

Anecdotes and Reflections in Celebration of the Fiftieth Birthday of NIEHS

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I owe my career to NIEHS, to Norton Nelson and to Nikita Khrushchev. When Khrushchev built the Berlin Wall, President Kennedy responded by increasing the size of the US Army, resulting in virtually all male 1962 medical school graduates being drafted. Fortunately, I ended up as a USPHS Commissioned Officer in the Division of Air Pollution where my hematology training led me to propose that ozone produced lipid peroxidation and to study this effect using human red cells as a model. In 1968 I returned to the New York University School of Medicine as a beginning faculty member in the Department of Medicine. In this position, I planned to focus on the role of active species of oxygen in hematological disorders. An indication of the lack of impact at that time of environmental medicine on academic medicine is that I had spent 8 years at NYU medical school (1958-1066) as a medical student, resident, and NIH post-doc without knowing that this department existed. But due to the formation of NIEHS, the Department of Environmental Medicine, also known as the Institute of Environmental Medicine, was given more recognition. It was not just the rapid award of an NIEHS Center, although this helped, as the Department of Environmental Medicine already had an NCI center for the work it was doing in experimental carcinogenesis. It appeared to me, as a young medical school faculty member, that the establishment of NIEHS led to recognition of the scientific validity of environmental health as a focus for research. My continued research using ozone to probe the pathways and the impact of the oxidation of red cell membranes led to my meeting Dr. Norton Nelson, the Department Chair. Dr. Nelson utilized the prospect of the newly funded NIEHS Career Development Award program to convince me, and the Division of Hematology, of the value of a joint appointment in Environmental Medicine. Fortunately for me, some of our work on the role of free radical reactions and lipid peroxidation in ozone toxicology began to be published, including a paper in *Science*, leading to my receipt of a five year NIEHS Career Development award in what I believe was the first year it was offered. This provided a firm basis for my career trajectory, without which I now likely would be a retired hematologist.

My initial impression of NIEHS was that it had a chip on its shoulder – that it felt it needed to prove that an Institute-level component of NIH in far off North Carolina which did not have a disease or organ system in its name was at least the scientific equal of other NIH Institutes. My personal recognition of

this scientific strength came when I was elected to the American Society for Clinical Investigation, from which future medical school Departments of Medicine chairs and division directors usually come. I realized that my major scientific contributions had come from involvement in the NIEHS Center more than from my interactions with faculty in the Department of Medicine. This confirmed my choice of environmental health as my career path. Through this NIEHS center I was able to work with superb scientific investigators, including Roy Albert and Edward Palmes and too many other NIEHS supported investigators to name. Particularly notable was a study with Frank Mukai, published in *Science*, showing that a lipid peroxide decomposition product was mutagenic - an area of research that has again become active. Also, with Walter Troll and his colleagues we provided the first scientific evidence that free radicals and active species of oxygen could be involved in tumor promotion. However, the greatest and most profound impact on my career were the benzene toxicity studies begun under the leadership of Sidney Laskin, a creative force in inhalation toxicology, which led to much NIEHS funding and a fruitful collaboration with Gisela Witz, an organic chemist from Ben Van Duuren's group. Without the NIEHS center supporting such a wide range of scientists from different disciplines, these collaborations would not have been possible.

The flexibility of NIEHS funding support and the depth of the NYU Institute of Medicine included the availability of funds to rapidly respond to issues. One example is the response to the reports of an increase in spontaneous abortions and fetal malformations in women working in surgical operating rooms. The usual reaction was to begin investigations of each anesthetic agent singly in various animal models. However, building on our knowledge of ozone formation, we demonstrated that various energy-producing devices within the operating room, including lasers, X-rays and germicidal fluorescent lights, were likely reacting with anesthetic agents to produce chemical species of potential concern. This research was among the reasons for the requirement that surgical suites must have one pass ventilation. While this outcome ended our research into the formation and effect of these reactants, it made the point that the primary role of NIEHS research was to prevent problems.

