluid, etc., one would wish to be very sure that such a program of management offered real advantage over the gradually developed methods in current use in large premature centers.

These comments are pure baloney; these infants do require infusion of fluids. Lee, in this author's opinion (AJP) was lying.

James L Wilson, University Hospital, Ann Arbor, Michigan. (Communication dated March 4, 1953).

> The authors are describing the physiologic deviations from normal, which are generally known to exist in premature babies and attributing them all rather generally and quite vaguely to adrenal defect. I would not agree that some of the variations from normal in physiology that are described are accurate, but certainly it is naïve to ascribe them all to deficiency of the adrenal.
>
> The statement that if the food intake is not adequate, the pH tends to become rapidly and severely acidotic is simply subject to interpretation and depends on how rapidly and how severely an acidosis exists. We have shown that the normal pH of premature babies is somewhat low.

This of course is wrong because the normal pH of the infant is 7.40.

> **Lula O. Lubchenco, University of Colorado, Denver, Colorado**
> (Communication dated March 1, 1953.)
> Several procedures in the Rockford plan seem not without risk: (1) Early feeding and handling, with regurgitation and aspiration as possible complicating effects, (2) Large and frequent transfusions which do not seem necessary, which carry the dangers of any transfusion, and which in premature infants may overload the circulation, (3) The addition of salt, which in our experience produces edema, (4) Arbitrary schedules which reduce emphasis on individualized care.

This is all nonsense **because premature infants are currently treated in the manner she states is dangerous.**

> **David Weintraub, The Children's Hospital, Buffalo, NY**
> (Communication dated March 3, 1953.)
> One interesting statement is that the premature infant has an unusual susceptibility to dehydration and that he dehydrates rapidly and in some cases irreversibly within the first 24 hours. We have yet to observe this in the five years that our Nursery has been in operation. As a matter of fact, most prematures seem edematous at birth. This edema remains for several hours and seems to slowly disappear during the succeeding 24 to 72 hours. Rarely have we found it necessary to administer parenteral fluid within the first few days of life. Indeed, most observers would probably vote against the administration of fluid to an edematous premature infant for fear of further fluid retention.

This author has his head in the sand. That is why his mortality rate is so great.

> **Robert A. Ulstrom, University of Minnesota Medical School, Minneapolis, Minn.** (Communication dated February 25, 1953.)

> The work of Hepner regarding the relationship between retrolentalfibroplasia and high sodium chloride intake, as well as blood transfusion in prematures, and his observations that feeding a formula of low, NaCl content may be associated with regression of the vascular lesions of the eye, demands careful evaluation. The regimen recommended by the present authors is in disagreement with Hepner's concept. Unless a definite reduction in mortality can be demonstrated its routine use should not be encouraged.

The work of Hepner was wrong. Retrolentalfibroplasia is caused by excess administration of oxygen and has nothing to do with salt.

Angus McBryde, Duke University, Durham, North Carolina. (Communication dated February 25, 1953.)

> We do not usually find our small prematures dehydrated, nor do they tend to dehydrate sufficiently to need parenteral fluids except in rare instances. The loss of chlorides is not the usual finding in small prematures.
>
> It is our practice to avoid wherever possible those manipulations such as blood tranfusions, subcutaneous fluids, plasma, etc., which might be traumatic to the infant and therefore be more harmful than beneficial.
>
> Our premature infants average less than 1500 Gm. at birth, yet not one in twenty receives subcutaneous saline during his entire stay in the hospital.

I don't believe this author had the ability to measure electrolytes.

Lewis A. Barness, Philadelphia General Hospital, Philadelphia, PA. (Communication dated February 18, 1953.)

> The argument concerning early feeding of prematures still goes on. In this clinic we have had more satisfactory results and lower morbidity by withholding fluid until all peripheral edema disappears, as recommended by Clifford and Smith.

His mortality rate was still very high. Withholding fluids, as Sam demonstrated, results in death in most cases.

Henry L. Barnett, The New York Hospital, New York, NY (Communication dated March 5, 1953.)

> Actual figures are not given to validate many of the statements concerning the author's own data and consequently, the statements themselves appear to be extraordinary. For example, it is stated that, "In severe acidosis its (CO2 content) level becomes almost zero in the premature and fingertip blood.

He couldn't measure the CO_2, so he made this outrageous statement with no data.

Edward L. Pratt, New York University, New York, NY (Communication dated March 2, 1953)

> The Rockford group are not the only ones who have made measurements of serum concentrations in prematures. Their data are inconsistent, at least in the frequency and often in the magnitude of changes, with most of the similar laboratory studies. Some of their data may be the result of the methods used. At least, with the methods used, errors if they occur tend to produce values in the direction that these workers found "abnormalities" more frequently than in the opposite direction.
>
> These unusual data, the interpretations and the result (which parallel those achieved elsewhere with conservative measures) do not justify, to date, any recommendation for such a program of management of prematures in general.

He couldn't measure the electrolytes either.

Daniel C. Darrow, New Haven Hospital, New Haven, CT (Communication dated March 15, 1953)

> The views in this article seem obviously heretical but since the true prophet appears to be a heretic when he introduces new ideas, I do not believe in throwing stones at heretics although there are many false prophets.
>
> The first and worse heresy is the thought that premature infants can readily excrete large loads of salt—indeed that they need extra salt to survive. The second heresy is that premature infants suffer from adrenal immaturity and thrive on DCA. Other statements in the article are not generally accepted but dogma are not developed to contradict them.
>
> The findings on serum electrolyte form the basis of the second heresy of adrenal immaturity.

The most favorable comments of all.

Haddow M. Keith, May Clinic, Rochester, MN (Communication dated February 13, 1953).

> An important contribution of this study seems to be the publication of microchemical methods to determine the various blood chemistry factors. We are, however, not necessarily in agreement with the clinical part of the study. We have not seen the tendency in our prematures to become dehydrated and acidotic.

Another author who could not measure any of the analytes.

Final Comment **by the editor.**

> It is clear that many doubts and reservations attend the thesis that a good proportion of premature infants are suffering from adrenal glomerulosa hypofunction. Another aspect of the data from Rockford, not adequately stressed by the commentators, is that practically all of the laboratory results which form the basis of the conclusions were secured by heel puncture. Without questioning the precision of the laboratory methods employed, one wonders whether peripheral capillary blood is truly representative of the biochemical status of the blood in the visceral organs in premature infants.

The use of heel blood is now (2003) the standard.

Summary of the Impact of the Rockford Program
By Ethan Natelson

As you study the text of the ***Immature Infants*** booklet, it is not difficult to see Sam Natelson's contributions to the care of premature infants, including:

1. Early intervention with fluids and electrolytes based upon real time monitoring of the laboratory data.
2. Recognition that failure of salt retention (adrenal immaturity) occurs and could be combated by supplemental mineralocorticoids.
3. The more liberal use of blood transfusions (now very commonplace) in the low birth weight premature.
4. Reduction of protein (nitrogen) load in feedings, which elevated the BUN and contributed to acidosis.
5. Plasma volume expansion which also helped to correct acidosis.
6. Avoidance of lactose products, which could not be metabolized.
7. Use of chelated calcium compounds to increase calcium absorption.

These are all very obvious concepts today, even though not credited to him personally because of his non-physician status. In a very short time these observations caused a paradigm shift in the care of premature infants.

Sam and his group at Rockford were correct in their findings. He and his co-workers were vindicated by the works of later scientists, although this took many years. Sam cited the following publications for support.

> The fact that low weight prematures lose weight rapidly and require fluids containing salt for maintenance of electrolyte balance, and require adrenal cortical support in some cases, has been thoroughly documented in extensive research reports from numerous medical centers including Harvard and the Mayo Clinic. This was reviewed in 1979 in the February issue of *Pediatric Currents*. (See also; Shah, Vasan, Rave; *J. Pediatrics*, 91, 837-, 1978).

Thus Sam Natelson was cheated out of recognition for work which, in the biographer's mind, was worthy of a Nobel Prize. In fact, pediatricians to this day have yet to recognize his contributions to neonatology.

Chapter 6: Clinical Chemistry in New York

In 1957 Sam and his family left Rockford Illinois and returned to New York City. The major reason was financial. Sam had moved to Rockford in 1948. At that time he had a position, which paid $7,500 per year. It was equivalent to having a wage of $75,000 per year in the year 2000. However, Sam had not seen the great inflation that would occur in those years. His wage did not keep up with inflation. In 1957 his salary had only increased to $10,000 per year. Sam was discouraged by this wage particularly since the pathologist at the hospital had done very well during Sam's tenure. In those years the standard arrangement was that the pathologist received 15% of all the laboratory billing. Sam had increased this amount greatly, but was unable to get a fair salary. By one estimate the Rockford Pathologist was earning $50,000 per year or about $500,000 per year in year 2000 terms.

Because of his low salary in Rockford, Sam moved back to New York. He first took a position as the Head of the Department of Biochemistry at St. Vincent's Hospital of New York. He earned about $17,500/yr. and also did consulting work. A year later he moved to Roosevelt Hospital, in New York where he took a similar position, but at a higher salary. He continued to teach the entire time he was in New York. He lectured in Advanced Biochemistry at the Graduate School of Brooklyn College from 1958 -1965 and was also a Lecturer at the Graduate School of Medicine, Polyclinic Hosp, New York from 1962 - 1965

During these years he worked on developing an x-ray fluorescence technique into a clinical tool to measure many of the elements in blood. He recognized that this analytical method could potentially measure all of the elements in blood including sodium, potassium, chloride, magnesium, etc. It looked as if this technology could be used on a blood sample applied to filter paper. The x-ray fluorescence from the surface could be detected by the photomultiplier. The energy of the returned fluorescence was indicative of the element. The amount of energy was indicative of its concentration. He was not successful because he could not get an adequate signal. More than 40 years later this technique still holds promise. The latest models are small enough to be hand held and will readily measure the heavy metals such as lead on a surface.

My colleague Donald Forman recounted that as a student he went to Sam's laboratory at the Roosevelt Hospital to see this device. There was an old x-ray machine with a large power supply. Sam wanted to demonstrate how it worked. He turned it on and nothing happened. Sam then kicked the instrument whereupon it worked. Don was astounded. He asked why that happened. Sam then rolled up his pant legs and showed him the bruises he had obtained from kicking the machine.

Sam wrote of his accomplishments

> Note: In view of the fact that the facilities at these hospitals were inadequate for carrying on a research program, many of the studies were carried out at the Jewish Hospital of Brooklyn.)

During this period of time the results of the following projects were published:

- Several review articles were written for the Microchemical Journal on the progress in microchemistry as applied to biochemical investigations.
- X-ray spectrometry was explored as a tool for the analysis of various biochemical systems,
- Guanidino-succinic acid was discovered in the urine of uremic patients and this led to the discovery of a “guanidino cycle” which accounted for an alternate mechanism of nitrogen metabolism.
- The observation that polypeptides from the pituitary, especially ACTH rich fractions, were responsible for a rise in blood citrate levels accompanied by a sharp drop in calcium levels in the rabbit resulting in convulsions, was explored further.
- A cooperative study was begun with the National Aeronautics Space Administration (NASA) as a member of the **“**Ad Hoc Space Medicine Advisory Group” in connection with the proposed flight into space. This included the development of a suitable method for blood chemical analysis in space.

Sam continued his work on the alternate nitrogen cycle for the next 30 years. As we shall see NASA was pleased with his work for them.

Chapter 7: NASA Scientist

After moving from Rockford, Sam continued his research in the development of better analytical procedures. He worked with x-ray fluorescence as a method of measuring metals including sodium and potassium and strontium, and even a serum protein electrophoresis by measuring sulfur. This method of measurement was 40 years ahead of its time. Only now, in 2001, is it possible to measure these elements by this technique.

He was far more successful in developing a system of measuring analytes such as glucose and urea in a weightless environment, an innovative technique which was the forerunner of the Vitros analyzer. This project came about in the1960s when NASA approached him to design methods of doing clinical chemistry in a weightless environment, where one could not use standard techniques. Sam responded by inventing a series of methods using impregnated tapes analogous to, but predating, the film system used in the Vitros instrument of today made by the Ortho Diagnostics Division of Johnson and Johnson.

[Sam's work was described in a NASA contract report. Natelson, S. Analysis of components in biological fluids in a gravity free environment emphasizing procedures suitable for use in an orbiting laboratory. Progress Report for the National Aeronautic Space Agency (NASA) Contract # NSR 14-012-001, 9/1/66 - 8/31/67, Contract # NAS-9-7934 9/1/67 - 6/31/68 & Contract # NAS -9-7934 supplemental agreement #2, 9/1/68 - 8/31/69.]

