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Emeritus Member
AACR Member Since 1959

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1 received my doctorate in 1953, the same year that Watson and Crick published their seminal paper on the structure of the DNA. My degree was in developmental biology, identifying the proteins necessary for the first heart beat. It was not a big jump from developmental biology to oncology, since many oncogenes are developmental genes or mutated ones. I received a job offer from a pathologist at the Lilly Research Laboratories to start a program to develop therapeutic agents to treat human cancer. On my arrival I was involved with producing Jonas Salk's polio vaccine for his clinical trial; we became close personal friends. As a byproduct of my work with Jonas's vaccine, we became the reference lab for adventitious vital agents in the monkey kidney cultures where the polio viruses were grown. The pathologist who hired me insisted on a type of simian kidney cultures, which no other manufacturer used. While we got fewer cultures per kidney, we made 90% of the vaccine because the other manufacturers produced virus coated with a lipid which protected it from being inactivated by formalin. A large number of these adventitious simian viruses were potent oncogenic viruses in hamsters, which I revealed at the International Cancer Congress in Tokyo in 1966.

On the same trip, I also served as one of a 9-member NSF delegation which met with 15 Japanese scientists to discuss the biological effects of the two atomic bombs dropped on Japan with constant TV coverage with instantaneous Japanese translation. At that time there was a slight increase in thyroid cancer and leukemia.

I also became a close friend of Lilly's first and last Emeritus Director of Research. He was George Henry Alexander Clowes, one of the 13 founding members of the AACR. I eventually was able to establish the Clowes Memorial Award in the AACR, in his honor. He was a British biochemist first hired in the U.S. by the NY surgeon Roswell Park, who later convinced the NY legislature to found the Institute that bears his name. George was the first one to isolate Vitamin B12, and on hearing Banting and Best describe their work with depancreatized dogs, convinced Lilly to develop porcine and bovine insulin to treat diabetes in the 1920's. I did the same much later with human insulin by rDNA technology.

I was an associate editor of *CANCER RESEARCH* for several years, and a consultant to the NCI's Therapeutic Development Committee when Nixon declared his war on cancer. Nixon asked the world's pharmaceutical industry to submit organic compounds and fermentation beers to the Cancer Chemotherapy National Service Center (CCNSC). To my dismay the CCNSC took a typical bean counter's approach, and used a **single** murine leukemia (L--1210) which detected the highest percentage of the handful of drugs that had some modest clinical activity.

I returned to Lilly and suggested we expand our program in response to Nixon's war, but not do it the CCNSC's way, but my way, and make anything we found of interest available to the NCI. They agreed. I set up a tumor screen of rodent tumors of various histological types, hormone dependent/independent, virus induced (Rous), carcinogen

induced (oral DMBA) and rotated new tumors in periodically. I also included plant extracts which the CCNSC excluded. This led to the discovery of the indol-dihydroindole alkaloids of the periwinkle plant. Four of these almost 60 alkaloids had robust anti-tumor activity. The best was vinrosidine which was nontoxic and broad spectrum. Unfortunately we could not produce enough for a clinical trial, or make available if it were effective clinically. None of the vinca alkaloids have ever been synthesized, in spite of many strenuous efforts. It takes a ton of dry leaves to make one ounce of vincristine. When I published that the CCNSC's L-1210 system would not have detected them, we exchanged materials. After they got identical results to mine, they added plant extracts, and several useful drugs were developed from them. I received the Cain Award for Preclinical Research from the AACR for this work, and the First Annual Congressional Award for Science and Technology for my rDNA insulin work.

I was the first to-take a monoclonal antibody (MoAb) to the clinic for cancer. I had rights to a tumor specific MoAb from the Scripps Clinic called KS-14. I used it as a tumor seeking missile on which I hung vinblastine warheads. Unfortunately this was before procedures were developed to humanize them, and thus I knew we could only use it once. In animal models carrying human tumors, it worked like a charm. I had a contract with a pathology lab at Duke, where KS-14 was screened against every tissue, gender/race known with **no** reactions. Unfortunately they were all dead, fixed tissues. In the clinic we found a reaction with live intestinal tissue which required surgery, and we stopped the trial. Now there are many humanized MoAbs which are useful in several clinical fields.