In 1980 I was recruited by Rutgers Medical School to chair the Department of Community Medicine. We worked to develop an environmental health program response to increasing public concerns about environmental issues in New Jersey. Joining with colleagues at Rutgers University, such as Joanna Burger and Keith Cooper, and with the recruitment of Bob Snyder, Paul Liroy and many others, we built the Environmental and Occupational Health Sciences Institute. We were able to get funding by the State of

New Jersey in large part because David Rall let it be known that without such a building we had little hope of competing for an NIEHS Center – and it was this goal that unified so many scientists from different disciplines to work together. Attesting to how NIEHS has changed is the advice we were given at an early 1986 meeting of an advisory committee assembled to help us put together our NIEHS center proposal. The distinguished visitors, including Norton Nelson and Jim Whittenberger, told us that we should not even whisper about the health education and community based work being done in the EOHSI division, headed by Dr. Audrey Gotsch, which included participation in Irving Selikoff's NIOSH Center, as this would prejudice the peer reviewers against our program. We were also cautioned to limit our presentation of the first major environmental exposure assessment program, under the leadership of Paul Liroy, to those studies most closely related to toxicokinetics and to avoid presentation to the review team of work aimed at understanding community exposure. We did so, received our NIEHS Center, and with the evolution of NIEHS, particularly under the leadership of Ken Olden, the program Audrey Gotsch had built became the poster child for the required community outreach components of NIEHS centers, and exposure assessment was increasingly recognized as a core environmental health science.

Early NIEHS Memories

A major factor in jump starting the development of NIEHS was the establishment of task forces to perform extensive and intensive reviews of environmental health science. The first NIEHS Director, Paul Kotin, developed this approach during planning sessions held in 1967-68, by the NIH Division of Environmental Health Sciences, which became NIEHS. Under co-chairs Norton Nelson of NYU and James Whittenberger of Harvard, early leaders in the field produced a blueprint for the research activities of the new NIH component. Multiple coast-to-coast meetings culminated in a three week writing session in 1969, at Oregon State University, and the publication of a 252 page book "Man's Health and the Environment – Some Research Needs". This was followed up by similar volumes in 1977, also co-chaired by Nelson and Whittenberger, and in 1984 – although the title was changed from "Man's Health ..." to "Human Health ...". Dr. Arthur Upton, the former head of the National Cancer Institute, and I co-chaired the third volume - which is when I first became significantly involved. Dr. Rall had convinced Congress, and particularly Congressman Dave Obey of Wisconsin, a great admirer of Dr. Rall, to ask for this report to guide Congressional budget processes. Dr. Upton and I quickly recognized that there was little need to repeat the previous research needs assessments which were still valid. Instead we challenged the task groups to break new ground by considering the opportunity to use exciting new advances in biological

sciences to explore the role of environmental factors, and to do so in a much broader range of diseases and disease processes with a focus on the prevention of disease.

One early memory of Dr. Rall was accompanying him and Norton Nelson on my first visit to the White House Executive Office Building a short time after the Arab oil embargo began in 1973. OMB wanted to know if the recently instituted low sulfur oil requirement was really justified as it in essence discriminated against American oil supplies. My assigned role was to give a review of the health effects of sulfur oxides. In describing the London fog disaster, I said that there was an apparent increase in infant mortality. At which point an OMB economist asked whether the infant deaths were in males or females. In response to astonished looks he stated that infant females received more from the GDP during their lifetime than they contributed in earnings. After a shocked silence Dr. Rall asked me to proceed with my presentation.

