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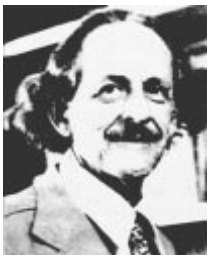

Current Comments®

EUGENE GARFIELD

INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST. PHILADELPHIA, PA 19104

The 1988 Nobel Prize in Chemistry Goes to Johann Deisenhofer, Robert Huber, and Hartmut Michel for Elucidating Photosynthetic Processes

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The 1988 Nobel Prize in chemistry was awarded to Johann Deisenhofer, Robert Huber, and Hartmut Michel, for revealing the atomic structure of a membrane-bound protein that drives photosynthesis in a purple bacterium. After briefly recounting the work that led to the prize, this essay examines the laureates' most-cited papers and the ISI® research fronts in which they appear.

Photosynthesis, as most schoolchildren learn, is the process by which sunlight is converted into chemical energy—a process essential to most life on earth. During the 1980s researchers made significant progress in elucidating the structural and chemical features of photosynthesis. The 1988 Nobel Prize in chemistry recognizes three West German scientists for their contributions to the understanding of photosynthetic processes and protein structure at the atomic level. The three are Johann Deisenhofer, Howard Hughes Medical Institute, and Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas; Robert Huber, Max Planck Institute for Biochemistry, Martinsried, Federal Republic of Germany (FRG); and Hartmut Michel, Max Planck Institute for Biophysics, Frankfurt am Main, FRG, who were honored for determining the three-dimensional structure of the photosynthetic reaction center in the purple bacterium *Rhodopseudomonas viridis*. As noted in the announcement from the Royal Swedish Academy of Sciences, Stockholm, "They are the first to succeed in unravelling the full details of how a membrane-bound protein is built up, revealing the structure of the molecule atom by atom. The protein is taken from a bacterium which, like green plants and algae, uses light energy from the sun to build organic substances."[1]

As Douglas C. Youvan, Massachusetts Institute of Technology, Cambridge, and Barry L. Marrs, E.I. du Pont de Nemours & Company, Inc., Wilmington, Delaware, point out, recent studies on photosynthesis have employed bacteria belonging to the genus *Rhodopseudomonas*. Although rhodopseudomonad photosynthesis differs in certain respects from that carried out by higher plants, it is generally similar; and these bacteria are well suited to the techniques of molecular genetics. The interiors of the bacteria are filled with photosynthetic membranes, which are small, hollow spheres (or stacks of membranes, depending on the species) made of lipid bilayers. The photosynthetic reaction centers, which are composed primarily of proteins, are embedded in the photosynthetic membranes.[2]

The challenge for researchers, as noted by Richard Henderson, Laboratory of Molecular Biology, Medical Research Council, Cambridge, UK, lay in releasing the proteins in undamaged and stable form from the lipid bilayers that constitute the membranes.[3] The next step would be to crystallize the proteins, so that their structures could be analyzed by means of X-ray crystallography. For decades, however, attempts at crystallization had failed. The proteins have components that are not soluble in water, since they must interact with lipids (within the membrane) and water (at the

membrane surface). As Roger Lewin, deputy news editor, *Science*, notes, the proteins are "partly hydrophilic and partly hydrophobic, and will not line up in neat crystalline arrays when exposed to water."[4]

In the late 1970s and early 1980s, Michel was one of many researchers attempting to crystallize membrane-bound proteins and wash them out of their membranes using a variety of detergents.[5] Working with the bacterial membrane protein bacteriorhodopsin, Michel and Dieter Oesterhelt, collaborating first at the University of Würzburg, FRG, and later at the Max Planck Institute for Biochemistry, began to experiment with a novel combination of detergents and small

Table 1: Papers authored by J. Deisenhofer, H. Michel, and R. Huber, cited in the *SCI*® from 1945 to 1988. The papers are arranged in descending order, according to number of citations. A = total citations. B = bibliographic data.

