Dankesrede

von

Prof. Dr. Anthony Cerami

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter-Preises

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Es gilt das gesprochene Wort!

Honorable guests,

I am greatly honored to be with you today to receive the Paul Ehrlich and Ludwig Darmstaedter Prize.

Paul Ehrlich has been a guiding force in my scientific career, and this influence forms the basis of my receiving this prestigious award. To explain that I'd like to tell you a little bit about my life.

When I was a child growing up on a farm in rural New Jersey, my school had four rooms for 8 grades. Every month or so an old converted bread truck arrived, filled with books. When I was about 10 years old, I entered the truck and by chance picked up a book by Paul de Kruif called "The Microbe Hunters" which outlined the work of Paul Ehrlich. After reading this book, I decided to be a scientist. Of course, I had no idea how to achieve this goal.

I decided to observe and note diseases effecting our farm animals and plants. One of the major puzzles that struck me was why chickens with coccidiosis, or cows with brucellosis, lost considerable amounts of weight before they died. Even people I knew that had cancer showed a similar wasting. Later, I learned from Mr. Arthur White, my teacher of Vocational Agriculture in High School that this wasting was called cachexia - a word derived from ancient Greek meaning "I have it bad". Cachexia is a prominent feature of many diseases, especially bacterial infections, parasitic diseases, and cancer, and this problem became a central question of my scientific life.

After High School I became a student at the College of Agriculture at Rutgers University and became the first person in my family on both sides to ever attend and graduate from University. Needless to say, my parents were happy and very proud.

As I approached the end of my college career, I came across a catalogue of a new Graduate School at the Rockefeller Institute for Medical Research in New York City. As an aside, Paul de Kruif, the author of the Microbe Hunters, worked at this Institution for a number of years. The Rockefeller Institute program admitted 25 students per year who had either a bachelors or MD degree. I found it interesting that most of the teaching was done by tutorials by a distinguished faculty. Fortunately, Dr. Detlev Bronk, the president, stretched the rule and admitted me as the 26th student.

For my thesis, I worked in the Laboratory of Edward Tatum, a Nobel Laureate in genetics under the direction of Edward Reich, a talented MD/PhD with a strong background in Pharmacology. When I finished my PhD, I realized that I needed to expand my knowledge of medicine and was able to audit the pre-clinical curriculum of Harvard Medical School through the good graces of Irving Goldberg, another Rockefeller University graduate, who was the Head of the Department of Pharmacology.

Eventually, I was able to return to The Rockefeller as an Assistant Professor and Head of my own Laboratory of Medical Biochemistry. I decided two areas of research to explore, diabetes and its complications and parasitology.

In the mid 1970's I received a grant for ten years from Ken Warren of the Rockefeller Foundation as part of the Great Neglected Disease Network which was created to encourage scientists to enter this neglected area of science. The best part was that I could work on any parasite. This was my chance to follow in the footsteps of my hero, Paul Ehrlich, and identify new drugs to kill trypanosomes, parasitic organisms spread by the tsetse fly which infected cattle in large areas of Africa. So off to Kenya I went to the International Laboratory for Research of Animal Diseases.

Cows infected with trypanosomes dramatically lost weight before they died. What was not obvious from just looking at the cachectic cow was how few parasites were present in the cow, certainly not enough to cause cachexia and death.

One day when I was suffering from my very own parasitic disease, I distracted myself by contemplating what was actually killing this poor cow. Suddenly I had an incredible epiphany. "What if the cow was over reacting to the presence of a very small number of parasites by making a toxic substance which was causing the wasting and death?" In a flash I decided to name this putative mediator- cachectin. In the minutes to follow I outlined in broad strokes the entire research outline for evaluating this idea. Now came the hard part of isolating and determining the structure of this mediator, with the implicit objective of eventually being able to identify and find ways to block the activity of this destructive agent. Subsequent studies carried out with Dr. Masanobu Kawakami revealed that in response to infection with trypanosomes there was an increase of serum lipoproteins which was associated with a decrease in the enzyme serum lipoprotein lipase. Utilizing this suppression of lipoprotein lipase on fat cells as a bioassay, we were eventually able to isolate cachectin to homogeneity from macrophages that had been exposed to bacterial products.

It was clear from a number of experiments that cachectin is a very powerful molecule with many biological activities which are damaging. Notably, a wide variety of pathogenic organisms, such as bacteria, viruses, and parasites, all stimulate the production of cachectin. The effects of cachectin range from causing tissue damage and production of other injurious molecules, to loss of appetite, fever, malaise, and death. For example, administration of cachectin to a mouse reproduced the cachexia and death which I had observed earlier in the African cow. Further experiments showed how devastating the effects of cachectin were. A baboon given TNF had a rapid cardiovascular collapse with a loss of blood pressure and heart rate, a decreased respiratory rate, and then died.

When we finally had enough purified cachectin, we were able to micro-sequence the amino terminal amino acids. In comparing the structure of cachectin to other molecules, we were shocked to see that the terminal amino acids of cachectin was identical to Tumor Necrosis Factor, a mediator which was being studied in a number of laboratories and bio-technology companies as a potential therapy to eradicate tumors in patients with cancer. Given the powerful destructive biologic effects of TNF, how could TNF be used safely in patients? After considerable discussion within the laboratory and the administration of the Rockefeller University, we decided that we had a moral obligation to report our results with cachectin to the Food and Drug Administration. We argued that the use of TNF as a clinical therapy would be impossible to achieve clinical effectiveness since TNF inherently could induce shock and death. Needless to say, we were subsequently accused by many people of trying to destroy the fledgling biotechnology industry.

What was clear to us was that blocking the effects of cachectin/TNF was an important target for a new kind of therapy. The idea was to develop monoclonal antibodies to TNF which specifically recognize the cachectin/TNF molecule and prevent it from activating its receptors. With Masanobu Kawakami, we developed antibodies against TNF and showed, as we had hoped, administration of anti-TNF antibodies completely blocked the biological effects of TNF. Kawakami and I wrote the cornerstone patent application for all anti-TNF therapies in 1981. In this patent we wrote that antibodies made against cachectin/TNF could be used as a new way to treat patients with a large number of inflammatory conditions which were caused by TNF activity. These included rheumatoid arthritis, inflammatory bowel disease, and overwhelming infection among others. Several inflammatory processes which are responsible for a large number of diverse diseases are dependent upon TNF and can be treated with neutralization of this molecule.

This has produced a worldwide market for these agents currently exceeding $35 billion US dollars per year. But of course, what is really important is the alleviation of pain and suffering that Anti-TNF therapies offer to patients.

It has been a long time since I first read about Paul Ehrlich and his groundbreaking work to prevent the scourges of bacterial and parasitic infections in humankind. His visionary accomplishments inspired me to embark upon a research career with a goal to alleviate human disease and suffering. It has been a very interesting journey guided by Paul Ehrlich and I am very honored to accept the Paul Ehrlich and Ludwig Darmstaedter Prize named in his honor.