At what I recall as the 20th anniversary celebration of NIEHS, I did manage to get Dr. Rall somewhat perturbed with me. I had been honored by his asking me to give a major presentation during the meeting. That morning, TV news featured an item about how the RJ Reynolds Tobacco Company, a North Carolina company, had fired their advertising agency because it had also developed very effective ads for the first airline that had put in a no-smoking rule. I was outraged and at my presentation, which focused on all of the good that NIEHS had done and the challenges for the future, I very briefly advocated for a ban of fig newtons, my favorite cookie. Fig newtons were made by Nabisco which was then owned by Reynolds tobacco, and it seemed to me to be that boycotting fig newtons was responsive to big tobacco flexing its muscles. I should have known better. The newspaper accounts the next day featured my “boycott fig newton” comments rather than covering the great news story about NIEHS.

Love Canal

Love Canal provided a contentious issue in 1977 for Dr. Rall whose reaction was important for the future of environmental health sciences. Although I was involved in the Love Canal issue at the time it developed, the following anecdote was mostly pieced together from EPA sources when I headed ORD in 1983-85, and from colleagues in New York. When I asked Dr. Rall about the issue when he was NIEHS Director, he diplomatically smiled and changed the subject. Russellyn and I became socially engaged with Dave and Gloria after he retired from NIEHS, but I never got around to asking him again before his sudden and untimely death.

An important background for this story is that President Jimmy Carter seemed to be constantly feuding with New York democratic political leaders, in this case Governor Hugh Carey to whom Love Canal was a difficult political problem. Accordingly, Dr. Rall's involvement in defense of science required great political finesse. (My own personal contribution was based upon my Bellevue Hospital experience which led me to point out at a closed door NY State Dept. of Health Love Canal advisory meeting that the one death then tentatively ascribed to exposure to toxins at Love Canal, that of a young male with pulmonary edema and liver abnormalities, was far more likely to be due to heroin. As this death was dropped from the Love Canal narrative, I assume I turned out to be right.)

Environmental Health Science needed to be defended because EPA lawyers had awarded a contract to an outside laboratory to perform cytogenetic studies on Love Canal residents, but had omitted the control group specified by the EPA Office of Research and Development scientists who had initiated and designed the study. The usual background levels of chromosomal abnormalities in circulating lymphocytes was widely and flamboyantly reported as evidence of genetic effects caused by Love Canal toxic wastes that would inevitably lead to cancer in these residents. Dr. Rall correctly saw this as a huge black eye to the overall scientific reputation of environmental health sciences. He became personally involved to the extent of going to the contract laboratory with other NIEHS scientists to evaluate the data – but being refused admittance. While it took many years for EPA's scientific credentials to be restored, Dave's forthright actions, along with those of Arthur Upton who was then head of NCI, were crucial in maintaining the scientific integrity of environmental health sciences to peers in the scientific community, and to clearly demonstrate why environmental health science could not be left solely in the control of regulatory agencies.

The Superfund Research program: Great outcome but not what I intended

Although not the outcome I initially wanted, I was very involved in the founding of the NIEHS Superfund Biomedical Research Program. I came to EPA as Associate Administrator for Research and Development from New Jersey. We clearly led the nation both in the number of Superfund sites and public concern about hazardous waste dumps. My recollection is that ORD had a \$14 million budget for hazardous waste research, for which I had very definite ideas. Very much to my surprise, EPA was adamantly opposed to performing any of that research on a Superfund site – the logical location to do the research. EPA lawyers believed that the primary goal of the Superfund program was to sue those responsible for

the waste, and that on-site research by EPA would inevitably compound the difficult legal process. When the original Superfund act came up for reauthorization and amendment, I did my best to argue the need for a Superfund research program. This was opposed by key EPA staff and the EPA Legislative Affairs office, on the grounds that it would require the EPA to compromise on some of the very tricky industry tax-related issues. The hero of this story is Lee Thomas, who had formerly headed the EPA Office of Solid Waste and Emergency Response, which was responsible for the Superfund program, and had replaced Bill Ruckelshaus as EPA Administrator. He agreed to meet with us about the issue, listened to our various arguments, and countermanded his staff.