To put Sam's inventions in perspective, one must realize that standard laboratory procedures in the 20's to the 50's were to use sample handling techniques that relied on gravity. That is the specimen was placed in a tube or similar device where gravity held it to the bottom of the tube. The liquid was then sampled by the analyzer. Sam overcame the problem of weightlessness by never placing the sample in a tube where it could disperse in a weightless environment. Instead the sample could be taken in a capillary device where it would be held in place by capillary action (not gravity) and then dispensed. The second part of his strategy was to use a media to hold the test sample and reactants. He accomplished this by using the absorptive properties of a paper matrix. He then used diffusion over small distances to mix the sample and reagent. This was done by taking the two paper surfaces and pressing them together. Finally the reaction was read not in a test tube, but by reflectance again avoiding any liquid solutions.

This is what Sam had to say about his invention (Awards Lectureship of the Ohio Valley Section of the AACC, University of Cincinnati Hospital, Feb. 28, 1992)

> Now, I didn't ignore the outcome or methodology. I kept looking for a convenient way of doing what everybody wants. Some method where you put the blood in and press a button . . . I developed this tape system, this

> analysis which is now called the Ektachem. [his patent #3,260,413, was issued in 1966]…Generally speaking, the present invention provides for a flat test medium or tape to which the sample will be transferred and upon which tape the sample or samples will be subjected to treatment for analysis; and, a porous flat medium or tape through which the sample to be analyzed will have to pass in order to reach the test tape.…I proposed that it be used in space and I went down to NASA and demonstrated it. Measurement is by reflection.

NASA was extremely grateful for Sam's efforts, because they showed how NASA research was helping advance medicine. To reward Sam and to showcase this work they arranged for the Apollo 16 astronauts to visit his laboratory at Michael Reese Hospital in 1972.

Quote from the Michael Reese Mirror, a newsletter published by the hospital.

> Hundreds of Michael Reese employees applauded and cheered the Apollo 16 astronauts when they visited our campus May 17. The three men, John Young, Charles Duke and Thomas Mattingly came to Michael Reese to meet Dr. Samuel Natelson and to visit with our pediatric patients. Dr. Natelson has developed techniques and instruments for automatically analyzing blood and urine components in manned orbiting laboratories and also contributed to designing the astronaut's diet in space. The equipment Dr. Natelson developed has been modified for use in clinical laboratories and is used in patient lab work here at Michael Reese.
>
> After visiting Dr. Natelson in his lab on 7, Dreyfus, the astronauts walked to Kunstadter Children's Center where they talked to pediatrics patients and signed autographs for patients, employees and parents in the area. Three boys in traction were especially pleased when the astronauts took time to visit their room and sign pictures for them. Chicago was the first city on the astronauts' tour of the United States. Their visit to the moon was a three-day visit by Young and Duke to an upland area of the moon never visited before.

Interestingly enough, the Chicago newspapers reported that the astronauts had visited Michael Reese Hospital, but never mentioned the ground breaking medical research done by Sam. They never did a follow-up interview with Sam to find out why this work was so important. This was another example of how he was cheated out of his well-deserved fame and respect. He and I agreed that the editorial agenda of the Chicago papers at that time was to push the US government to spend more money on welfare and not on NASA.

Not only did NASA like Sam's method, a company by the name of Eastman Kodak also saw the potential of this system. Years later, Sam was looking at the Ektachem system at a booth in the AACC meeting exhibit hall. He didn't have his name tag on, and

asked, “Where can we buy this machine?” And the representative from Eastman Kodak said, “Well, we are waiting for Natelson’s patents to expire.”

In the end, Sam was very pleased with the Ektachem system.

> “It is now the fastest growing system. At the time I showed this patent [to the rival Technicon people] they said to me, “We’re not afraid of any of these other systems but if this thing ever goes on the market we will close up shop.” And it is true. They are closing shop. As a matter of fact, you can’t buy a Technicon anymore. By the 1980’s my patents had expired and The Eastman Kodak Co. manufactured the system of analysis as the Ektachem system. This now grosses hundreds of millions of dollars annually for Eastman Kodak Co. [As of this writing the Eastman Kodak Company had sold the Ektachem Instrument to the Johnson and Johnson Company which had renamed the instrument the Vitros.] More importantly, however, it brings the diagnostic armamentarium of clinical chemistry to the smallest premature infant. Thus my objective has been finally achieved.”

By this he meant that ‘ultramicrochemistry’ was now available to virtually every premature infant. Kodak’s instrument only used about 10 microliters of plasma for each chemical analysis, which is well within the amount collected by the heel stick procedure he championed. This commercial instrument was built, partly, on the principles of analyses that Sam had developed over the decades, thus microchemistry was inherent in the design. The Kodak design was more sophisticated because of their expertise in film making. The Kodak scientists developed reactions of serum constituents that moved through reagents in layered films. Sam’s colorimetric assays were single step ones. Both used reflectometry for measurement of colorimetric reactions.

Chapter 8: Clinical Chemistry in Chicago

Michael Reese Hospital, 1965-1976

In 1965 Sam left New York for Chicago. He told me that he hated New York. The commuting was terrible and there was no place to park. Sam had accepted a position at Michael Reese Hospital located on South 31st Street almost on Lake Michigan. He rented an apartment about 4 miles away in a well-kept neighborhood. Michael Reese Hospital provided free parking for its staff.

Sam took a position as Director of the Chemistry Laboratory. The year 1965 was at a time when the efforts of clinical chemists, physicians and researchers around the world made possible the measurement of the biochemistry of the human in health and disease in an unprecedented manner. Previously immeasurable analytes could now be measured and automation allowed for large numbers of tests to be performed. In addition, Sam was in the forefront of implementing these developments for the physicians practicing at Michael Reese Hospital.

Data regarding the state of the laboratory in 1965 is unavailable because the biographer arrived at Michael Reese in 1967. However we do have a record of the state of the laboratory between 1973 and 1975 prepared by Sam. The "Triennium Report, January, 1973 through December, 1975 Biochemistry, Michael Reese Hospital and Medical Center" was prepared for the hospital administration. The breadth of the programs carried out under his leadership is impressive by any standards, then and now. Sam's staff included his Associate Director, William R. Nelson, Ph.D. and Assistant Director, Robert L. Murray, Ph.D.

> This report details the activities of the Department of Biochemistry of the Michael Reese Hospital, from the activities of a staff of over fifty individuals, engaged in a cooperative effort to serve the patients of Michael Reese Hospital and Medical Center and the public.
>
> This presentation is dedicated to these people, who make this complex service possible.

Sam's staff included 30 members with baccalaureate degrees, 5 with 2 or 3 years of college, but more interesting 3 with masters degrees, 1 Ph.D. and one Pharm. D. One of the reasons for the Ph.D and Pharm.D. staff members was that for all his brusque manner, he was a soft touch for giving out jobs to people down and out. Both of these well educated people had suffered problems, one a nervous breakdown. Sam gave them a job and respect.

The program at Michael Reese met the highest standards of quality. Sam subscribed to the CAP proficiency program. He noted that subscribing to such a program gave the technicians confidence in their results. The biochemistry laboratory provided service 24 hours a day seven days a week, meeting the needs of a 1000-bed hospital.

In the three years covered by the report, the increase in the number of tests was from 505,714 to 769,987, an increase of 52%. Sam accomplished this dramatic increase not by doing more routine tests such as glucose, but by adding new tests such as drug screening and those required for therapeutic drug monitoring.

> The Toxicology Service routinely screens for eight of the more commonly abused drugs around the clock, In addition, approximately forty different drugs were analyzed in patient's serum in 1975. Drug levels are determined to assist the physician in his treatment of several diseases, such as epilepsy and asthma. In addition to the common techniques found in most laboratories, the toxicology section employs such specialized techniques as fluorescence spectroscopy, atomic absorption spectroscopy, thin-layer chromatography, gas chromatography and radio-immunoassays, which require highly trained personnel and sophisticated equipment.
>
> The Toxicology Service at Michael Reese analyzed over 8,000 specimens for 1975. This is the most rapidly growing section of the chemistry laboratory. The rate of growth of this section is illustrated in Table 2.2, comparing the four quarters of 1975. There has been a 50% increase in volume for the year 1975, as compared to 1974.

This is one of the lessons that he taught me. That is, when the practicing clinicians have new tests available to them, they will order them. He explained that to show that value (current nomenclature), the clinical chemist must serve the medical staff by constantly adding these new services. He states this philosophy in the report.

> The Biochemistry Department performs analyses for over 100 components in blood, urine and other biological materials. If a component of blood becomes of sufficient interest to the physician, the Biochemistry Laboratory will develop procedures for assay for this component. The Biochemistry Department has both the material and technical personnel to develop such new techniques. An example of this policy is the introduction of Isoenzyme studies for LDH and CPK on a routine basis. "

Sam was able to carry out his educational goals in large part because of his enormous energy. His philosophy on education is illustrated by the following excerpt.

> The Department of Biochemistry carries on vigorous programs, whose objective is the dissemination of clinical biochemistry to individuals with varying background. These include Doctorate Chemists who wish to train in the field of Clinical Chemistry, Clinical Pathology residents, Technicians and also to some measure, the Medical Staff at Michael Reese Hospital and Medical Center.

To train doctoral level clinical chemists Sam applied for and obtained a 5-year grant from the National Institutes of Health. He drafted Dr. Kenneth Robbins and me as

participating faculty. The program started in 1971. The goals of his training were:

> The training program is to develop leaders to raise the level at which Clinical Chemistry is practiced in the United States. Candidates are selected who have a strong background in basic chemistry and show leadership qualities. Intensive training ensues to orient their interests and capabilities to the problems of clinical chemistry. The duties of each candidate are:
>
> 1) To participate in a research program to develop a better understanding of the chemistry of the human in health and the changes which take place in disease.
>
> 2) To be able to organize a teaching program to train clinical chemists and chemical technicians.
>
> 3) To be capable of organizing and supervising a clinical chemistry laboratory and act as a consultant to the Medical Staff on problems related to clinical chemistry."

The program was wildly successful. At the time many chemists could not find jobs. This was particularly true for physical chemists. A number of them were poorly trained in chemistry and actual hands on chemical procedures. They were very anxious to study a field where employment was almost a guarantee. The program was set up to train these postdoctoral fellows for two years. However, many of them obtained jobs in about 18 months. Sam was happy at their success. In fact many of them did become leaders in the profession of Clinical Chemistry. The list of some of the graduates is presented in the Table.

CLINICAL CHEMISTRY TRAINEES WHO HAVE BEEN PLACED WITHIN THE LAST THREE YEARS

Name & Period Of Grant Training	**Date Received Doctorate & Institution**	**Present Position**
Arnold L. Schultz (7/71 – 6/72)	1970 Univ. of Colorado	Director of Clinical Chemistry - Laboratory Service Center Veterans Administration Hospital 1055 Clermont Denver, Colorado 80220
Arthur Tomisek (3/72 – 6/74)	1947 Oregon State Univ.	Research Chemist – Dept. of Biochemistry Michael Reese Medical Center 2929 S. Ellis Chicago, Illinois 60616

Donald J. Pochopien (1/72 – 6/73)	1971 Illinois Institute of Technology	Central Community Hospital 5701 S. Wood Street Chicago, Illinois 60636
Myron M. Warshaw (9/72 – 9/73)	1965 Univ. of California at Berkely	Director of Clinical Chemistry – Dept. of Pathology Northwest Community Hospital 800 W. Central Arlington Heights, Illinois 60005
William P. Vorkink (10/72 – 10/74)	1972 Univ. of Arizona	Laboratory Supervisor Fairbanks Memorial Hospital 1650 Cowles Fairbanks, Alaska 99701
Edward H. Winkler (1/73 – 6/74)	1973 Kansas State Univ.	Director of Chemistry Memorial Hospital of DuPage County Avon Rd & Schiller Ave. Elmhurst, Illinois 60126
Robert L. Murray (7/73 – 7/74)	1974 Illinois Institute of Technology	Asst. Director of Biochemistry Michael Reese Medical Center 2929 S. Ellis Chicago, Illinois 60616
Bernard Century (10/73 – 6/74) (Salary paid by Michael Reese)	1946 Univ. of Chicago	St. Mary's Hospital 56 Franklin Waterbury, Connecticut 06702
John E. Sherwin (1/74 – 7/74)	1969 Univ. of California	Director of Pediatric Biochemistry Michael Reese Medical Center 2929 S. Ellis Chicago, Illinois 60616
Lawrence E. Webb (4/74 – present)	1965 Univ. of Chicago	Director of Clinical Chemistry Kenosha Memorial Hospital Kenosha, Wisconsin

With all these responsibilities, Sam continued to both write and do research. For the Tiennium report he cites some 22 scientific articles. More impressive is that during this time he prepared and published the following books:

Natelson S, and Natelson EA, Principles of Applied Clinical Chemistry, 1, Plenum Press, N.Y. & London (1975).