I have had other successes and a few disappointments.

One success was an anti-estrogen I had made to compete with Tamoxifen. 1knew it was more tissue specific and less toxic, but irrational marketing refused to support it in CTs unless it worked in tamoxifen resistant breast cancer. After I retired, they took it to the clinic, and it failed as I predicted. A new bone biologist from NIH suggested they try it in osteoporosis since he knew that women on Tamoxifen never got that disease. There it worked like a charm, and now is also approved as Evista by the FDA to prevent recurring breast cancer. That was a salvaged disappointment, but another was not. I discovered an old antibiotic (1890's) which destroyed rodent tumors with no toxicity. In the clinic it was totally inactive until we were concerned it might cause obesity as we escalated the dose. Retrospectively, I examined metabolism and discovered that there were only two species, rabbits and humans, that glucoronided the antibiotic immediately, which was totally inactive even in rodents as well as humans. I knew psoriatic plaques contained betaglucoronidase, and suggested using it in psoriasis. It worked well, was nontoxic, but the FDA refused to approve it after having approved 6-azauridine p.o., which killed some people with blood clots. We produced it for over 10 years under a compassionate IND for psoriatic patients who had never responded to any other treatment, including methotrexate.

My biggest disappointment with the AACR was a few years ago when the CEO asked me what kind of a program/conference would appeal to me. I informed her I had such a plan, and would be happy to discuss it. We met in San Diego, and she and the then-current president of AACR met with me and Dr. Ron Evans, and telephonically with a

gentleman from Princeton U. My plan was fairly simple and involved how to fight lung cancer, which is the leading killer of those who die of cancer, but gets the least research funding. The American Lung Association will tell you that for every $15,000 breast cancer gets, lung gets $1500. While they used to worry about asthma and COPD they now realize that lung cancer is their major problem. American Lung Association is good at fundraising, but AACR knows more about cancer. I suggested that the AACR approach the Lung Association to collaborate on a lung cancer research and clinical trial program.

There are several areas that need to be explored. First in CTs, drugs should not be evaluated by survival time alone. There are five histological types: 4 NSCLC, plus small cell lung cancer. There are gender differences in receptors and never-smoked and smokers. There has been about 10% in male never-smoked for decades, but over 20% in female never-smoked and rising, and in Asia is almost 60%. There are estrogen receptors in some female lung cancer and testosterone in some male lung cancers.

All steroid hormones and cholesterol, Vitamin E and thyroid hormone have nuclear receptors, which is a field in its own right. One of the intriguing facts is that one can modify or mimic agonists/antagonists so that one can eliminate some of the undesired activities of the natural ligand and keep some of the desirable ones. Evista is an example before the field was delineated by Dr. Evans. There are no support groups like many other malignancies have, because the majority of patients are dead within 6 months of diagnosis. That is where I thought the American Lung Association could help. I suggested all lung tumors have biopsies, which could provide histological types, microarrays, SNP sequences and potential biomarkers by smoking history/gender/hormone receptors, etc., and that all clinical trials be evaluated based on those parameters. Today one could add more categories such as signal pathways, genomics, proteomics, and perhaps many others. I was told by an assistant to the CEO that the AACR's scientific advisory board would review my proposal. He then informed me that they felt it was a good idea, but they did not want to run it, and it dropped through the cracks! I still feel the concept or derivatives of it have merit!

There are many highlights in my 50 years as an AACR member. One is the many AACR icons I have met and/or worked with. These include C. P. Rhodes, Sidney Farber, David Karnofsky, Joe Burchenal, Emil (Tom) Frei, Emil (Jay) Freireich, and Jim Holland… Another highlight was visiting Jay at M.D. Anderson in November, and while making rounds with him, I asked "Where are the leukemic kids?" He replied·"We sent them all home for Christmas!" A second such moment was attending an award ceremony at Columbia-Presbyterian Hospital where Tom, Jay, Jim, and a gentleman who ran St. Jude's whose name I can't remember, received an award for a four-drug protocol which **cures** 85% of acute lymphocytic kids. One of the drugs was vincristine from the periwinkle plant!