But what none of us realized at the time, was that Congress would not let the research money come to EPA. Basically, one of the few areas of agreement among three contentious Democratic congressional leaders, John Dingell, Henry Waxman and James Florio, was that they did not want to share the high profile Superfund issue with a fourth Democratic Congressman, James Scheuer of New York. Scheuer chaired the House Science and Technology committee that was involved in authorizing ORD's budget. If ORD received any of the superfund money, Scheuer could hold hearings on the subject.

In essence, I had made a dumb bureaucratic mistake which was going to lead to setting up a research program potentially in competition with the EPA research program I headed. The obvious candidate for this research program was CDC, not NIEHS, as CDC was to be involved through the nascent Agency for Toxic Substances and Disease Registry. This was because Congressman Florio of my home state of New Jersey was intent on involving the USPHS. Congressman Florio was the driving force for the establishment of the ATSDR because of his belief that all one needed to do was to develop a registry of citizens living around hazardous waste sites and follow their health over time to show the adverse impacts of these sites. I lobbied hard for NIEHS rather than CDC and like to think that this effort had something to do with the final decision. Also related is that one of my arguments for funding EPA's Office of Research and Development was that ORD had major ecological and engineering research programs which should be integrated with the superfund health research. Congress apparently bought the argument, but only to the extent of requiring such research to be funded by the NIEHS Superfund program.

One example of the battle within HHS as to who would get this funding is a meeting that Vernon Houk, a superb public health champion who headed the CDC Center for Environmental Health, and I were

scheduled to have on the issue with key congressional staff. Friends told me that Vernon always came to these meetings early so I better do so as well. I arrived about 30 minutes early but he was already there. As I walked in I could hear him loudly insisting that the head of NIEHS should not be listed as a member of a planned Superfund research oversight committee.

NIEHS International Impact

David Rall and Norton Nelson were particularly interested in developing international collaboration in Environmental Health Sciences. In 1973 President Nixon and Soviet President Brezhnev held a summit meeting which included an agreement for scientific exchange in the area of environmental health.

David Rall was put in charge of the US side of the effort. His counterpart was Academician Nikolai Sidorenko of the Sisyn Institute in Moscow. Parenthetically, both Dr.'s Sidorenko and Rall were smokers and subsequently made a bet as to who would stop smoking first. Dr. Rall lost. At our first meeting of the US scientists involved in the program, Dr. Otto Bessey, who led extramural science at NIEHS, told us that we should never argue politics with the Soviet scientists with whom we were paired. Instead, just let them see what we had, as they were smart people who would make the obvious comparisons. The initial Soviet visitors were high level dignitaries such as the Minister of Health of the Russian Soviet Socialist Republic. The small groups would usually visit Research Triangle Park, Washington, Cincinnati, and end in New York. As I was the only member of the US group living in Manhattan, I served as the tour guide. This included being briefed by the State Department as to who the KGB-designated person was in each delegation, and how even a minor change in the tour agenda should be directed by me to the head of the delegation in such a way that the KGB designee would be visible to the delegation head but not to me. Memorable experiences included showing my recently funded NIEHS grant to Dr. Sidorenko and his colleagues in the presence of Dr. Rall and Dr. Nelson. No matter how hard the translator worked, we could not convince the visitors that the grant did not represent Dr. Rall deciding what should be done, and then providing the money to the NYU vice-president for research whose name was on the grant face page, who then told Dr. Nelson to fund me to do that explicit research. I was not believed when I said that if either NIEHS or NYU told me how to perform my research I would leave and go elsewhere. Another memory is of a farewell dinner for a senior Soviet delegation at the Rainbow Room in Rockefeller Center. The delegation's head, a Soviet General in full uniform who was said to be President Kosygin's personal physician, added to the usual thank you toast an indignant protest about the US government making the US press intentionally carry newspaper stories in each city they had visited

about Giardia in Leningrad's water supply. Both Dr. Rall and Dr. Nelson tried to gently convince the Soviet delegation leader that no one could control the US press, but I suspect they were unsuccessful.