Natelson S, Scommegna A, and Epstein MB, Amniotic Fluid, J. Wiley & Sons, N.Y., London, Sydney, Toronto (1973).

Natelson S, Techniques of Clinical Chemistry, 3rd Edition, C. Thomas, Springfield, IL (1972).

At the end of 1975, I think Sam felt that there was a conspiracy designed to destroy him. He was very discouraged by the response of the administrators of Michael Reese Hospital. As noted elsewhere in 1972 the Astronauts came to visit him at Michael Reese. He was the recipient of an NIH training grant, he had increased hospital revenues to more than $4,000,000 per year on a budget on the order of $800,000 per year, but he could only get $900 for new equipment for the year 1975.

My own opinion was that this was true. Sam was an “in your face” person. He was a scientist and quite sure of himself. He was not urbane and discrete. He would tell administrators what the issues were and they would ignore him. To this day, I do not understand hospital administrators who do not understand the business of hospitals. The best explanation I ever heard from an administrator was that he was an expense administrator and not a revenue administrator. Therefore logical plans to increase revenues and make more money were not his purview; his job was to cut the budget. I think this is the administrative incompetence that Sam encountered.

Michael Reese Hospital, 1977-1979

In 1977 Sam was forced out as Director of the Biochemistry Department at Michael Reese Hospital. His view of clinical chemistry was different from those of the pathologists and the Hospital Administrators. At that time the Technicon Autoanalyzer was the be-all and end-all of biochemical determinations. The instrument was capable of analyzing 60 samples per hour on 12 or more different analytes. It was termed a 12 channel analyzer. The physicians wanted this large set of analyses done on every patient, often every day while they were hospitalized. The results were presented on easy to read graph paper. The Hospital Administrators loved the instrument because of the large revenue increase. Sam was opposed to the instrument and favored a more focused ordering pattern by the attending physicians. He knew that to provide service 24 hours a day the instrument reagent costs would be greatly increased. However the sales people at Technicon knew that their targets were the hospital administrators and the pathologists. Sam was out and the instrument was brought into the hospital. Sam was given a research position and the hospital paid his salary until he was 70 in 1979.

During this time Sam focused on his research projects and finishing the third volume of his series in *Applied Clinical Chemistry*. Sam wrote these books himself aided by his son Ethan. The books were 500 plus pages in length. All of the facts were taken from the literature and every article cited in the book was read by Sam.

Sam was of course correct in his assessment of this large instrument performing un-needed testing. The US Federal Government in 1983 was alarmed at the dramatic

increases in costs of the Medicare program. One of the most striking increases was in laboratory testing. To curb this abuse the Government passed the Tax Equalization Fiscal Reform Act (TEFRA) in 1983. In this reform hospitals were no longer paid on a fee for service, but a fixed fee depending on the severity and type of disease. The hospital biochemistry laboratory was no longer a major revenue center for the hospital, but now became a cost center. In addition the 15% professional fee paid to pathologists as part of the laboratory bill was eliminated.

As a result of this reform, discrete testing was the rule not complete profiles. This fit with Sam's invention of the discrete analyzer that he had developed for NASA.

Chapter 9: Research Scientist

In 1980, at age 70, Sam moved to Knoxville, Tennessee to be near his son Stephen. He continued his research, primarily becoming a well-recognized plant biochemist working on the amino acid properties that conveyed plant resistance to pests.

Ethan Natelson describes his father's later research:

> At the University of Tennessee College of Veterinary Medicine he was given the use of a lab in exchange for teaching courses, editing manuscripts, helping to write research grants and doing glass blowing of broken equipment, among other things. One of the innovative projects he did there was in the area of agriculture, a field he had never worked in before. Many species of plants will have a varied resistance to harmful organisms. For example, certain pears are sensitive to fireblight (a pseudomonas bacterial infection) while others are resistant. Usually, the biochemical cause for the susceptibility (or resistance) is unknown. Today, the cutting edge technology is to simply introduce foreign genes to provide the resistance. Heretofore, it was simply trial and error – one grew several varieties of a particular crop and selected the one with most resistance for wider planting. This is usually very labor intensive. In Tennessee they had a problem of weevil damage to certain alfalfas. How do you select the one with the most resistance, without having to resort to large, test plantings? He reasoned that resistance had to do with "bad taste" toxicity to the weevil and analyzed the amino acid ratios in several cultivars (see page 537 in his volume 3 of publications). He was able to determine that "resistance" related to the ratio of canavanine to arginine in the plant, so that by measuring this ratio first, you would know if you had a winner before setting out large plantings. Apparently, this type of analysis has become a standard in the field. Thus, you want an alfalfa that has good growth vigor but also has the proper amino acid ratio.
>
> He also continued several other research projects:
>
> **Ektachem competitor.** In the1980's, Fuji Film of Japan explored the possibility of going in competition with Eastman Kodak's Ektachem system. They sent a representative to see Natelson to see if an improved system could be developed. This resulted in Patent II 48. Fuji Film, however, decided not to go ahead with the project.
>
> **Calcitonin and Epilepsy**. This work was done in fits and starts [*piecemeal*] over many years, when he had the time to spare. He originally got involved when he was doing extracts of endocrine glands for Armour and isolating ACTH for them. He also had developed early assay systems for catecholamines. He noticed that some of the extracts

would cause seizures in rabbits, associated with substantial drops in their calcium levels. I believe he first thought the calcium lowering substance was a sequence of ACTH but eventually came to the conclusion that it was a distinct peptide. This turned out to be identical with calcitonin. Later, when more sensitive assays for citrate and other hormones were available, he became convinced that some forms of idiopathic epileptic seizures were caused by shifts of citrate and calcium and were an exaggeration of the alert or fear response exhibited best in the rabbit model. He never had the resources to fully investigate this and at one time kept after my brother to allow him to study seizure patients with assays of these systems. He even applied for an NIH grant in this area, but it was not funded (one of the criticisms was that he was not a physician). Perhaps someone will eventually carry out this work. I don't know if he was on to something, or not.

Chapter 10: Leader

Founding of the AACC

Sam was one of the founders of the AACC which started in NYC. Sam moved to Rockford Illinois about the time of the founding of the AACC. He was passionate about the profession. At a meeting of the American Chemical Society held in Chicago in 1950, he requested that individuals interested in forming a Chicago Section of the AACC get together. At the meeting he gave an impassioned speech for the need for this organization, and as a result, the Chicago Section of the AACC was formed.

Sam wrote on the need and scope of this new profession (4). His forward thinking still rings true today: in his words, "The patient has the right to a qualified chemist." (3).

Sam proselytized chemists to enter the field of clinical chemistry. My own conversion occurred in 1968. I arrived at Michael Reese Hospital after having struggled with physical biochemistry for years and had finally realized that I was not cut out to be a physical biochemist. I became Director of Biomedical Research for the Research Division at Michael Reese Hospital, working under Victor Pollack, the Chief of the Renal Division. Dr. Pollack introduced me to Sam, whose office was two floors up from mine. Sam said to me, "Pesce, what do you do?" And I said, "Research." He said, "The grants are going to run out one day and you are going to have to earn an honest living." "So," I asked, "What am I to do?" He replied, become a clinical chemist. He said he would teach me clinical chemistry if I spent an hour a day with him. After six years of daily lessons, lo and behold, I became a clinical chemist. Fortunately, I took his advice and have been gainfully employed, and even useful to society, for more than 30 years.

Another one of his teachings which I did not fully appreciate was his comments about research grants. He was well aware that in the traditional sense, one could not do research without grant support, but this was erratic and a researcher could not be guaranteed support over their entire career. When I explained that I liked doing research, he stated that if I became a clinical chemist, I could always do research. His logic was simple. A clinical chemist has a laboratory, it is always funded by the hospital, why do you need to write grants? Later in my career, when I became Director of the Toxicology Laboratory at University Hospital, I appreciated this advice. During a 15 year period, I had little research support, yet we were able to write some 50 scientific papers in the areas of therapeutic drug monitoring. One of which was published in the Lancet.

This excerpt is indicative of Sam's view of the role of the clinical chemist.

> The clinical chemist was not interested in the methodology. He was interested in using it. Liebig who was a clinical chemist studied urine and he made urea. Louis Pasteur was a clinical chemist. Berzelius was a clinical chemist. He used the word organic chemist. He was responsible for isolating uric acid from urine and so on. So, the profession of clinical chemistry has been an honored profession since the days [when] chemistry was invented. Chemistry was invented by clinical chemists. Clinical

> chemists were the people who were able to take silver and make it black with sulfur. And that is what the word chemist means "The people who make things black". And, therefore, if you could take silver and make it black, obviously you could cure diseases.
>
> The alchemist used to say, "The purpose of alchemy is not to make anyone rich, but to cure disease, and we have to find cures for disease." Von Helmont was a clinical chemist who invented the balance that was used for many, many years, the gravity balance, and he was also a clinical chemist. He called himself an iatro chemist because the word iatro means medicine. So, the clinical chemist was called an organic chemist, an iatro chemist, a biochemist. When the biochemists first formed a society, there was clinical chemistry. Today we have a new class of clinical chemists, the analytical clinical chemists who have replaced and virtually have nothing to do with the physician. He doesn't cooperate with him [the physician]. The clinical chemistry lab used to be the center of the hospital. A lot of research went on in that hospital. I remember. It was true in every single hospital.

To work with Sam and to be taught by Sam was to try to take a drink from a fire hose going full force. Sam never stopped talking, did not repeat himself, and described much of the field of clinical chemistry in the six years that I spent learning from him. It was truly amazing to see him build instruments, take apart methods and rebuild them so they worked. Sam read voraciously everything that came into his office. The amount of information that his students gained from him in one year was impressive. Many of the PhDs in his post-doctoral program have been gainfully employed as clinical chemists with only one year of training with Sam. He held his students to a very high standard. He once described a postdoctoral fellow who was just starting with him as one who performed miracles. "Miracles?" I asked. He explained, "He does an experiment once and gets one result and then he can never repeat it again."

As cited above, Sam developed a postdoctoral training program for Clinical Chemists at Michael Reese Medical Center, which was approved by the National Institutes of Health in 1971.

A large part of Sam's legacy is the clinical chemists he produced. These include: Dr. Norbert Tietz, who became president of the AACC and wrote the leading textbook on clinical chemistry; Drs. John Sherwin and Myron Washaw, who served as presidents of the NACB; Drs. Sasaki and Takahara of Japan; Drs Bernard Century, Richard Dods, Peter Haux, Anthony Koller, Robert L. Murray, Donald J. Pochopien, Arnold Schultz, Arthur Tomiseck, William Vorkink, Lawrence Webb, Edward Winkler, and many others. The number of clinical chemists directly trained by Sam Natelson probably numbers more than 30, many of whom are still actively contributing to the field. Thus Sam's legacy is continuing to this day.

Sam's energy was enormous. When asked why he worked so hard, his answer

was that he had lived through the Depression and he could never accumulate enough money to feel secure. One of our Nephrology fellows at Michael Reese would find Sam Natelson in the library on the weekends, poring through books and journals to prepare for the writing of his reference text series, *Principles of Applied Clinical Chemistry*. Such a level of commitment and effort was the standard that he set for his students. Thus, it is not surprising that so many have been successful just by trying to attain this standard.

The role of a leader is to attract and motivate good people. Sam was exceptional in his ability to get people to use their maximum ability. Ethan Natelson describes these interactions.

> One of the things my father did wherever he was located was to befriend an unusual cast of characters (like Sherlock Holmes' irregulars) from highly skilled professionals to simple shopkeepers and laborers. Each had a skill he would learn from. As I mentioned, Hilde Bruch was Karl Landsteiner's daughter and the librarian at Rockford Memorial Hospital. She helped him obtain and translate certain foreign references. Frank Matranga was the photographer at the hospital who helped him with medical illustration. My father was quite good in mathematics but he had a friend (I think his last name was Varney) who was a world-class math and physics expert and the chief scientist for Barber-Coleman, an engineering firm in Rockford. Varney helped him with certain equations - I think one had to do with calculations for the microhematocrit head for the centrifuge, which my father devised.