A	B
361	**Deisenhofer J, Epp O, Miki K, Huber R & Michel H.** X-ray structure analysis of a membrane protein complex. Electron density map at 3 Å resolution and a model of the chromophores of the photosynthetic reaction center from *Rhodopseudomonas viridis*. *J. Mol. Biol.* 180:385-98, 1984.
344	**Deisenhofer J & Steigemann W.** Crystallographic refinement of the structure of bovine pancreatic trypsin inhibitor at 1.5 Å resolution. *Acta Crystallogr. B—Struct. Sci.* 31:238-50, 1975.
300	**Huber R, Kukla D, Bode W, Schwager P, Bartels K, Deisenhofer J & Steigemann W.** Structure of the complex formed by bovine trypsin and bovine pancreatic trypsin inhibitor. II. Crystallographic refinement at 1.9 Å resolution. *J. Mol. Biol.* 89:73-101, 1974.
282	**Deisenhofer J, Epp O, Miki K, Huber R & Michel H.** Structure of the protein subunits in the photosynthetic reaction center of *Rhodopseudomonas viridis* at 3 Å resolution. *Nature* 318:618-24, 1985.
264	**Ruehlmann A, Kukla D, Schwager P, Bartels K & Huber R.** Structure of the complex formed by bovine trypsin and bovine pancreatic trypsin inhibitor. Crystal structure determination and stereochemistry of the contact region. *J. Mol. Biol.* 77:417-36, 1973.
221	**Huber R, Deisenhofer J, Colman P M, Matsushima M & Palm W.** Crystallographic structure studies of an IgG molecule and an Fc fragment. *Nature* 264:415-20, 1976.
194	**Deisenhofer J.** Crystallographic refinement and atomic models of a human Fc fragment and its complex with fragment B of protein A from *Staphylococcus aureus* at 2.9- and 2.8-Å resolution. *Biochemistry* 20:2361-70, 1981.
194	**Huber R & Bode W.** Structural basis of the activation and action of trypsin. *Account. Chem. Res.* 11:114-22, 1978.
181	**Epp O, Colman P, Fehlhammer H, Bode W, Schiffer M, Huber R & Palm W.** Crystal and molecular structure of a dimer composed of the variable portions of the Bence-Jones protein REI. *Eur. J. Biochem.* 45:513-24, 1974.
159	**Huber R, Kukla D, Ruehlmann A, Epp O & Formanek H.** Basic trypsin inhibitor of bovine pancreas. I. Structure analysis and conformation of the polypeptide chain. *Naturwissenschaften* 57:389-92, 1970.
153	**Huber R, Epp O, Steigemann W & Formanek H.** Atomic structure of erythrocruorin in light of the chemical sequence and its comparison with myoglobin. *Eur. J. Biochem.* 19:42-50, 1971.
152	**Huber R & Hoppe W.** Zur Chemie des Ecdysons, VII. Die Kristall- und Molekulstrukturanalyse des Insektenverpuppungshormons Ecdyson mit der Automatisierten Faltmolekulmethode (Chemistry of the ecdysones. 7. Crystal and molecular structure analysis of the insect pupation hormone ecdysone with the automatic molecular method). *Chem. Ber.* 98:2403-24, 1965.
140	**Michel H.** Three-dimensional crystals of a membrane protein complex. The photosynthetic reaction center from *Rhodopseudomonas viridis*. *J. Mol. Biol.* 158:567-72, 1982.
128	**Huber R, Epp O & Formanek H.** Structures of deoxy- and carbonmonoxy-erythrocruorin. *J. Mol. Biol.* 52:349-54, 1970.
122	**Huber R, Kukla D, Ruehlmann A & Steigemann W.** Pancreatic trypsin inhibitor (Kunitz). I. Structure and function. *Cold Spring Harbor Symp.* 36:141-8, 1971.
118	**Colman P M, Deisenhofer J, Huber R & Palm W.** Structure of the human antibody molecule Kol (immunoglobulin G1): an electron density map at 5 Å resolution. *J. Mol. Biol.* 100:257-78, 1976.
99	**Deisenhofer J, Colman P M, Epp O & Huber R.** Crystallographic structural studies of a human Fc fragment. II. A complete model based on a Fourier map at 3.5 Å resolution. *Hoppe Seylers Z. Physiol. Chem.* 357:1421-34, 1976.
88	**Michel H & Oesterhelt D.** Light-induced changes of the pH gradient and the membrane potential in *H. halobium*. *FEBS Lett.* 65:175-8, 1976.
85	**Deisenhofer J, Jones T A, Huber R, Sjodahl J & Sjoquist J.** Crystallization, crystal structure analysis and atomic model of the complex formed by a human Fc fragment and fragment B of protein A from *Staphylococcus aureus*. *Hoppe Seylers Z. Physiol. Chem.* 359:975-85, 1978.