Roger Glass, currently head of the NIH Fogarty Center, was a young CDC physician working with Dr. Rall who spent a great deal of time in the Soviet Union and was key actor in developing the program. On one visit of a group of us to Moscow he organized a meeting with Dr. David Goldfarb, a noted Soviet scientist who was being punished by losing his laboratory and graduate students because his son had become an active Jewish refusenik representing those who wished to leave for Israel or the United States. The meeting was held in a noisy restaurant with our table as close to the orchestra as possible so no one could overhear. I attended the meeting because it was wisely decided that it would not be politic for Dr. Rall to be at the meeting. I learned much about what it meant to stand up for basic human rights from a very brave man and rejoiced when he finally was able to come to the United States in 1986. Another anecdote, reflective of the time, concerns two midlevel Soviet scientists who had worked at NIEHS for a few months before coming to New York City on a Saturday. One was to return to Moscow the following evening and the other to work at NYU's Institute of Environmental Medicine. On Sunday morning my wife and I, as their tour guides for the day, were told that their highest priority was a visit to the United Nations. I told them that as the Yom Kippur war had just begun it would be very difficult to do so because of demonstrations, but they insisted. We did spend time in the area but were unable to get inside the UN. Nothing was said about the unruly demonstrations they had seen, until we were on the way back from Kennedy Airport. The remaining Soviet scientist asked many questions, including some about police procedures for mob control, clearly indicating that this very observant individual, who had only experienced choreographed demonstrations in the Soviet Union, was keenly interested in what he had seen. But he would not ask any of these questions in the presence of another Soviet scientist who might report him.

This top down approach of the USSR later provided a situation in which Dave Rall's finesse and integrity was put to the test by the American scientists in the program. The first formal combined meeting of the US/USSR scientists was held in Riga with a virtually complete attendance of all those involved. Unfortunately, when we subsequently hosted the meeting, only the leaders of the Soviet institutes were allowed to come to the US. They read the papers prepared by our scientific colleagues, but could not answer questions about the work nor participate in informed discussions. At a hastily called rump meeting with Dr. Rall we basically told him that if the goal was science, we were wasting our time.

However, we were willing to continue if it was simply to support the flag. Dr. Rall, disarmingly but firmly, asked us to continue to support the flag – which we did.

Dr. Rall's interest in international environmental health sciences led to substantial NIEHS investment in the Scientific Group on Methodologies in the Safety Evaluation of Chemicals – with the unwieldy acronym of SGOMSEC. This organization, initially headed by Norton Nelson, consisted of a core group of international experts, including David Rall and Jack Moore, and the focus was specifically on facilitating and validating newly developed methodologies, central to environmental health sciences. The meetings consisted of core SGOMSEC members and invited content experts. NIEHS leaders, including David Hoel, Chris Schonwalder, Terry Damstra and Bill Suk, were active in many of the week long meetings as were many Europeans from both sides of the Iron Curtain, as well as scientists from the rest of the world. SGOMSEC also served as a health component of the Scientific Committee on Problems of the Environment, headquartered in Paris. I replaced Dr. Nelson as chair and eventually had the sad task of closing down SGOMSEC, which was partly due to the lessening of NIEHS funding after Dr. Rall retired, and to the development of more formal multinational efforts, such as the International Program for Chemical Safety and the harmonization efforts of OECD, thus making SGOMSEC no longer necessary. During its existence SGOMSEC published many authoritative books on methodological issues and had a major impact on the performance of environmental health globally. Dr. Rall's continued interest in international environmental health led him to be appointed as the IOM Foreign Secretary once he retired from NIEHS.

One should also not overlook the important role played by *Environmental Health Perspectives* in fostering global environmental health sciences. I know from experience on sabbatical in Malaysia and Singapore that the presence of a high quality journal with a high impact factor which was willing to accept and promote research from the developing world made a very big difference in the career choices of budding academic health scientists.