A leader gains followers in a profession in part because they realize the leader believes in the profession. Sam became disillusioned by the leadership of the AACC in the early 1970's. When the organization was set up, Board Certified individuals, that is, Diplomats of the American Board of Clinical Chemistry were classified as Fellows. Membership in the AACC required educational credits in the sciences and the recommendation of a member. These were typical standards of medical professional societies in the 1940's when the AACC was formed. In the 1970's to increase membership, these educational requirements were dropped and the Fellow designation was eliminated. This angered Sam. He felt that his profession was being undermined. That is, how could he gain respect in the medical community if uneducated individuals could call themselves clinical chemists. After lobbying and failing to change the minds of the AACC leadership, Sam and others in the Chicago area founded a new professional organization, the National Academy of Clinical Biochemistry. To be a member, one had to be Board Certified. The goal of the organization was to improve human health and understand disease processes. The organization did ultimately achieve its goals and after many years of separation is now considered the Academy of the AACC. Sam was asked by the leadership of the AACC not to form the NACB because it would compete with the AACC. Of course Sam felt that he was right and ignored these requests.

Sam's view of the role of an organization was unique. He stated that one of the goals of an organization was to make awards to its members. as way for the profession to get recognition. In addition, awards should not be limited to members. Selection of recipients should result in the award doing more for the association, than for the recipient. That is if a very prominent scientist accepted the award of the Academy, then most likely the Academy would be considered worthy by prominent scientists.

Sam also tried to get recognition by the National Institutes of Health. One way was to have the NIH recognize the profession by awarding grants to clinical chemists. Sam's concept of a clinical chemist was a scientist who studies humans in health and disease. He thought that a study section for clinical chemists should be established to review grants in the field. An NIH study section accepts research proposals. Because science is so specialized the NIH reviews grant proposals for research by sending them to very specialized scientific review groups termed study sections. These proposals are reviewed and prioritized for funding. Sam reasoned that if clinical chemists had their own study section, the reviewers would be better understand the science and medical need upon which they were based. Sam failed in these efforts and to this day few clinical chemists get NIH funding even though their work has revolutionized medical laboratory testing and as a result patient care.

One of Sam's long time but losing battles was legal recognition of the chemist to be a laboratory director. During the 1940's this was not a problem. During the 1950's with the advent of the autoanalyzer and the increased number of tests being performed, hospital laboratory testing became very lucrative with chemistry being the most lucrative area. The College of American Pathologists was able to get state laws passed that prevented the chemist from being in charge of the chemistry laboratory. The role of money in the laboratories went as follows. A professional fee of 15% of all laboratory billings went to the pathologist. For a medium sized hospital, this meant professional fees of $200,000 to $500,000 per each pathologist (these were 1950, 1960, 1970 dollars). Congress in its wisdom stopped this practice in 1983 with the passage of TEFRA, Tax Equilization Fiscal Responsibility Act. Pathologists were not allowed to collect professional fees on the performance of laboratory tests. The fee could only be collected as interpretation and then only if requested by the patient's ordering physician.

Sam had approached the Institute of Chemists and the American Chemical Society to turn back these rulings without success. Sam and the biographer went to an ACS Division of Professional Relations meeting but failed to get concrete action.

In the end the law was changed to permit chemists to be laboratory directors. It was changed because the Congress of the United States decided pathologists were getting too much money. TEFRA allowed clinical scientists, not only pathologists, to be in charge of the laboratory. So Sam won his battle not on professional grounds but because of excessive cost to the public.

Chapter 11: Patents

Sam was a lifelong inventor. I think it was a natural talent. His first invention was a personal disaster. His professor stole the invention and fled with the royalties to South America. I think his mind worked in such a way that he saw solutions to problems and because of his mindset he had to show the solution and get credit for it.

Sam dedicated Volume II of his works to his cousin, George Bernard Oujevolk, a patent attorney, "whose skill in writing and obtaining patents is unequaled. He is the patent attorney of record for most of these patents."

Volume II contains descriptions of the 48 U.S. patents Sam accumulated during his career. The fact that Sam held 48 patents was impressive both in terms of the numbers and the range of inventions. The patents include everything from freeze-dried coffee to measuring chemistries in an orbiting laboratory. This number was also impressive in light of the patent process itself. In the early 1970's, I had failed to obtain a patent and I discussed this with Sam. He responded by telling me that the job of the patent office was to give patents and that they were very good about this. However, the trick to obtaining a patent was to negotiate with the patent officer. The next time I had a patent, which was initially rejected, I followed his advice and negotiated the claims with the patent officer. Sam was correct, our patent was granted.

Sam was most proud of his work in organic chemistry. In truth, he was an exceptional organic chemist. He invented a process of producing rose oil an important intermediate in the plastics industry. He developed an inexpensive way to make polystyrene, and methods of producing vitamin D, and extracting wool grease.

In order to do chemical analyses on pediatric patients, Sam had to develop methodology. A lot of the methodology was developed in Brooklyn before he went to Rockford. The methods were simple and practical. For blood collection he used an open-ended tube. After puncturing the heel, the blood was allowed to run in by itself. Sealing wax was used to close one end and the tube containing the blood was centrifuged. Sam was very careful with use of this sample. He would first measure the hematocrit, which would not use any of the sample. He would cut the tube and allow the plasma to flow into various types of pipettes and do all his tests. He could also sample the red cells for purposes such as measuring ATP.

Sam's early application of microchemistry extended into many areas of clinical chemistry as well, and other chemists and manufacturers started to design instruments that could use micro samples. Blood gas measurement, which originally required 30 mL of blood, could now be done on microliter quantities. This made open-heart surgery possible adding to the numbers of lives saved by this pioneer clinical chemist.

Sam describes his invention of the microgasometer in this way. "One of the doctors whose name was Roarke said to me, 'Natelson, you could have all these methods,

but you are not going to develop a micromethod for CO_2,' so I did." The Natelson microgasometer was widely used for several decades.

Yet Sam was somewhat disappointed by his link to the microgasometer. He stated People know Natelson not for what he did for premature or milk, they know him for the methodology, which is nonsense. None of this methodology is in use today. Anybody who goes about spending his life developing methodology is not looking ahead to the future. If you use the methodology, you do it for a purpose…If you look at this very carefully you can see that all I did was take the old Van Slyke apparatus, where we had leveling problems, and replace it with a plunger and make everything smaller, and that was the microgasometer. So you can credit Van Slyke with this history more than me….I had to develop methods for 10 microliters or less. That's routine today. Remember, in that day, that was considered insane. Some of the people who criticized my work "With due respect to Natelson" one fellow wrote, "I just don't believe these results with micromethod gasses were that reliable." "

In order to develop micro-methods Sam adopted the most advanced technology of the day.

> I had a friend in the Bronx at the Farrand Optical Company who was an expert in light. He was the one who developed the interference filter. An interference filter is two pieces of glass with a little glue in between, and you push them together. The distance between the two determines what color goes through.

Sam knew that the application of the interference filter would improve the specificity of the measurement of the colorimetric procedures. He demonstrated an increase in sensitivity by a factor of at least two by using an interference filter. But no one had actually ever done it before. Of course, use of interference filters is routine today.

"Now, these microcuvettes were not available in those days. I had a fellow in Rockford by the name of Kopp and he made them for me." These cuvettes had the same path length as the ones using a larger volume. He reduced the required volume from 3.5 cc to only 0.5 cc.

Sam's Patent # 9 was the highly successful microgasometer. This earned over $300,000 per year for 20 years for Scientific Industries. Sam received only about 10% of the royalties due him. Finally a suit was brought to bear and Scientific Industries settled for a modest sum, which made it possible for Sam to send his children to graduate school.

The other patents obtained while at the Rockford Memorial Hospital are instruments Sam Natelson built in order to monitor the well being of premature infants. These included, Patent # 11, used in chloride estimation and Patent # 12, used to measure micro amounts of blood for pH.

In the 1970's the biographer was working on solid phase enzyme linked

immunoassays. At that time he used a test tube format comprised of 12mm x 100 mm plastic tubes. The tubes were coated with antibody, the excess antibody solution was removed by washing the tubes with buffer. A second step was the addition of the test solution, followed by a similar removal and washing step. The final step was delivery of the indicator solution to the test tube. Without formally requesting him to automate the test Sam designed, built and patented the first automated device for these types of immunoassays and gave the biographer a working model! (Patent number 3,951,605 Instrument for Automated Immuno-Chemical Analysis filed 7/8/74 and issued 4/20/76.) As with all methods the lifetime of the test tube solid phase assays were limited. They were replaced by microtiter plastic trays, which held 96 wells. These in turn have been partially replaced with plates which hold several hundred or several thousand wells. His comments about methodology only being transient still hold true.

Another of his thoughts on patents was that the purpose of a patent was to allow the inventor to work on it. That is instead of thinking about the patent as a method of preventing people from using your idea, it was a method of allowing the inventor to further develop it.

Chapter 12: Up Close and Personal

Zoo Consulting. Ethan Natelson writes:

My father had a great love of zoos and animals and was always associated with them, from the Bronx Zoo in New York to the Lincoln Park Zoo in Chicago. He would establish the normal ranges for animal chemistries for the vets at the zoo. It was this relationship that allowed him to establish that the cause for blindness in certain Siberian tigers was consequent to an unusual form of galactosemia which caused premature cataracts and could be totally prevented by a slight change in diet.

The Chicago Zoo had some Siberian tigers who developed cataracts and asked Sam for help. Sam reasoned that the cataracts could be due to a genetic defect due to the inbreeding. This was similar to a genetic defect in humans. Sam then did a number of experiments showing in fact that there was defect in the metabolism of galactose due to low levels of one of the enzymes in the pathway.

What is remarkable about this work is that Sam did not have a laboratory experienced in testing for genetic defects. He simply set up all the required assays to test his hypotheses about galactose metabolism in cats. Knowing how much effort it takes to set up assays, I am to this day impressed with his work.

His logic in searching for the genetic defect in cats is described in the subsequent paragraphs taken from his Clinical Chemistry paper. Rabinow, B.E., Wong, P.W.K., Maschgan, E.R. and Natelson, S. Screening for errors in Galactose Metabolism with the erythrocyte. Clin. Chem. 22: 2010-2017 (1976)

> The problem of screening for genetic defects is complicated by the many different enzyme activities one would be required to determine in order to assay for the numerous reported deficiencies (1). In addition, the returns are small for the amount of time invested, because of the relatively low prevalence of a particular defect. For this reason, many institutions limit their programs to one particular enzyme or metabolite. An example of this is the phenylketoniuria screening program.
> A more efficient approach would be to exploit the interdependence of enzymatic pathways. Thus, a single screening procedure could be used to test the integrity of an entire metabolic system, which would eliminate further sturdy of the vast majority of specimens and so would focus on a few aberrations that require more specific identification.
> For these reasons, we decided to explore the overall metabolism of galactose and glucose by the ertythrocyte (2,3), the strategy being that if glucose was metabolized normally while galactose was not, then one was necessarily dealing with a case of galactosemia. This finding could be caused by a deficiency of anyone of three enzymes: galactokinase (EC

2.7.1.6), galactose-1-phosphate uridylyltransferase (EC 2.7.7.10) or UDP glucose 4-epimerase (EC 5.1.3.2) (4). In this case, the defect could be pinpointed by measuring the activities of these enzymes. Relatively few clinical assays would then need to be done on a given case.
If glucose were not being metabolized normally, then one would be prompted to look elsewhere. By judicious use of the short common screening procedures, such as for glucose-6-phosphate dehydrogenase (EC 1.1.1.49) or pyruvate kinase (EC2.7.1.40), one could then identify most of the problems. The others would then be the subject of further study. *In all of these cases it would be ascertained first that a defect did in fact exist, making the detailed studies fruitful.*

Discussion
Three types of galactosemia have been reported (12), corresponding to deficiencies in one of the three enzymes: galactokinase (ATP:D-galactose 1-phosphotransferase, EC 2.7.1.6) (13), hexose-1-phosphate uridylyltransferase (UDP glucose: α-D-galactose-1-phosphate uridylyltransferase, EC 2.7.7.12) (14), or UDP glucose 4-epimerase (EC 5.1.3.2) (15). Figure 1 shows the interdependence of these enzymes.

