Dankesrede

von

Prof. Dr. Cesare Montecucco

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Es gilt das gesprochene Wort.

Ladies and Gentlemen,
distinguished guests,
colleagues and friends,

I am honoured and very grateful to the Paul Ehrlich Foundation and to its Scientific Committee for awarding to me the 2011 Prize.

Let me say that I believe their choice was not only that of one scientist, but also that of a line of research that ideally begins with Robert Koch, Luis Pasteur, Paul Ehrlich, Daniel Bovet and has then been followed by many others, including myself. This research has contributed, at the same time, to the advancement of biomedical knowledge and to human health.

Pathogenic organisms cause diseases by producing pathogenic factors that alter the physiology of the host to the advantage of the pathogen. Pathogenic factors are kind of biological weapons! By studying the mechanism of action of the pathogenic factors, produced by organisms that cause major human diseases, one can achieve, at the same time, four different types of goals.

The first is to increase the understanding of the molecular mechanism of pathogenesis of the disease under study.

The second goal is that of increasing the knowledge of our own physiology. This second type of possible achievement may sound surprising: how is it possible that by studying a pathogen we can learn about ourselves? The fact is that pathogenic organisms co-evolve biologically with us and during this process of intimate frequentation of our body they learn much about us.

The third type of result is practical, and it is that by studying the mechanism of action of pathogenic factors we can develop novel therapeutics and vaccines.

The fourth type of result is that we can learn to use the virulence factor itself as a therapeutic and this is well illustrated nowadays by the example of botulinum toxin, the most poisonous pathogenic factor, known in the world, which thanks to biomedical resesearch could be developed as a therapeutic now used in millions of doses.

Let me illustrate these principles with some results taken from my own experience.

In 1984, I was working in the laboratory of Jean-Pierre Changeux at the Institut Pasteur in Paris on the post-synaptic nicotinic receptor when I begun to study the literature regarding two diseases of the synapse caused by pathogenic bacteria. One was Tetanus, a disease first described by Hyppochrates and believed to be of nervous origin until 1884, when two young Italian doctors in Turin, about 24 centuries after Hyppochrates, demonstrated that tetanus was caused by a microbe. This was a major breakthrough that led soon after to the isolation, by three different groups at the same time, of a toxin named tetanus toxin. This toxin was shown later to be sole cause of the disease and to act by blocking the transmission of the nerve impulse within the spinal cord. The discovery of tetanus toxin soon led to the first treatment of tetanus, a disease that had killed, in a dreadful way, millions and millions of human beings along history. First, in Berlin the laboratory of von Behring developped an anti-tetanus antiserum and then Ramon at the Institut Pasteur provided the definitive solution by generating the anti-tetanus vaccine, which was first tried on a large scale on German soldiers during WW2, and it is still used. I believe everybody in this room has been vaccinated with an anti-tetanus vaccine, and if was vaccinated long ago should have an injection soon. This preventive type of medicine has cancelled this dreadful disease from all the earth, except in those poor regions of the world where preventive medicine is not enforced.

At variance from tetanus, botulism was first described only at the begin of the nineteenth century in Svevia by Kerner. The reason of this late definition is probably due to the fact that the major symptom of botulism is a flaccid paralysis that rarely causes death by respiratory deficit. Botulism is caused by a poison released from bacteria growing in anaerobic food. Seven immunologically distinct toxins were discovered so far: they are similar to tetanus toxin, in that they block as well the transmission of the nervous signal, but at peripheral nerve terminals.

How tetanus toxin causes tetanus and the botulinum toxins a flaccid paralysis was the major unsolved problem in the study of these two diseases in 1984. I decided that this problem could be tackled by my small laboratory. My first contribution was the elaboration of a model that could explain the absolute neurospecificity of these neurotoxins. This model envisaged that these toxin would bind first to a polysialoganglioside molecule and then to a protein receptor and, ten years later, was shown to be correct. But the breakthrough came after the sequence of these proteins was reported by the groups of Heiner Niemann in Giessen and of Neil Fairweather in Wellcome.

A protein sequence is like a written page, but it is not self-explanatory. It has to be interpreted. I noted that it contained a signature that could signify that these proteins could be kind of molecular scissors. Immediately, with Giampietro Schiavo we designed a coherent set of experiments to test this hypothesis. Within few years we were able to prove it. More, we found that tetanus toxin and the seven botulinum toxins were very specific scissors: they only cutted, at single sites, three proteins that are now known as: VAMP/synaptobrevin, SNAP-25 and syntaxin.

