NOBEL LECTURES

PHYSIOLOGY OR MEDICINE

生理学或医学诺贝尔奖讲演集

1991-1995

World Scientific
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INCLUDING PRESENTATION SPEECHES
AND LAUREATES' BIOGRAPHIES

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OR
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FOREWORD

Since 1901 the Nobel Foundation has published annually "Les Prix Nobel" with reports from the Nobel award ceremonies in Stockholm and Oslo as well as the biographies and Nobel lectures of the laureates. In order to make the lectures available for people with special interests in the different prize fields the Foundation gave Elsevier Publishing Company the right to publish in English the lectures for 1901–1970, which were published in 1964–1972 through the following volumes:

Physics 1901–1970	4 vols.
Chemistry 1901–1970	4 vols.
Physiology or Medicine 1901–1970	4 vols.
Literature 1901–1967	1 vol.
Peace 1901–1970	3 vols.

Thereafter, and onwards the Nobel Foundation has given World Scientific Publishing Company the right to bring the series up to date and also publish the Prize lectures in Economics from the year 1969. The Nobel Foundation is very pleased that the intellectual and spiritual message to the world laid down in the laureates' lectures, thanks to the efforts of World Scientific, will reach new readers all over the world.

Bengt Samuelsson
Chairman of the Board

Michael Sohlman
Executive Director

Stockholm, October 1996

PREFACE

The Nobel Prizes in Physics, Chemistry, Physiology or Medicine, and Literature are awarded by the King of Sweden during a ceremony in the Concert Hall of Stockholm. This event takes place on December 10 each year. At the same time the Bank of Sweden Prize in Economic Sciences in Memory of Alfred Nobel is also presented. Simultaneously in Oslo, Norway, the Nobel Peace Prize is awarded.

Before the Laureates receive their prizes they give a Nobel Lecture which, in the case of Physiology or Medicine, is held at the Karolinska Institute in Stockholm, usually on December 8. The audience consists of students and scientists from the Karolinska Institute and nearby academic institutions.

Giving the Nobel Lecture is the only formal duty of the laureate. Since the Nobel Prizes were first awarded in 1901 the lectures have been published in the original language in a series called *Les Prix Nobel* together with the introductory speeches given by a member of the Medical Nobel Assembly that elected the laureate(s). In the present volume the Nobel Lectures given by the Laureates in Physiology or Medicine have been reprinted in English together with the autobiographies submitted by the laureates.

Reading the Nobel Lectures and the autobiographies gives an overview of the developments in the biomedical sciences during the past century. These articles also illustrate how scientists interact with each other in national and international networks and about conditions necessary to form a creative scientific environment.

As a member of the Nobel Assembly since 1976 and now, since 1993, secretary-general of the Nobel Assembly and the Nobel Committee at the Karolinska Institute, I have had the pleasure of meeting most of the laureates during the past two decades and to hear their lectures. I hope the reader will find them as interesting as I do.

Nils Ringertz
M.D. Professor

April 1997

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ERWIN NEHER and BERT SAKMANN

for their discoveries concerning the function of single ion channels in cells

THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

Speech by Professor Sten Grillner of the Karolinska Institute.
Translation from the Swedish text.