The screening test for the galactosemias proposed in this paper examines the integrity of the system from galactose to 6-phosphogluconate formation and decarboxylation, by measuring the end product of metabolism, carbon dioxide. “

Analysis of the data obtained from samples of blood from the cats shows very low values of galactose metabolism when whole erythrocytes were used to generate CO_2. In the case of the lions, this metabolism is much lower than would be expected from the appreciable activity of galactokinase and hexose-1-phosphate uridylyltransferase found from tests performed on hemolysates. It is important to note that the assay for transferase activity depends on adequate enzyme activity of UDPglucose 4-epimerase, phosphoglucomutase, glucose-6-phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase. The fact that appreciable transferase activity was found shows that, in addition, a metabolic block did not exist in those enzymes in the erythrocytes of the lions.
One must conclude, therefore, that the ability of galactose to permeate the membrane of the erythrocyte of the lion is blocked.

As can be seen from the above paragraphs his logic is exceptional. How to find a mutation in metabolism when there are many possible ones and when the mutation is not known? By examining the overall metabolism he was able to focus on the most likely affected pathway.

The end result of this work is that he identified a new mutation in galactose metabolism. The cure for blindness in these animals was simple. They were given milk formulas and diets free of galactose

Children: Ethan Natelson writes

> My father loved children and had the knack for bringing out their personalities by taking them to the zoo, to baseball games, out hunting where he served as the bird dog, to swimming lessons etc. He always would round up the neighborhood children, especially seeking out those with absentee parents, and take them to see the Rockford Peaches (immortalized in the movie, "A League of Their Own") play baseball. His green, 1949, Mercury was always loaded with my classmates on the way to school, or other events." He was appointed to the school board in Rockford, Illinois and rapidly became a force in designing land acquisitions for the local public schools to include adequate areas for athletic fields, as well as pushing salary increases for teachers.
>
> **His Curse**: My father described "his curse" as an unnatural ability to view problems and their potential solutions entirely differently than most people and then to have the uncontrollable urge to prove his conclusions by some type of experimentation. A typical example was his sudden realization that the standard test tube was actually the wrong shape. Instead of a cylinder requiring a holding rack, it should be in the shape of an Erlenmeyer flask, so that it could stand alone, and additionally could be centrifuged on its axis, requiring very little force, compared with a typical centrifuge. To prove this concept, he designed and patented a test tube made in this design. He then built a centrifuge that looked like a small cabinet and, remarkably, could be continuously loaded and unloaded with these unusual test tubes, while it was running. Because of the design of the test tube, somewhat similar to the Haemonetics plasmaphoresis bowl, the red blood cells sedimented immediately, making it easy to aspirate the clear plasma. Had the company he assigned this invention to (Rhohe Scientific) been better in engineering and in marketing, we might have had a paradigm shift in test tubes and centrifuges.

On reviewing scientific papers: Sam was a reviewer for several scientific journals. One day he stated that he was reviewing a paper that was terrible. I asked him if he was going to recommend rejection. His comment was that he never rejected a paper. His review would describe how the authors could improve their work. He felt that it was wrong to reject a paper, that since the authors had put so much time and effort into the work, they should be encouraged not discouraged.

On writing prefaces for his books: Sam felt that the preface should be written so that the reviewer of the book did not have to read the entire book to write the review. The preface should be descriptive enough that the reviewer could crib enough to write a positive review.

Personal glimpses: Sam's personality was aggressive, but he cared deeply for people. His efforts to save children are just one manifestation of his deeply held caring nature. Since it is hard to describe him, I will quote here my own and other people's observations.

From Tom Puckett

I was Sam's research assistant on the NASA grant looking into developing instrumentation and chemistry methodology for use in a weightless environment. We finished the project in 1969 and saw the results of our labor in the space lab program. I had a lab on the 7th floor of Dreyfus and another on the 3rd flood of the adjacent building. But most importantly, this was my first real job following graduation from college. I met Sam during the Christmas holidays, 1967 while I was in Chicago visiting my wife Judy's family. I knew I was graduating in February and needed a job. I stopped into the lab unannounced and by chance met Sam. We talked for 10 minutes and he offered me a job. I subsequently wrote him a letter, realizing that I had not prepared an application, or anything, and stating I needed a place to live and could he recommend something. When I arrived in February, 1968, he had procured me an apartment at Prairie Shores and set up my lab. A real man of his word. No formality, no false promises, no paperwork. Just did it!

Sam and I often would disappear on a sunny summer afternoon for a visit to Wrigley Field, where I would be treated to more information about baseball that I could ever comprehend nor remember. But, his professional and personal influence on my life was most significant. My wife and I loved him and his wife, and exchanges gifts and many hours of delightful conversation. I have many antidotes that Sam left us with that had changes our lives forever and for the best. Not only did Sam teach me everything I know about Clinical Chemistry, he taught me about life, professionalism, good (and bad) business practices, children, and the meaning of friendship and mentoring.

I was drafted into the Army in 1969 and Sam was very concerned about my safety and expressed himself in ways that the old gruff Natelson has not been know for in the past. I remained in contact throughout my military service and on leaves was able to visit him. Bob Murray, Brian Levin, David Johnson, Peter Haux, Shigeko Nakanishi, Kehaichiro Takahara, and many others remain in my mind as touched by this great man.

Cigars, spittel, and Natelsonisms, fill my memories today. Here are just a few:

- Cigars: for Christmas, 1968, Sam gave me a white shirt to replace the

one he practically set on fire with his up-close-and-personal tirade on politics.

- Intelligence: Sam liked catching people in the laboratory off-guard. He would impromptu-to give you an intelligence test. If you were technically oriented it may have something to do with Chemistry, but, if you were not, it would have to do with world events. My wife told me Sam caught her off-guard once with "What do you think of BUSING?" Fortunately, Judy passed by giving an answer that Sam agreed with! It pays to be married to a school teacher.

- Baseball: There wasn't anything that Sam didn't know about baseball...or, at least, could convince you he did. Our many sunny afternoons in Wrigley Field were always educational and embarrassing with the yelling of "YOU'RE A BUM".

- Social Unrest: Because Judy and I lived in Prairie Shores, Sam was concerned about our safety during the unrest following Dr. King's death. He would encourage us not to leave our apartment and have young people from the neighborhood bring us food.

- Diversity: I believe there were over 20 countries represented within the Dept. of Biochemistry at Michael Reese in '68-'69. Sam loved the stories and the conversations with people, professionals of varied backgrounds. It made us enriched!"

From Don and Flo Forman

Thanks for recalling my visit to Sam's lab in Roosevelt Hospital in NYC in December 1961 to discuss X-Ray fluorescence spectrometry, its value and applications. I had joined Mercy Medical Center and Northwestern Univ. Med School, Chicago IL in 1960 and we were considering buying the instrument. We did purchase the equipment shortly afterwards and studied intracellular iron in cultured mammalian cells using x-ray fluorescence analysis (published: Fed. Proc. Soc., 22:372, 1963). The power supply (Phillips) was balky at times but I had Sam's solution to keep us operational.

In Fall 1974-Winter1975 the Chicago Section of American Chemical Society and Chicago Section of AACC organized a lecture series held at Northwestern University Medical School as part of a continuing education program for clinical chemists, biochemists, and pathologists. It was the first volume in the ACS Symposium Series to be sponsored by a local section of ACS as well as local section of AACC. I helped organize the program and Sam and Ed Bermes, Harry Weisberg, were on the

Committee to enable the presentations. A book "Clinical Chemistry", ACS Symposium Series No. # 36 was published in 1976 by Amer Chem. Soc. (see attachment).

I joined the Dept. of Pathology and Laboratory Medicine at Univ. of North Carolina as professor and director of clinical chemistry in November 1978 and I invited Sam to UNC to present a seminar in Sept. 1979 for Path and Lab Med. Sam spoke on clinical biochem of epilepsy and calcium and citrate metabolism. A unique presentation that was mind bending.

A final anecdote: My wife Florence and I stayed with the Natelson's in Knoxville in September of 1980. We wanted to visit the World's Fair in Knoxville and looked forward to being with Sam and Ethel.

They went out of their way to make us comfortable. Sam was very proud of his garden as I recall and was treating his plants with a variety of trace metals to improve their growth. He also liked to cook, especially breakfast. He made French toast one morning and I can still hear him saying "no, no Ethel, that's not the way to do it!" His way was to use the thickest piece of bread possible, dipped in egg and fried. This was French toast Natelson style.
Just like his life it was big and his own way.

Sam loved to talk and his conversation centered on his children and his work.
When we left to go to the fair, Sam gave us detailed directions so that we would not get lost and also find our way back.

That was Sam, a man of direction who found his way in life for himself and others.

From Barrett Rabinow

This is a trip down memory lane. I entered Sam's program, after I had completed a Ph.D. in physical organic chemistry at the University of Chicago. After this intensive but narrowly focused experience, I was looking for something more related to healthcare and contiguous with a large breadth of other disciplines. Clinical chemistry met this goal, and I was fortunate to have Sam's program in my backyard. I entered his program around March 1975.

My first meeting with him exposed me to the whirlwind of activity that was his life. I remember sitting in his office, staring at the red, white, and blue guppies, vaguely aware of his carrying out three conversations simultaneously: one with one of his post-docs, another with Gary(?) the

medtech in charge of the lab, and his biophysics engineer, who was designing another gadget involving a bicycle chain driven lucite block impregnated with holes to accommodate Natelson capillary tubes for the automatic determination of CO2. I thought to myself, Yes!, this is the kind of atmosphere that was vibrant, vital, that I was looking for, after having been sequestered in a graduate student program at the U. of C.

In the subsequent months, Sam's influence was infectious. There was the meeting with Dr. Swerdlow, the Pathologist, and Sam's boss, whom Sam depicted as Darth Vader. We went to see him in his office. I admired a large wagon wheel, mounted on the wall behind his desk. There were the names of the different clinical labs etched into the spokes: clinical chemistry, hematology, microbiology, radiology, endocrinology, etc. They all pointed to the hub, presumbably the queen of these disciplines, upon which was engraved, Autopsy. Afterwards, as we were leaving, Natelson whispered confidentially to me,
"Do you see now how venal the man is? What kind of a person who has that kind of training and could make an impact on the lives of healthy people would consider autopsy as the most esteemed field of study?"

There was the profusion of inventions designed for the clinical lab: Natelson capillary tube, jet clamp, vortex shaker, amidst a host of others in other disciplines, such as polyethylene and freeze-dried coffee. Freeze-dried coffee?, I exclaimed. You must be making a fortune from that!
"NO", he answered, "The bastards stole it from me. All of the coffee companies knew that I had something great here, but didn't want to share the profits with me. So they just started producing it, cutting me out." "But couldn't you sue them?", I gasped.

"Sure, sure, I'd hire a lawyer, a number of them, and they would just be bought off by the large companies. There was no way I could compete," he explained.

We would get into discussions about all sorts of things, most of which are probably unprintable in our current age of tolerance to diversity. But, coming from the atmosphere of intellectual arrogance at the U. of Chicago, I didn't think there was anything strange. He would talk about the shapes of people's earlobes, and what this indicated about their ancestry. He would go up to the lab techs, with me in tow, and point out and fondle their earlobes, pointing out which were Caucasian, and which indicated a distant Mongolian heritage.

His research projects were well thought out, practical, and guaranteed to result in publications. I was fascinated by the conversion process I underwent from a physical organic chemist to a clinical chemist.

Measuring the CO2 liberation from red cells of tigers anesthetized at the Lincoln Park Zoo, we found an inborn error of galactose metabolism. This resulted in a publication as we profiled a number of the members of the cat family with regard to their sugar metabolism. We surmised that the reason for the cataracts found in the eyes of the Siberian tiger was that they were fed milk at the zoo, which was a major problem since they had complete red cell deficiency of galactose. Six months after we published, I got a call from some entrepreneur in Wyoming, who thanked me profusely. I was happy, but inquired , Why?

"Well, you see, it's like this. I started a shooting farm, where folks could go in on horseback and shoot wolves. I bred the wolves. Trouble is I was feeding them milk, and couldn't figure out why they wouldn't grow. But after I read your article about the reduced galactose content in breast milk of carnivores, it put me on the right track. Now I've got a thriving business!"

"Oh great," I shuddered.

I asked Sam about his homelife, and were there any problems because he spent so much time at work. He said the best thing you could do for your kids is to show them a good role-model for fanatical involvement in work.