"amphiphilic" molecules, which have both hydrophilic and hydrophobic elements. As Youvan and Marrs point out, the hydrophobic ends of these molecules bind to the hydrophobic parts of the membrane proteins, exposing the hydrophilic ends of the small molecules. The resulting combination of small molecules and proteins can then be dissolved in a water-based solution and thence crystallized.[2]

Using these techniques, Michel and Oesterhelt managed to get true three-dimensional crystals of bacteriorhodopsin; however, the crystals were not sufficiently well ordered for a high-resolution X-ray crystallographic analysis. Michel then turned his efforts to crystallizing the photosynthetic reaction center of *Rh. viridis*. In 1981 he succeeded in producing large, well-ordered crystals of *Rh. viridis*. He published his results in the *Journal of Molecular Biology* in 1982.[6]

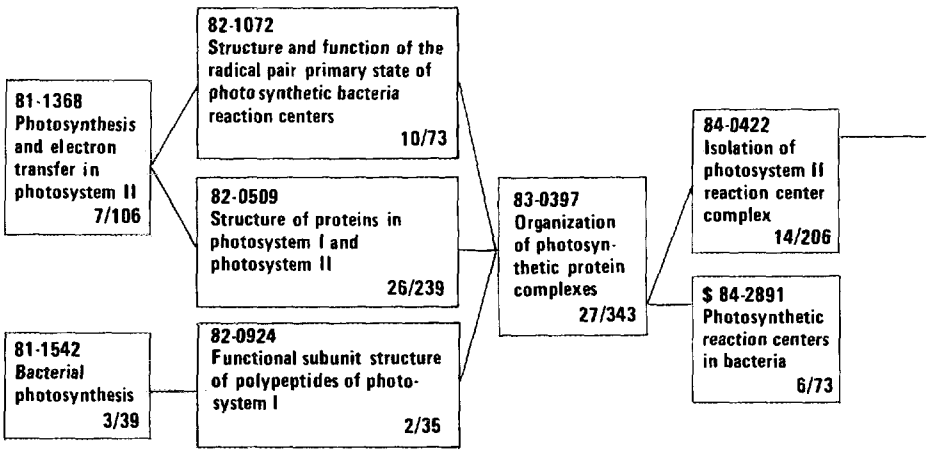
The next step was to analyze the structure through X-ray crystallography. At this point, Michel began his collaboration with Deisenhofer, who worked in the protein-structure laboratory in Martinsried (located outside Munich) headed by Huber. Within two years, in 1984, the team (including colleagues Otto Epp and Kunio Miki) solved the structure.[7] One year later, in *Nature*, they gave a complete description of the *Rh. viridis* reaction center—making it the first membrane protein whose structure was solved at the atomic level.[8]

The structure elucidated by Michel, Deisenhofer, and Huber confirmed much of what had been learned about *Rh. viridis* in previous studies. There are four protein subunits, denoted L, M, H, and C, in the reaction center. The heart of the reaction center consists of four molecules of chlorophyll, two of pheophytin, and two quinones. The work of the laureates helped clarify the role

Table 2: *SCI*® research fronts from 1974 to 1988 in which papers by J. Deisenhofer, H. Michel, and R. Huber occur as core documents. A = number of core papers. B = number of citing papers for that year.