Your Majesties, Your Royal Highnesses, Ladies and Gentlemen,

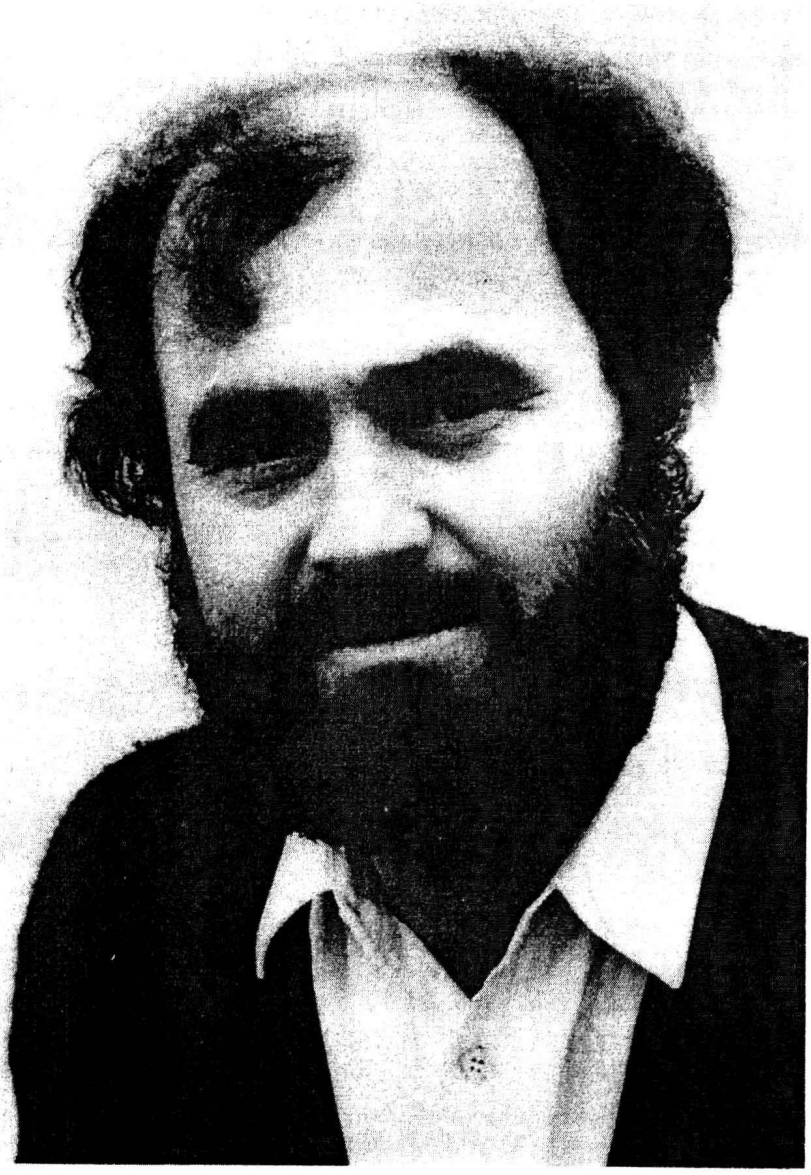
Our cells constitute the small working units of the body. Each organ consists of a bewildering number of cells. The nervous system alone has a larger number of nerve cells than there are human beings on earth. Every little cell is surrounded by a thin membranous wall, like a soap bubble. This membrane surrounds the interior of the cell in which there is a high level of activity; large and small molecules are being manufactured. Each cell has power plants of its own, which produce chemical packets of energy for the cell factory. The interior of the cell is very sensitive to change, it is demarcated by the cell membrane. The cell must continuously make new molecules, distribute its different products, and handle its waste products efficiently. Therefore, the cell membrane contains a number of specific transport systems, which bring different agents in and out of the cell. *This year's Nobel Prize is concerned with such a transport system — the ion channel system.* It transports electrically charged atoms, commonly called ions. The body fluids consist mainly of sodium, potassium, and chloride ions. The interior of the cell has a high concentration of potassium ions, whereas sodium ions dominate on the outside. This leads to a difference in electric potential between the inside and the outside of the cell, which can amount to as much as a tenth of a volt. This membrane potential is used for a number of different tasks. It permits, for example, nerve cells to send rapid electrical signals along their processes, and many of the cells in the body to communicate with each other.

Ions are transported through ion channels, which can be specific to one type of ion like sodium or potassium. Every single ion channel consists of one protein molecule or a molecular complex, which forms the walls of a thin channel, connecting the interior of the cell with its exterior. The ion channel has such a small diameter that it corresponds to the width of only one single ion, and it is thus incredibly small. The ion channel is opened or closed as its molecule changes shape. When, for example, the ion channel molecule for sodium is opened, sodium ions in a long row will pass through the minute ion channel into the cell, because there are more sodium ions outside the cell than on the inside. Since ions are electrically charged, an electric current will also pass through the open ion channel. This year's Laureates, Erwin Neher and Bert Sakmann, succeeded in making a conclusive demonstration that ion channels exist, by developing a technique by