From John Sherwin

Dr. Natelson was a true mentor and it is through his training and support that I have been successful as a Clinical Chemist. I remember my interview
with him for my training position very vividly. He told me by telephone to
meet him at his office at 10:00 Saturday morning. We met and I was prepared
with all sorts of potential responses to probing questions. He looked a my CV and asked if I liked his fish in the aquarium. I indicated that yes they seemed quite nice. He then asked "when can you start?" I began 2 weeks later as the first Clinical Chemist trainee under the AACC program of interest free loans to postdoctoral trainees.

From Peter Haux

I can't even claim to have left Germany because I wanted to work with the renowned SN. I joined his staff through mediation of Peter Jungblut (who had tutored part of my thesis and spent a few years at the Universitiy of Chicago in hormone receptor research), initially to do **bio**chemistry but got redirected by SN to **clinical** chemistry. It is to SN's merit that I never regretted it. He had such a talent to "sell" the field and to explain complicated circumstances that I thought: this is all that easy, crystal clear,

> interesting and a rewarding job. It wasn't quite that simple as I found out, but yet worthwhile to pursue it.
>
> *I remembered that everybody* got a Christmas present, *every* year... kind of nice, wasn't it?!
> At times he wanted to chat and if he addressed you, you had no chance to escape. Once I (others tried the same trick also in vain) fled to the toilet but he was undeterred and simply followed and continued the conversation standing in the door frame.
> Others are even less kosher or not so nice: every so often I had to remind him to close the fly when he came from the toilet his mind always focused on less banal things.
> Or that we used to follow the fresh coffee spots on the floor to track him down.
> ...or that he called his wife "a pest" not caring who else might hear it, she, who combed the libraries for so many hours for his papers.
> ...or that he taught his son - I believe it was Ethan - a thorough lesson: he caught his playful son jumping from the table a couple of times then - without any warning - backed up and the kid fell to the floor. His comment: "you must learn to never trust anybody not even your own father". Maybe this was not true, just well invented!
> I recall also that employees calling in sick were all "liars and pretenders". But he himself never had a simple flue or a plain headache; he suffered from pneumonia or observed symptoms of a brain tumor.
> He could be really funny, too: each and every German had to go through this: "let me explain to you" - one of his favorite opening sentence - "why Mercedes is a bad car...." It had not the slightest bearing whether you cared for cars at all, you got your treat...

Biographer's Comments
Sam described himself as being different from other people in the following ways.

> When I was a child in one of my classes the teacher showed a picture and asked what it was. The class responded that it was a mouse. I said it was a rat. I was right.

In many ways this is an accurate self-assessment. He always though differently than the mob. The current phrase is "out of the box" thinking. He would focus on political issues and make you think about ideas that were truly different. He was in many ways a very conservative politically. He once explained his dislike for socialists (in this case the Democratic party) in the following way.

> Conservatives try to keep things as they are, following the laws, etc. Liberals try to change the laws. The courts, such as the Supreme Court, have a role to defend the laws not to break them. Now a socialist party is

the greatest threat to a democracy. The best example is Hitler. What was the name of Hitler's party – The National "Socialist" party.

That is why he was so against socialists.

Notable Quotes

"If a physician has a choice between saving face and saving the patient, he always saves face."

"One incorrect concept held by physicians is that bicarbonate is a buffer in the body. This is not true. The pKa of carbonic acid is three logarithms from the body's pH of 7.4."

When reviewing a paper: "I do not reject a paper, I tell the author how to improve it. If a person has put in a lot of work they should not be rejected."

"The champion knows he is the champion."

"The patient has the right to a qualified chemist."

Chapter 13 Epilog:
Part 1

Web Citations

The biographer was trying to put together some concepts of Sam Natelson's legacy. In the year 2003, one of the ways to do that is to search the Web. A Google search turned up several interesting items. The first one displayed here is the Samuel Natelson Senior Investigator Award. This as discussed in the biography was to honor the founder of the Chicago Section of the AACC. What surprised the biographer was the number of prominent scientists who have won this award and have proudly listed it on their Web biographies.
The description is from the AACC website.

Chicago	Samuel Natelson Senior Investigator Award	Significant body of work for career; must have scientific impact on profession.	$500 and an engraved plaque; sponsored by Instrumenta-ion Laboratories	3/15	Must be nominated by a Chicago section member; contact Section Chair Jack A. Maggiore, PhD, jmaggiore@ebiosafe.com, phone

Another item about Sam appeared in the Microchemical Society History.
http://www.microchem.org/History.html

"So the 1960 Symposium was the last of the independent microchemical symposia of the Society except for a special one on April 18, 1963 to honor Dr. Donald D. Van Slyke on his 80th birthday. Speakers were Dole and Kirk, with panel discussions on the uses of the Van Slyke apparatus, including microanalysis led by Steyermark, medical research lead by Sendroy, and clinical analysis lead by Natelson. The Symposium was well attended and one of the most successful ever held by the Society".

Sam Meites wrote about Sam Natelson's impact in his "History of Clinical Chemistry in a Children's Hospital (1914–1964)" describes Dr. Natelson's impact.

http://www.clinchem.org/cgi/content/full/46/7/1009

"The Department of Laboratory Medicine in 1954 consisted of perhaps 25 personnel. Two technologists manned my chemistry/urinalysis laboratory. Although blood chemistry in the United States was making much progress in this era, it was, as mentioned, unintentionally oriented toward adults. Although Bang in the World War I period and Natelson, particularly in the early post-World War II years (3)(4)(5)(6), had published on the use of ultramicro blood samples, much of the methodology was very "labor-intensive" and arguably impractical to meet the large, ever-increasing demands of a 220-bed children's hospital. Natelson's microgasometer, however, was a blessing, and his systematic approach to ultramicro chemical analysis and instrumentation was a model to

be emulated by anyone entering the pediatric field, including the manufacturers of products for clinical chemistry. The pressing need remained to avoid venipuncture of newborns and infants because almost all of these patients were receiving intravenous therapy and their few venous or arterial sites were sacrosanct for that purpose."

Another citation that turned up was the use of the microgasometer as a method for CO_2 analysis in a scientific journal article published in 2001. It shows that Sam's designs were sturdy.

Trying to correct the record

The biographer tried to publish a correction article on the 50th Anniversary of the Quarterly Review of Pediatrics which discredited Sam's publication the "Immature Infant". The Journal of Pediatrics turned it down. Clinical Chemistry also rejected the article. The argument of the latter reviewer was that the pediatricians were only attacking the use of DOCA. The biographer disagrees with that assessment. The articles of the foremost pediatrician of the time who Sam refers to in his 1992 presentation (Dr. Stewart H. Clifford) dealt with anoxia, and not with electrolyte balance. Part of the problem was that Sam was the only one who could measure electrolytes.

The biographer reviewed the following articles by Dr. Clifford:

Clifford SH, Care of the Newborn New England Journal of Medicine 240:61-67 1949
Clifford SH, Role of the pediatrician in prevention of needless neonatal deaths. Journal of the American Medical Association 153: 473-476 1953
Clifford SH, Diarrhea of the newborn: Its causes and prevention. New England Journal of Medicine 237: 969-976 1947
Clifford SH, Management of emergencies. American Journal of Diseases of Children 73: 706-712 1947.

The article which most clearly describes the medical bias that Sam had to work against was summarized in this article.
Clifford SH, Fetal anoxia at birth and cyanosis of the newborn: Differential diagnosis and management. American Journal of Diseases of Children 76: 666-678 1948.

Excerpt from page 677 (italics mine)
"To summarize the treatment of neonatal asphyxia: the first rule is to clear the airways; the second is to provide oxygen. The third is to keep the baby warm, and *the fourth rule is to withhold the administration of all food and fluids in the presence of edema. To offer added fluid to an already waterlogged baby may increase the existing pulmonary or cerebral edema to fatal proportions*."

It is clear that Clifford fostered the concept that the premature infant was edematous. His treatment of no fluids was wrong and to the mind of this biographer was responsible for the deaths of tens of thousands of premature babies.

The people legacy

Another way to judge Sam's legacy is to follow the careers of the people he trained. As you will note from the list many became leaders in the field.

Norbert Tietz was influenced by Sam while he was at Rockford Illinois to become a clinical chemist. Norbert published the first comprehensive text on the discipline and this work continues today as the leading text in the field. Norbert published several other influential texts. In addition he held positions as Director of clinical chemistry at Mount Sinai Hospital in Chicago and at the University of Kentucky in Lexington. Norbert also was very active in the AACC and was elected President.

Bernard Century Ph.D. worked as a clinical chemist at Waterberry Connecticut for many years.

Richard Dods Ph.D. is teaching at the Illinois Mathematics and Science Academy.

Peter Haux Ph.D. describes his career. "After Chicago I worked for 4 years at the University of Goettingen in the clinical chemistry lab, than I followed my Goettingen boss to the **University of Heidelberg, Mannheim Campus**, a medical center with over 1.600 beds. It has the third-oldest institute for clinical chemistry in Germany (now nearly 100 years old). The greater part of a working day I spent with management of the routine lab, the rest with research and teaching future medical technologists and medical students. I tried to do it the way SN did it! My papers dealt mostly with methodology and some with clinical topics, as a co-author."

Tony Koller Ph.D. DABCC was one of Sam's assistants at Michael Reese Hospital and practiced Clinical chemistry. He then became Director of Chemistry at Sparrow Health Systems Lansing Michigan

Robert Murray Ph.D., J.D. DABCC was Director of Chemistry at Lutheran General Hospital and also obtained a law degree while working there. He has been very active in both the AACC and NACB serving in a number of offices.

Amadeo J. Pesce Ph.D. DABCC became Professor of Pathology and Laboratory Medicine at the University of Cincinnati. He was Director of the Toxicology Laboratory of University Hospital for many years. He was very active in the Ohio Valley Section of the AACC serving in various offices including Section Chair. At the AACC national level he was Chair of the House of Delegates. He was also a member of the Board of Directors of the American Board of Clinical Chemistry and served as President of the Board. (The ABCC is the certifying board for clinical chemists.) He also served on the Board of Directors of the NACB and was its first newsletter editor. Dr. Pesce published or edited a number of texts in clinical chemistry.

Donald Pochopien Ph.D., J.D. worked for several years as a clinical chemist, earned a law degree and became a patent attorney at a Chicago law firm, McAndrews, Held & Malloy, Ltd.

Barrett E. Rabinow, Ph.D. is Senior Director, Strategic Technical Development Medication Delivery Baxter Healthcare Corporation.

Masahide Sasaki M.D., Ph.D. Worked with Sam at Michael Reese Hospital in the early 1970's. He became Professor at the Kochi Medical School Clinical Laboratory Medicine Oko-cho Nankoku City Kochi 783-8505 Japan.

Dr. Sasaki is credited with developing the first automated clinical laboratory system in the 1980s. This work is the foundation for many of the current robotics systems now in place worldwide. (Reference Clinical and Diagnostic Laboratory Immunology, May 1999, p. 293-294, Vol. 6, No. 3)

John Sherwin Ph.D. DABCC was Director of Pediatric Laboratories at Michael Reese Hospital in Chicago, the Director of Clinical Chemistry at Valley Children's Hospital in Fresno, California, Technical Director and General Manager of Damon Reference Laboratory in Newbury Park, California. He is currently the Director of the Genetic Disease
Laboratories for the State of California. He is very active in the profession of clinical chemistry serving in many offices including the Board of Directors and President of the National Academy of Clinical Biochemistry. He has been the secretary, program chair and chairman of the
Northern California Section of the AACC. He served as councilor for the section and has been a member of the House Steering Committee and as such was an ex officio member of the AACC board of directors.

Arnold Schultz Ph.D. served as the clinical chemist at the Veterans Administration Hospital in Denver Colorado.

Dr. Kihachiro Takahara had both MD and PhD degrees. Most of his career was spent on the PhD side. He was Director of Clinical Laboratories, Japan Monopoly Corporation, Hospital of Tokyo, Tokyo, Japan. Later became involved with clinical research studies at Japan's Sano Surgical Clinic. He is essentially retired from the private sector, but has a title of School Physician and Instructor at the Daitoh Bunnka University, in Tokyo.

Arthur Tomisek Ph.D. worked for a number of years at Michael Reece Hospital.

William Vorkink Ph.D. worked in Alaska as a clinical chemist. His subsequent career is lost to follow up.

Myron Warshaw Ph.D. DABCC was the Director of Chemistry for West Suburban Hospital near Chicago Illinois for thirty years. He was very active in the profession of clinical chemistry, particularly in the National Academy of Clinical Biochemistry serving in many offices and also as its President.

Larry Webb Ph.D. worked for a number of years at Baxter Laboratories.