Number	Name	A	B
74-0408	Proteinase inhibitors	14	120
76-1369	Trypsin-trypsin inhibitor complexes	3	49
77-0062	Protein structure	51	492
77-0455	Human platelet glycoproteins	12	162
78-0151	Structure and conformation of immunoglobulins	10	126
78-0537	X-ray structure of proteins	5	89
78-0594	Structural basis of action of trypsin	2	41
78-1119	NMR spectra of macromolecules	5	67
78-1633	Structure of globular proteins and nucleic acids	3	46
79-0124	Light energy conversion in *Halobacterium halobium*	32	528
79-1123	NMR of pancreatic trypsin inhibition	9	126
79-1725	Activity and inhibition of bovine trypsin	3	44
79-1726	Three-dimensional structure of immunoglobulins	4	42
81-0365	Protein-protein interactions	4	58
82-1042	Crystallographic and NMR studies of the serine proteases	4	68
82-1799	Structural analysis of immunoglobulin binding to protein A receptors produced by staphylococci and streptococci	2	27
83-1221	Molecular dynamics of protein	11	245
83-5197	Studies of protein A binding to immunoglobulins and other antibodies	5	117
84-2891	Photosynthetic reaction centers in bacteria	6	73
85-2777	Peptide synthetic chemistry	3	35
85-4691	Study of conformational states of proteins	5	79
85-4692	Photosynthetic reaction centers	3	76
86-0853	Photosynthetic membrane	40	532
86-2054	Photosynthetic light reactions	10	200
86-6704	Enzyme catalysis in trypsin	3	47
87-1182	Photosynthetic electron transport chain	47	665
87-3576	NMR studies on conformational properties of the Fc-fragments of human immunoglobulins	2	44
87-6801	Folding and association of proteins	2	32
88-0623	Photosynthetic bacteria and photosynthetic reaction centers	35	572
88-3482	Structure and function of Fc-receptors	4	69

Figure 1: Historiograph of research on the photosynthetic reaction center. Numbers of core/citing papers are indicated at the bottom of each box. Asterisks (*) indicate research fronts in which J. Deisenhofer is a core or citing author; dollar signs ($) indicate research fronts in which H. Michel is a core or citing author.



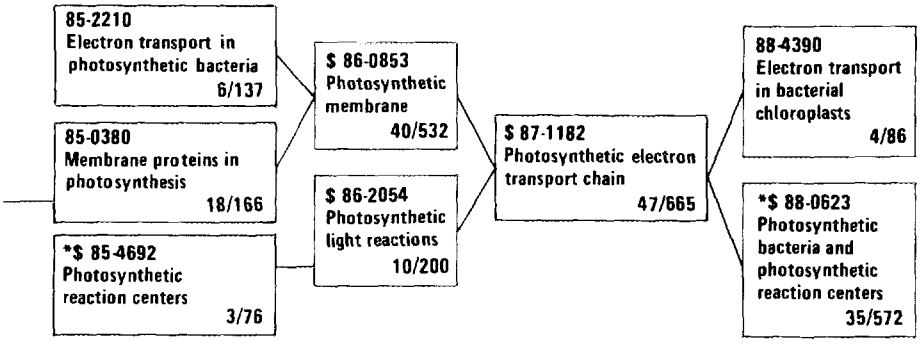
of two chlorophyll molecules—known as the special pair—that sit at the head of the complex with one molecule each of chlorophyll, pheophytin, and quinone arranged in symmetrical chains on either side around a single iron atom. However, for reasons that remain unclear, the electron transfer that is set in motion by the absorption of light proceeds along just one of these chains.[5]

As the Swedish Academy points out in their announcement, the determination of this structure will aid in our understanding of photosynthetic processes in higher plants. The work also has many ramifications beyond the immediate study of photosynthesis. Other biological functions involving membrane proteins include the transport of chemical substances between cells, hormone action, and nerve impulses.[1]

The prizewinning work of Michel, Huber, and Deisenhofer followed the related contributions of several previous Nobel laureates. The German physicist Max von Laue, for example, won the physics prize in 1914 for his investigations into the diffraction of X rays by crystals. In 1915 the English physicists Sir William Henry Bragg (father) and Sir William Lawrence Bragg (son) shared the physics prize for their methods of studying crystal structures by means of X rays. Seventy years later, Americans Jerome Karle and Herbert A. Hauptman shared the chemistry prize for their mathematical "direct methods" designed to solve the three-dimensional crystal structures of important molecules. We discussed the work of Hauptman and Karle in a 1986 essay.[9]