which the miniscule currents, flowing through a single ion channel molecule, could be measured. These are currents of a thousandth of a billionth of an ampère. The technique is nevertheless, in principle very simple. A thin glass-tube filled with fluid is used as a recording electrode. The tip of the tube is pulled out to a width of only some thousandth of a millimeter. When it is brought in very close contact with the cell membrane, they form as it were, a chemical unity with each other. The ion channels, which are present in the cell membrane under the pipette opening, will then form the only connection between the interior of the cell and its outside. When one of the channels is opened a very small current will flow, which can be measured through the ingenious technique of Neher and Sakmann. We can thus measure exactly when a single ion channel is opened or closed, that is when a single molecule changes its shape. *This is a totally unique level of resolution.* This technique was combined with the new methods for biochemical microsurgery on single molecules, through which different parts of the ion channel molecules can be modified or exchanged. Through this procedure, it has been possible to elucidate the function of the different parts of the molecule, for instance, what makes an ion channel select only one type of ion, or be sensitive to a particular type of chemical transmitter. This technique has in one single blow changed our ability to study the different ion channels, which influence the life of every little cell. Thousands of laboratories throughout the entire world now use this technique to understand the roles ion channels may play in different tissues in animals or plants. Ion channels are, for instance, engaged when the cells in the pancreas secrete insulin, when the heart is contracting, or when we think or remember something. A number of diseases are either influenced or caused by a modified ion channel function. Many drugs act directly on the specific type of ion channel, which is of importance in a particular disease. Examples include, anxiety, cardiovascular disease, epilepsy, and diabetes. Our life as a unique individual actually starts with an activation of the ion channels in the egg cell by the sperm at the instant of conception. This prevents other competing sperms from gaining access to the egg cell.

Professors Neher and Sakmann,

On behalf of the Nobel Assembly at the Karolinska Institute I wish to convey to both of you our warmest congratulations for having enabled us to understand how ion channel molecules function. They are a prerequisite for biological life. You will now receive the Nobel Prize from the hands of His Majesty the King.



Li Nelson

ERWIN NEHER

Buchloe is a small town in Bavaria, situated in a rolling countryside in view of the Alps, 70 km west from Munich. This is where I grew up and spent most of my life until 1963, when I entered university. I was born in Landsberg, another town close by on the 20th of March 1944. My father, Franz Xaver Neher, was involved in the administration of a dairy company. Fortunately, this was considered to be of importance for food supply during the wartime, such that he was spared from military service. My mother Elisabeth (née Pfeiffer), who had received an education as a teacher in the early 1930s, was caring for the family of five, which included my two older sisters. Thus, in spite of the difficulties of the postwar period, I had the privilege to grow up in an intact family. Our family home was situated in a big, park-like garden, in which I spent hours by myself, watching plants and animals, and where I knew almost every pebble.

At the age of 10, I entered the 'Maristenkolleg' at Mindelheim. Mindelheim is another nearby town, and the local 'Gymnasium' is operated by a catholic congregation, the 'Maristenschulbrüder'. The big advantage of this school was that our teachers—both those belonging to the congregation and others—were very dedicated and were open not only to the subject matter but also to personal issues. During my years at the Gymnasium (1954 to 1963) I found out that, next to my interest in living things, I also could immerse myself in technical and analytical problems. In fact, pretty soon, physics and mathematics became my favourite subjects. At the same time, however, new concepts unifying these two areas had seeped into the literature, which was accessible to me. I eagerly read about cybernetics, which was a fashionable word at that time, and studied everything in my reach on the 'Hodgkin-Huxley theory' of nerve excitation. By the time of my Abitur —the examination providing access to university—it was clear to me that I should become a 'biophysicist'. My plan was to study physics, and later on add biology.

In the fall of 1963, I took up the study of physics at the 'Technische Hochschule' in Munich. The Technische Hochschule, in some contrast to typical German universities had a pretty tight schedule with quite an amount of problem-oriented course work supplementing ordinary lectures. Such training was of great help for many aspects of my subsequent research work.

In 1966, I won a Fulbright Scholarship to study in the US. I had applied for this with the idea, that it might provide access to biophysics. This was, indeed, the case. During my year at the University of Wisconsin at Madison, I was fully integrated into a biophysics laboratory involved in low angle X-ray scattering. My own project, directed by Prof. W.W. Beeman, was an early attempt at producing molecular beams of macromolecules for mass

spectrometry. In a little more than a year I earned a 'Master of Science' degree. With this formal conclusion of a physics education I felt ready for switching to biology. I returned to Munich in 1967 and looked around for some PhD project in biophysics, preferably related to nerve excitation. Fortunately, my search led me to the Max Planck-Institut für Psychiatrie, where H.D. Lux was investigating synaptic mechanisms in motoneurones and ion currents in snail neurones. We readily agreed on a project on voltage-clamping snail neurones. To circumvent space-clamp problems Dieter Lux suggested to use suction pipettes for local measurement of current density.