Michael Winkler Ph.D. is Professor of Chemistry at Illinois Benedictine University in Lisle, IL

Epilog: Part 2

Dr. Samuel R. Natelson died March 31, 2001, in his ninety-third year. He was the last surviving founder of the American Association for Clinical Chemistry, a founder of the National Academy of Clinical Biochemistry and a pioneer in the field of Clinical Chemistry.

Sam's wife Ethel preceded him in death, in 1998. He is survived by his children; Dr. Stephen E. Natelson, Dr. Ethan A. Natelson, Dr. Elissa R. Allen, and Nina Natelson-Cohen. A brother, two sisters, and seven grandchildren also survive him.

For his grandchildren Sam wrote a number of short stories, (The Editor has these in electronic form) exhibiting even more of his many talents.

In addition to the estimated million children that he saved, Sam lives on in the work of his students and their students.

Appendix prepared by Samuel R. Natelson

Samuel Natelson Ph.D.

Career Development

1928-1931 Sc.M. and Ph.D. conferred 3 yrs. after entering graduate school. Published 5 papers during those 3 yrs.

Condensation of alkyl phenols with diisobutylene (Ph.D.) thesis resulted in the commercial production of octyl phenol, one of the largest bulk chemicals produced today. (Ph.D. *thesis* and ref. 9). A major base for the commercial detergents is octyl phenol.

Practical synthesis of rose oil (phenyl ethyl alcohol) from ethylene oxide and benzene. This is the manner in which rose oil is produced commercially. (ref. 6).

Developed a theory of free hanging drops in capillaries resulting in a practical instrument for measuring surface tension. (Ref. 5).

1931-1932 Self-employed, at the New York Testing Laboratories, as a consulting chemist to the chemical industry. Developed a process for manufacturing styrene resins by devising a practical procedure for making ethyl benzene from ethylene and benzene. Dow Chemical Co. chemists, writing in Industrial and Eng. News, cite these papers as being of major significance in the development of their plant for making styrene resins. This paper was nominated as one of the most significant papers published in Ind. and Eng. Chemistry Journal in the first 50 years of the 20th century, by the Am. Chem. Soc. (ref. 10, 11)

1932-1938 Moved to the Jewish Hospital of Brooklyn to carry on research problems related to the preparation of Vitamin D. Developed a process for irradiation of ergosterol and dehydrocholesterol to make vitamin D. Developed assay methods for cholesterol assay. Developed a process for the manufacture of cholesterol from wool grease. This is of major significance today. (Ref. 13, 14, 19, 24, 29).

1938-1939 Ventured into industrial field of employ, at Endo Products. Developed method for manufacture of the diethyl amide of nicotinic acid (Coramine, Nikethamide).

1939-1942 Organized a company to make fine organics, such as semicarbazide, phenyl and butyl urea, uric acid, sodium nitroprusside and others.

1942-194~ Returned to academia, dissatisfied with the industrial field, to continued work on the synthesis of biologically important compounds. Developed methods useful in the synthesis of steroids, alkaloids and related compounds (25-32).

Carried out a project for the production of radio-opaque substances (iodinated compounds) for the visualization of body organs (Ref. 34-36, 56).

1946-1949 In 1946, was asked to supervise the chemistry laboratory at the 3ewish Hospital of Brooklyn, where certain problems had developed. This marked my entry totally into the field of clinical chemistry. With this position, was also appointed as a lecturer in biochemistry at the then Long Island School of Medicine (now Downstate Medical School of New York).

With Drs. Benjamin Kramer and Joseph B. Pincus, two leading pediatricians, studies were initiated on the biochemistry of the newborn infant.

Studied the problem of carbohydrate utilization in the infant and discovered that lactose needed to be hydrolyzed prior to its absorption. Thus lactose is well absorbed and metabolized from human milk, or raw cow's milk, but is not well utilized from pasteurized milk. This set a rational basis for the utilization of partially hydrolyzed starch (Dextri-maltose) instead of lactose in infant feeding formulas (Ref. 40, 48).

Studied convulsions in infants. This led to the study of convulsions in epileptics. Observation of abnormal metabolism of glucose and citrate in these infants led to a study of citrate metabolism (Ref. 38, 339, 41, 44, 45, 49).

Developed several procedures for utilization in the routine laboratory (Ref. 37, 38, 50, 52).

Studies with citrate led naturally to the study of changes of Ca levels with citrate levels. This led to the discovery of factors in the pituitary which lower serum Ca levels. In rabbits, this could cause convulsions. These polypeptides, first discovered in 1949, have now been identified as calcitonin, which lowers Ca and citrate levels, alpha MSH, Beta MSH and ACTH which lower Ca levels, and raise citrate serum levels. These latter three polvpeptides have a 7 amino acid sequence in common (60). This discovery was discounted until 1968 when calcitonin was found to he secreted by pituitary tumors.

1949-1958 Moved to Rockford, Illinois to set up a study of the premature infant. This

was partly motivated by the fact that these infants had a tendency to convulse, in the way that they were managed at that time. Introduced techniques for assay of minute amounts of blood, including the microgasometer, flame photometer and others. Demonstrated the adverse effects of high protein milks on premature infants, resulting in a revolution in the composition of infant formulas. This was summarized in the text, Immature Infant and the book, Microtechniques of Clinical Chemistry. At several pediatric meetings, I have been introduced as the "Architect of the Neonatology Laboratory." (Ref. 61-64; 66-68, 71, 72, 75-82).These studies made the Clinical Chemical Laboratory a focal point in the management of the premature infant. It also stimulated the development of Pediatric Laboratories and the development of the specialty of Neonotology.

During this period, defined the High Salt Syndrome as a definite syndrome, distinctive from dehydration. First discovered this syndrome in 1937. In these studies and the pediatric studies above, used what is now called "hyper-alimentation" in maintaining patients on l.V. fluids, extending for several months (Ref. 64, 70, 73).

1958-1965 Returned to New York City and continued the research on the metabolic background of convulsive disorders with Dr. J.B. Pincus. Confirmed previous observations and separated the pituitary polypeptides for identification (Ref. 103, 104, 115, 116, 120).

Studied X-ray spectormetry as a tool in clinical chemistry and established reference values for Ca, Na, K, Cl, P, Au, Pb, TI, Mg, 1, S, and others by this method. Summarized this work in Vol. XII of Click's, Methods in Biochemistry (Ref. 90-97, 100-102, 107-110).

Invented and developed the multi-tape system of analysis for use in the routine laboratory, space travel and an advanced base army hospital (112, 127, 129). This was invented in 1959, and perfected by 1965. See under list of many patents on this subject. A modified system is now being marketed by the Eastman Kodak Co.

1965-1979 Continued studies of guanidino compounds in mammalian tissue, and established a quanidino cycle paralleling the urea cycle, which reutilizes urea nitrogen in times of starvation (Ref. 125, 128, 130, 137, 139, 142, 144, 146, 148, 150, 152, 160, 166, 169).

Continued studies defining a mechanism for control of Ca concentration, involving ACTH, calcitonin, parathormone, insulin, glucagon, thyronines, and adrenalin through control of citrate concentration (167. 168).

1979-present (1981)

Continue studies on guanidine metabolism, the mechanism of convulsions and development of the Multi-layer System of Analysis.

Teaching Experience

Have taught at every level of education. Hold a license to teach in elementary schools of New York City. Actually taught for 3 months. Hold high school teaching licenses (NYC) in General Science and Chemistry, and have taught in the NYC high schools. Have taught at the University (NYU) undergraduate in organic chemistry for 3 years. Have given courses in graduate schools of chemistry (Brooklyn College and Ill. Inst. Technol.) for many years. Have taught in medical school (Long Island Medical College) and post-graduate medicine (N.Y. Polyclinic Hosp. & Med. School). Have maintained and lectured in a post-doctorate program for Clinical Chemists. Am now located in a Veterinary Medical College. Have given a course in Clinical Biochemistry to the faculty, and am planning a course in Veterinary Clinical Chemistry for the graduate students. In this connection, have acted as a consultant in clinical chemistry at the Lincoln Park Zoo and a chapter, on the chemical findings, in a book on the Biology of the Gorilla is written with the data supplied by my laboratory. Also helped in the organization of the chemistry clinical laboratory at the Lincoln Park Zoo.

Major Achievements (research)

1. Developed practical methods for the manufacture of octyl phenol, rose oil and styrene resins. All of major importance in industry today.

2. Developed method for isolation of cholesterol from wool grease.

3. Laid a rational basis for infant feeding formulas.

4. Demonstrated the importance of the clinical laboratory in the management of the newborn, especially the premature. Devised micro-techniques used in the neonatology laboratory.

5. Discovered the high salt syndrome (neuroqenic hypernatremia and hvperchloremia).

6. Discovered the presence of calcium controlling factors in the pituitary. Elaborated a mechanism for serum Ca control.

7. Discovered and developed the guanidine cycle, and urea N reutilization, which explains survival during prolonged periods of starvation.

8. Invented and developed the multitape system of analysis.

Contributions to Clinical Chemistry

With A.E. Sobel and H. Sobotka conceived and developed the idea of an Association of Clinical Chemists.

Solicited and obtained the Ernst Bischoff award in Clinical Chemistry, to stimulate interest in Clinical Chemistry. (Ernst Bischoff Co. was a client of mine in my consulting practice). This is now the Ames award.

Organized "Standard Methods". This was taken over by Sobotka, and Reiner was made editor of the first volume.

Organized the series, Current Topics, of which Amniotic Fluid is the first volume.

Organized the Chicago Section of the AACC.

Raised 25,000 dollars for the 1st International Congress at the Barbizon Plaza Hotel in NYC.

Played a major role in the organization of Clinical Chemistry as a Journal.

Have trained over 20 Clinical Chemists who are now active in the field, mostly board certified.

A major factor in the organization of the Academy of Clinical Biochemistry.

Influenced the writing of texts in Clinical Chemistry with the book, Micro-techniques of Clinical Chemistry.

At all times, attempted to raise the status of the Clinical Chemist by various means, such as with texts (Applied Clinical Chemistry, 3 vol, Clinical Immunochemistry). In this regard have testified before the various congressional committees, and the National Research Council. Have carried on a campaign to get the NIH to set up a study section labeled Clinical Chemistry. Attempted to get the AACC to support the idea that a Board Certified Clinical Chemist only, should direct a hospital clinical laboratory. When this failed, and when the AACC eliminated the Fellow category for Board Certified members, helped to organize a society made up only of Board Certified Clinical Chemists (National Academy of Clinical Biochemistry). Supported the upgrading of the journal, Clinical Chemistry, by submitting the results of my biochemical research there, rather than to other journals. Served on many occasions as a referee in reviewing papers. Served on the Beckman Committee, especially in the organization of the Symposium on Aging.

Curriculum Vita

Samuel Natelson Ph.D

EDUCATION:

Degree	Year	Scientific Field	Institution and Location
B.S.	1928	Chemistry	College of the City of N.Y.
SC.M.	1930	Chemistry	New York University
Ph.D.	1931	Chemistry	New York University

HONORS:

SIGMA XI, 1932
Van Slyke Award Medallist 1951
Certified, American Board of Clinical Chemistry, 1953
AMES Award Medallist of the AACC. 1965
Scientific Award of the Ill. Assoc. of Clinical Laboratories,1971
Chicago Section.of the AACC. Award, 1972
Chicago Section of the American.Association for Clinical Chemistry. The Award is now called the Samuel Natelson Award.
Fellow Am. Institute of Chemists
Fellow National Academy of Clinical Chemistry
Fellow N.Y. Academy of Science
New Jersey Section of the AACC Award, 1989
Awards Lectureship, Univ. Cincinnati Medical Center, Feb. 28, 1992

MAJOR RESEARCH INTERESTS:

Application of Chemistry to Synthetic Organic Chemistry
Convulsive Seizures and Ca Metabolism in Pediatrics
Guanidino Compounds in Health and Disease

SCIENTIFIC SOCIETIES:

American Association for Clinical Chemistry
American Chemical Society (50 yr Member),
American Association for the Advancement of Science (50 yr Member)
American Micro Medical Society
American Society of Biological Chemistry
Harvey Society
Illinois Academy of Science
National Academy of Clinical. Biochemistry
New York Academy of Science
SIGMA Xi
Society for Applied Spectroscopy
Society of Experimental Biology and Medicine

PROFESSIONAL EXPERIENCE

1928 - 1931	Teaching Fellow in Chemistry , New York University
1931 - 1932	Research Chemist, New York Testing Laboratories
1932 - 1938	Research Chemist Jewish Hospital of Brooklyn
1938 -1939	Research Chemist Endo Products
1939 -1942	Chief Chemist American Carbazide Co., Manufacturer of Fine Organic Chemicals.
1942 - 1949	Research Chemist Jewish Hospital of Brooklyn
1942 - 1949	Lecturer to Senior Medical Students, Long Island University, Brooklyn, N.Y.
1946 -1949	Lecturer to Graduate Students in Biochemistry at Brooklyn College Graduate School.
1949 - 1957	Chairman Dep't Biochem. Rockford Memorial. Hospital
1957 - 1958	Head, Dep't Biochem. St. Vincnt's Hosp. Of New York
1958 - 1965	Lecturer in Graduate School of Brooklyn College in Advanced Biochemistry
1958 - 1965	Head, Department of Biochemistry, Roosevelt Hospital, New York
1962 - 1965	Lecturer at the Graduate School of Medicine, Polyclinic Hosp, New York
1964 – 1970	Consultant to National Aerospace Administration (NASA). Member of Space Medical Advisory Group (SPANAG)
1965 - 1976	Director, Department of Biochemistry, Michael Reese Hospital and Medical Center, Chicago, Illinois.
1966 - 1978	Lecturer in Graduate School of Chemistry at the Illinois Institute of Technology in Biochemistry
1974 - 1979	Consultant in Clinical Chemistry to Lincoln Park Zoo, Chicago, Ill.
1977 - 1979	Senior Research Chemist at Michael Reese Medical Center in Chicago, Ill.
1980 - 2001	Adjunct Professor, Univ. Tennessee College of Veterinary Medicine, Department of Environmental Practice.