This was a magic period for us and for the field. In fact, these findings demonstrated that tetanus and botulism were due to a single molecular lesion taking place inside neurons and that the opposite symptoms of tetanus and botulism are symply due to the different neuron targets of the toxins: for tetanus toxin the spinal cord and peripheral nerve terminals for the botulinum neurotoxins.

At the same time, these results told the wider scientific community that, if the cleavage of VAMP/synaptobrevin, SNAP-25 and syntaxin were sufficient to block neurotransmitter release, these three proteins had to be essential components of the nano-machine which mediates the transmission of the nerve signal at the synapse.

These results were highlighted by their convergence with those obtained by genetic methods in yeast by Randy Sheckman in California and by others and those obtained by biochemical methods by the laboratory of Jim Rothman in New York, which lead to a biological general principle: each event of vesicle fusion with the target membrane within any cell of our body, any cell of the animal and plant worlds, is mediated by the same three proteins: VAMP, SNAP25 and syntaxin. When there is in science a convergence of different lines of research that provide a quantum leap in knowledge then I ensure you is a kind of magic.

But perhaps more astonishing for many people has been to see botulinum toxin type A to be used in million of doses as the best therapeutics for dystonia and spastic diseases and other human diseases as well: indeed the fact that the same toxin that can kill a man in a dose of few tens of billionths of a gram is, at the same time, the best therapeutic for many diseases of human nerve terminals is indeed astonishing. Perhaps, we have to remember what Paracelsus said: it is the dose that makes the poison, and we can add: and not the molecule by itself. Any molecule is not good or bad by itself: it is the use that we make of it that makes it bad or good to us !!!

During these studies, the sequence of the anthrax leathal factor became available and I and others noted the same signature present in tetanus and botulinum toxins. Together with an expert of anthrax, Michele Mock of the Institut Pasteur, we begun a competition with a group of the NIH Laboratories in Bethesda to discover the target of its action. About at the same time, with different methods, we came at the same conclusion: that the anthrax lethal factor is a molecular scissor that interrupts specifically a major way of transmission of signals within the cell. This led us in the study of the pathogenesis of anthrax, and we were the first to visualize the activity of a bacterial toxin within a cell. Together with the group of Tatiana Baldari of the University of Siena, we were able to show that the anthrax toxins target mainly the immune system and depress its activity thus permitting to the bacterium, discovered by Robert Koch, to proliferate in the body leading to systemic infection and death.

This disease became very famous with the outbreak of bioterrorism in USA in the fall of 2001. We had begun to work on its molecular pathogenesis long before, in 1994, and this fact provides two messages of generale value: the first is how important it is to choose promising fields not occupied by others. The second message is that sometimes interesting results can be obtained by studying neglected diseases. However, in other cases, may be important to enter a field when it has just started and it presents itself as a novel ground to be dwelled.

This was the case when, in 1990, we begun to study the mechanism of action of virulence factors produced by a bacterium, *Helicobacter pylori* that was shown to be associated with severe gastroduodenal diseases by Barry Marshall, a previous Ehrlich Prize and Nobel Prizes laureate. Most gastroenterologists at the time were still not believing that gastroduodenal ulcers could be caused by a bacterium ! We soon found out that the Helicobacter vacuolating cytotoxin was acting in a totally novel way among toxins. It was forming small holes both in the plasma membrane and in an intracellular compartment in such a way as to cause a kind of traffic jam within the cell. Very much like the traffic jams that we experience sometimes in our cities ! We also found that it was depressing the immune response and that it was decreasing the barrier of permeability existing in the stomach between the acid lumen and the mucosa. This toxin has been studied in several laboratories around the world and it has emerged as a major pathogenic factor of Helicobacter. At the same time we focussed on another factor termed neutrophil activating factor and showed how it was capable of recruiting and activating inflammatory cells within the mucosa. At the same time, Antonello Covacci and colleagues at the Novartis Vaccines Research laboratories in Siena and other groups had proven that the major role in disease pathogenesis was played by a pathogenic factor termed: cytotoxin associated gene A. And I am very pleased to tell you that these three virulence factors: cytotoxin associated gene A, the cytotoxin and the neutrophil activating factor are present in a non pathogenic, but very immunogenic form into the Novartis anti-Helicobacter pylori vaccine, currently under trial. I like to think that this kind of research which translated rapidly from the laboratory to the patient is very much in Ehrlich style and would have pleased him.

I think it is about time to close and, in closing, I would like to send my grateful thanks to all those who contributed to the results which have been recognized with the present award. At the same time I would like to name and thank Professors Massimo Aloisi and Giovanni Felice Azzone who created at the Department of Biomedical Sciences of the University of Padova a rather special environment where meritorious young people could develop their own ideas and experiments in a critical and stimulating atmosphere.