Service on NIEHS Council

I have served twice on the NIEHS National Advisory Environmental Health Council. The second time was after receiving a phone call from Ken Olden asking if I would agree to be nominated to serve again as the Council was being packed by HHS Secretary Tommy Thompson, an appointee of George W. Bush, with non-scientists from right wing organizations who were skeptical of the value of environmental research.

About a month later I was called by a young man who said he worked for Secretary Thompson to vet candidates for positions and that I was being considered for the NIEHS Council. He then began a series of irrelevant questions about my politics which I ducked by saying as a Dean I had a meeting I could not miss. I asked if we could talk later and but told him that I wanted to be sure he was aware of the fact that I had been a political appointee in the Reagan-Bush administration as Assistant Administrator of EPA. I didn't tell him that I had been nominated for Senate confirmation by Bill Bradley, or that the White House had initially turned me down because I was not fully supportive of President Reagan. The young man from HHS said that it was great that I had been a Reagan appointee and that he would no longer have to interview me. Unfortunately, Ken Olden was right about many of the recent appointees who had no business being on an NIH advisory council.

NIEHS as a public health organization

In a paper arguing for the role of animal toxicology in preventing disease, David Rall contrasted this approach to prevention with that of a colleague who directed another NIH Institute. This colleague had argued that cardiac transplantation was a preventive measure because it saved a patient's life. Prevention is, or should be, an important part of NIH activities which usually focus on bedside medicine. Illustrative of how NIEHS differs from other NIH Institutes in its need to balance more toward public health prevention than bedside medicine is one of the circumstances surrounding the short tenure of the NIEHS Director who succeeded Ken Olden in 2005. This outstanding physician-scientist was appointed by NIH Director Zerhouni who had focused the NIH on translation of research in response to Congressional criticism concerning a perceived lack of health relevance to NIH research. Director Zerhouni defined translation as bench to bedside. NIEHS research arguably had prolonged many more lives than had other NIH institutes through its research, but the translation was primarily to policy makers who developed and enforced laws, regulations and standards related to controlling the environment or to preventing environmental problems from occurring. Bench to bedside was a model that in essence limited NIEHS success. It also cut off NIEHS from community approaches developed under Director Olden's leadership, with a resultant backlash against the new NIEHS Director. Fortunately, current NIEHS Director Linda Birnbaum understands well this role of NIEHS. But we must remember that the tension caused by the NIH being more oriented to the bedside than is NIEHS will always be there.

This affinity of NIEHS for public health was documented in a paper in *Environmental Health Perspectives* by my colleagues and I, in which we benchmarked larger US academic programs in environmental health sciences research. Using the presence of an NIEHS Center of Excellence as the criterion for being included in the study, we found that those academic programs within schools of public health had twice as many faculty and close to triple the amount of external funding than those programs with NIEHS centers that were not within schools of public health.

Involvement with the National Academies of Sciences through NIEHS – and a concluding thought

Through the years I have had the great fortune of chairing about a dozen NRC or IOM committees, most of them at least partially funded by NIEHS. Judicious use of the NAS has been a hallmark of effective NIEHS strategies to develop the field and continues under Director Linda Birnbaum. Among those that seemed to make a difference was the Committee on Biological Markers. This committee developed the conceptual basis for considering biomarkers of exposure and effect as operating on a continuum in a sea of susceptibility markers. From this, various other subcommittees were formed for biomarkers related to specific organ systems.

Another particularly effective committee for its time was the IOM Committee on the Role of the Physician in Occupational and Environmental Medicine which was funded by many agencies including NIEHS. Our 1988 report documenting the need for more involvement of physicians in occupational and environmental medicine had sufficient traction to lead to the committee being asked to make specific recommendations in a subsequent report. Among these was one taken up wholeheartedly by NIEHS who provided support for five year career development awards to young physicians. These “young physicians” are now senior leaders in occupational and environmental medicine in medical schools and schools of public health. This program, so ably lead by Annette Kirchner and Anne Sassaman, deserves reconsideration before the retirement of the generation of those funded earlier leaves a major gap in academic health involvement in environmental and occupational health.