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Natelson, S. Pesce, A.J. & Dietz, A.A., *Clinical Immunochemistry* American Association for Clinical Chemistry Publication, Washinton, D.C., 1978.

JOURNAL PUBLICATIONS

I. New York University

i Mechanism for the rearrangement of desyl amine on treatment with nitrous acid. "Sc. M. Diss.", New York University (1930). 15 pp.

1. Addition of phenols to the ethylenic linkage. Reaction mechanism and synthesis of certain phenolic ethers. J. Am. Chem. Soc.53, 272-7 (1931), J.B. Niederl and S. Natelson.

2. The rearrangement of saturated alkyl phenyl ethers. Synthesis of isopropyl phenol and cresols. J. Am. Chem. Soc. ~, 1~28-34 (1931). J. B. Niederl and S. Natelson.

3. Condensation of unsaturated hydrocarbons with phenols. Mechanism for the condensation of the ethylenic bond with phenols. Ph.D. Dissertation, New York University. April 1, 1931, 13pp.

5. A micromethod for the measurement of surface tension. Jour. Phys. Chem. ~, 1931-34, H. Mouquin and S. Natelson.

6. The action of aliphatic oxides on aromatic compounds. The preparation of substituted dibenzyls. J. Am. Chem. Soc. ~, 3475-9, (1931). RA Smith and S. Natelson.

7. Equilibria forces acting on free drops in irregular capillaries. Mikrochemie, Vol. 12,
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8. The synthesis of diisobutyl mono, di and tn hydroxy phenols. J. Am. Chem. Soc. 55, 2571-5 (1933).

9. Rearrangement of alkyl phenyl ethers on heating at moderate temperature. Synthesis of tertiary amyl, tertiary butyl and diisobutyl phenols. Journal Am. Chem. Soc. 56, 1583-6 (1934). S. Natelson.

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II. New York Testing Laboratories [1931 – 1932]

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III. Jewish Hospital Of Brooklyn [1932-1949]

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15. Salts of ergosteryl sulfate; preparation and antirachitic activity on irradiation in aqueous medium. J. Biol. Chem.105, 761-5 (1934). S. Natelson, A.E. Sobel and B. Kramer.

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IV. Rockford Memorial Hospital [1949 – 1957]

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V. St.Vincents And Roosevelt Hospitals [1958 – 1965]

(Note! In view of the fact that the facilities at these hospitals were inadequate for carrying on a research program, many of the studies were carried out at the Jewish Hospital of Brooklyn.
The numbers continue sequentially with those of Volume I. For review articles only the first pages are shown in the text.)

During this period of time the results of the following projects were published:

- Several review articles were written for the Microchemical Journal on the progress in microchemistry as applied to biochemical investigations.
- X-ray spectrometry was explored as a tool for the analysis of various biochemical systems,
- Guanidino-succinic acid was discovered in the urine of uremic patients and this led to the
- discovery of a “guanidino cycle” which accounted for an alternate mechanism of nitrogen metabolism.
- The observation that polypeptides from the pituitary, especially ACTH. were responsible for a rise in blood citrate levels accompanied by a sharp drop in calcium levels in the rabbit resulting in convulsions, was explored further.
- A cooperative study was begun with the National Aeronautics Space Administration (NASA) as a member of the **“**Ad Hoc Space Medicine Advisory Group” in connection with the proposed flight into space. This included the development of a suitable method for blood chemical analysis in space.

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VI. Michael Reese Medical Center (1965 – 1979)

At Michael Reese Medical Center concentrated on the following activities:

- Carried out a training program and trained eight chemists who had specialized in other fields to become Clinical Chemists, with a grant from the N.I.H.
- Edited two books, Clinical Immunochemistry and Amniotic Fluids after holding symposia on these topics.
- With E.A. Natelson wrote 3 volumes of Applied Clinical Chemistry.
- Revised Microtechniques of Clinical Chemistry.
- Worked out a mechanism for convulsions observed in idiopathic epileptics, relating this to citrate and Ca metabolism.
- Worked out the "Guanidine Cycle" and explained re-utilization of nitrogen in starvation.
- Developed numerous methods and instruments for, operation in the routine laboratory.
- Collaborated with the Lincoln Park Zoo on the Clinical Chemistry of animals. Discovered a new type of galactosemia in tigers.

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VII. University Of Tennessee College Of Veterinary Medicine (1980-2001)

- At the University of Tennessee concentrated on the chemistry of canavanine and related products and their potential use as anti-tumor agents.

- In the study of the origin of canavanine discovered the lactam of homoserine as a ready material for the formation of homoserine hydroxamic acid. Suggested its function as a carrier of hydroxyl amine.

- With E.A. Natelson demonstrated the hydroxamic acid of homoserine as an antitumor agent vs human tumors in nude mice.

- Also discovered that stimulation of the growth of tumors with mitogens makes them more susceptible to the action of antitumor agents particularly when attacking the ribonucleotide reductase system.

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U.S. PATENTS

Sam dedicated the Volume II of his works to George Bernard Oujevolk, Patent Attorney, "whose skill in writing and obtaining patents is unequaled. He is the patent attorney of record for most of these patents."

This volume is devoted to a listing of the 48 U.S. patents Sam accumulated during his career. The fact that Sam held 48 patents was impressive both in terms of the numbers and the range of inventions. These include everything from freeze-dried coffee to measuring chemistries in an orbiting laboratory.

	Patent #	**Title**	**Filing Date**	**Issue Date**
1)	2,054,438	Surface Tension Measuring Device	7/2/35	9/15/36
2)	2,112,242	Activating Provitamins	3/13/36	3/29/38
3)	2,220,114	Method for Isolating Cholesterol		11/5/41
4)	2,295,600	The Preparation of Pyrrolidone Carboxylic Acids and Their Esters and Products Thereof	5/19/39	9/15/42
5)	2,400,433	Organic Acids (Radio-opaques)	2/18/40	5/14/46
6)	2,431,496	Coffee Powder (Freeze Dried Coffee)		11/25/47
7)	2,496,064	2, 5 Diiodo-4-Hydroxy Phenyl Cyclohexane Carboxylic Acids		1/13/50
8)	2,587,556	Apparatus for Preparing Coffee Concentrate in Continuous Operation		2/6/52
9)	2,680,060	Ultramicro Gasometer for Determining Gases in Body Fluids		6/1/54
10)	2,685,800	Pipet for Microanalysis of Blood		8/10/54
11)	2,765,955	Universal Automatic Titrator	10/19/53	10/9/56
12)	2,866,938	Vacuum Tube Voltmeter	3/9/55	12/30/58
13)	3,036,893	Automatic Chemical Analyzer	3/14/60	5/29/62
14)	3,133,009	Antidromic Electrophoresis	11/13/59	5/12/64
15)	3,171,722	Gas Extractor and Ejector for Gas Chromatography	9/4/62	3/2/65

16)	3,192,990	Film Type Liquid Concentration Apparatus	9/4/62	7/6/65
17)	3,216,804	Automatic Chemical Analyzer and Sample Dispenser	1/31/62	11/9/65
18)	3,219,416	Apparatus for Automatic Sequential Treatment and Analysis of Small Quantities of Material	10/31/62	11/23/65
19)	3,245,152	Tray Lyophilization Apparatus	5/12/54	4/12/66
20)	3,260,413	Automatic Chemical Analyzer	8/21/64	7/12/66
21)	3,261,668	Chemical Analyzer Tape	8/14/62	7/19/66
22)	3,293,772	Tray Lyophilization Apparatus	10/4/65	12/27/66
23)	3,305,097	High Pressure Peristaltic Pump for Separation Apparatus	5/21/63	2/21/67
24)	3,324,628	Preparative Treatment of Samples for Subsequent Processing in a Gas Chromatograph	9/8/64	6/13/67
25)	3,331,665	Sample Dispenser for Automatic Chemical Analyzer	9/30/65	7/18/67
26)	3,346,479	Preparative Separation by a Combination of Gel Separation and Electrophoresis	4/9/64	10/10/67
27)	3,368,872	Automatic Chemical Analyzer	3/31/64	2/15/68
28)	3,408,166	Gas Extractor and Injector for Gas Chromatography	6/21/63	10/29/68
29)	3,450,624	Apparatus for the Separation of Chemical Components by Electrophoresis and Gel Filtration	7/20/66	6/17/60
30)	3,453,082	Automatic Analysis of Gases	7/3/67	7/1/69
31)	3,489,525	System of Automatic Analysis	6/25/67	1/13/70
32)	3,495,541	Apparatus for Separation of Chemical Components by the Combination of Electrophoresis and Gel Filtration	8/20/66	2/17/70

33)	3,502,438	Automated Tape Chemical Analyzer	11/13/67	3/24/70
34)	3,578,977	Reflection Tests Having Photocell with Aperture	2/19/68	5/18/71
35)	3,635,394	Automated Clinical Laboratory	11/7/69	1/18/72
36)	3,681,030	Hand Automatic Sampler Dilutor	8/19/70	8/1/72
37)	3,687,632	System for Transferring Liquids Between Containers	12/04/070	8/29/72
38)	3,722,790	Sequential Treatment of Liquid Samples	7/30/69	3/27/73
39)	3,740,173	Peristaltic Pump	9/16/71	6/19/73
40)	3,802,782	Chemical Analyzer Performing Sequential Analysis of Samples	6/24/71	4/9/74
41)	3,826,622	Container for use in an Automated Centrifuge	5/15/72	7/30/74
42)	3,837,534	Compact, Flexible, Multiple Fluid Dispenser	10/16/72	9/24/74
43)	3,841,838	Centrifuge Cups for Automatic Chemical Analyzer	11/03/72	10/15/74
44)	3,859,051	Means for Transferring Liquid in a Capillary Open at Both Ends to an Analyzing System	8/16/73	1/7/75
45)	3,915,652	Means for Transferring Liquid in a Capillary Open at Both Ends to an Analyzing System	12/16/74	10/28/75
46)	3,951,605	Instrument for Automated Immuno-Chemical Analysis	7/8/74	4/20/76
47)	4,004,150	Analytical Multiple Component Readout System	5/1/75	1/18/77
48)	4,264,560	Clinical Analytical System	12/26/79	4/28/81

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About the Biographer

Amadeo J. Pesce received his BS in Biology from MIT in 1960, his Ph.D. in Biochemistry from Brandeis University in 1964, and received an NIH postdoctoral fellowship to study Biophysics at the University of Illinois at Urbana in 1965. He worked as a research Scientist at Michael Reece Hospital in Chicago from 1967 to 1973. It was there that he fell under the spell of Sam Natelson. Dr. Pesce has been on the faculty at the University of Cincinnati since 1973, being the Director of the University Hospital Toxicology Laboratory from 1982-1997. Currently he is the Director of Laboratories at Adams County Hospital and Drake Center.He has edited or written 19 books 8 CD-ROM publications and has authored more than 200 hundred of articles in the fields of biochemistry, immunology, clinical chemistry and toxicology.

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