During my years in Dr. Lux's laboratory I met Bert Sakmann, who did his PhD project in the same institute. Bert was very interested in the basic neuronal mechanisms that we were studying, we had many lively discussions, and became friends. Following his interests Bert decided to go to London to work in the biophysics laboratory of Sir Bernhard Katz. We met again in Göttingen in 1973, where I had joined a physical chemistry laboratory to get experience with single channel recording in artificial membranes. Bert brought with him the experience on the neuromuscular junction and it required only little discussion to agree on a collaboration, aiming at the measurement of single channel currents. In 1976, we published the first single channel records while I spent a year in the laboratory of Charles F. Stevens at Yale University. Afterwards, our heads of department, Hans Kuhn and Otto D. Creutzfeldt, established independent 'Young Investigator Laboratories' for us. This was very helpful for close collaboration, and allowed us to attract a number of excellent postdoctoral fellows: Joseph P. Patlak, Fred Sigworth, Alain Marty and Owen P. Hamill. Together we perfected the technique, and developed the different recording configurations. I feel very much indebted to these collaborators as well as to colleagues who later joined the laboratory. After 1983, my interests shifted away from the channels themselves to processes they initiate inside cells, eventually leading to a cellular response-like secretion of hormones and neutrotransmitters.

Just before starting to assemble my own laboratory I met my wife, Eva-Maria—in the laboratory, of course. We married in 1978, such that my family at home, and my 'research family' grew in parallel. We now have five children: Richard (12), Benjamin (11), Carola (10), Sigmund (7), and Margret (4). My wife has given up her own scientific carreer and given me constant support for the benefit of my research.

Honorary degrees:

– Honorary Professor	University of Göttingen 1986
– Dr. h.c.	Limburgs Universitair Centrum 1988

Awards (mostly together with Bert Sakmann):

- Nernst-Haber-Bodenstein, Award of the German Society for Physical Chemistry 1977
- Feldberg Award, Feldberg Foundation, London 1979
- K. C. Cole Award, Biophysical Society 1982
- Harold Lamport Award, New York Academy of Sciences 1982
- Spencer Award, Columbia University 1983
- Adolf Fick-Preis, Universität Würzburg 1984
- Louisa Gross-Horwitz Award, Columbia University 1986
- Fidia Research Award Lecture, Fidia Research Foundation 1986
- Schunck-Preis, Universität Giessen 1986
- Leibniz Award, Deutsche Forschungsgemeinschaft 1986
- Gairdner Award, Toronto 1989
- Hans Hellmut Vits-Preis, Universität Münster 1990
- Bristol-Myers Squibb Research Award, New York 1990
- Gerard Prize, American Neuroscience Association 1991

ION CHANNELS FOR COMMUNICATION BETWEEN AND WITHIN CELLS

Nobel Lecture, December 9, 1991

by

ERWIN NEHER

Max-Planck-Institut für Biophysikalische Chemie, D-3400 Göttingen, Germany

Around 1970, the fundamental signal mechanisms for communication between cells of the nervous system were known. Hodgkin & Huxley (1952) had provided the basis for understanding the nerve action potential. The concept of chemical transmission at synapses had received its experimental verification by detailed studies on excitatory and inhibitory postsynaptic potentials (see B. Katz, 1966, for a concise description of the electrical signals in nerve and muscle). The question of the molecular mechanisms underlying these signals was still open, however. Hodgkin & Huxley (1952) used the concept of voltage-operated gates for a formal description of conductance changes, and by 1970 the terms Na-channel and K-channel were used frequently (see review by Hille, 1970), although no direct evidence for the existence of channels was available from biological preparations. This was different for the case of artificial membranes. Müller & Rudin (1963) introduced 'black-lipid membranes' as experimental model systems, which in many respects resemble the bimolecular lipid membrane of living cells. These membranes are rather good insulators. However, when they are doped with certain antibiotics or proteins they become electrically conductive. R.C. Bean et al. (1969) and Hladky & Haydon (1970) showed that some of these dopants induce discrete, steplike changes in conductance when they are added in trace amounts . All the evidence suggested that the conductance changes observed represented the insertion of single pore-like structures into the membranes.

In biological membranes similar measurements were not possible at the time, since the methods available for recording currents in living cells typically had background noise levels higher, by about a factor of a hundred, than the 'single-channel currents' observed in bilayers (see Fig. 1). Indirect methods, however, provided strong evidence that channels similar in conductance to those in artificial membranes should be operative in nerve and muscle cells. Early attempts to count the number of Na channels by Tetrodotoxin binding indicated that the contribution of a single channel to Na conductance might be as much as 500 pS. Later, the technique of noise analysis (Katz & Miledi, 1972; Neher & Stevens, 1977) provided more