Nobel committees have recognized a number of discoveries based on X-ray diffraction methods. The elucidation of the chemical structure of DNA, for which American molecular biologist James D. Watson and his English colleagues Francis H.C. Crick and Maurice H.F. Wilkins shared the physiology or medicine prize in 1962, is one example. Another is the structural studies of globular proteins by English biochemists Sir John C. Kendrew and Max F. Perutz, honored with the 1962 chemistry prize.

The 1961 chemistry prize also recognized research into photosynthetic processes. Organic chemist Melvin Calvin was honored for his work at the University of California, Berkeley, on carbon dioxide assimilation in plants. The cycle by which carbon dioxide is converted to carbohydrates bears Calvin's name. Also applicable is the work of English biochemist Sir Peter D. Mitchell, who received the chemistry prize in 1978 for his chemiosmotic theory, which sought to explain energy coupling in the mechanisms of oxidative and photosynthetic phos-



phorylation—the means by which aerobic organisms and plants obtain their energy.

Most-Cited Papers

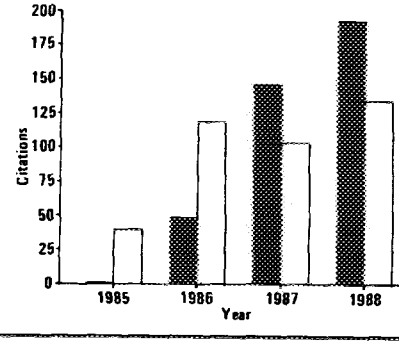
Table 1 lists the most-cited papers by the three laureates. At the top of the list is the 1984 paper from the *Journal of Molecular Biology* announcing the structure of the membrane protein in *Rh. viridis*.[7] This paper has attracted over 360 citations. It is one of three core papers in the 1985 research front "Photosynthetic reaction centers," #85-4692. As we've noted previously, research fronts are formed when papers in a given year collectively cite a common, core group of older papers. Research front #85-4692 and others are shown in Figure 1, a historiograph of research on the photosynthetic reaction center.

The second most-cited paper in Table 1, with approximately 340 citations, is a 1975 paper from *Acta Crystallographica Section B—Structural Science* by Deisenhofer and his colleague, W. Steigemann.[10] This paper, discussing the crystallographic structure of bovine pancreatic trypsin inhibitor, is one of five core documents in the 1985 research front "Study of conformational states of proteins," #85-4691.

The work of Huber, Deisenhofer, and Michel can be found in several ISI® research fronts, as far back as 1974. For example, a 1973 *Journal of Molecular Biology* paper coauthored by Huber, "Structure of the complex formed by bovine trypsin and bovine pancreatic trypsin inhibitor"[11] (appearing in Table 1 with A. Ruehlmann as first author, with approximately 260 cites), is one of 14 core documents in the 1974 front "Proteinase inhibitors," #74-0408. Table 2 is a complete listing of the research fronts in which their work appears as core documents. As can be seen, the fronts cover a variety of research on protein structure and activity.

Also among the most-cited papers in Table 1, with over 280 citations, is the 1985 paper from *Nature* giving a complete description of the reaction center.[8] This paper also appears in Figure 1, one of 35 core papers in a 1988 front, "Photosynthetic bacteria and photosynthetic reaction centers," #88-0623. Figure 2 is a graph of year-by-year citations to this paper and to the 1984 *Journal of Molecular Biology* paper in which the researchers initially announced the structure.[7]

Figure 2: Year-by-year citations to J. Deisenhofer et al., *Nature* 318:618-24, 1985 (black bar) and J. Deisenhofer et al., *J. Mol. Biol.* 180:385-98, 1984 (white bar).



Michel's 1982 paper from the *Journal of Molecular Biology*, reporting the successful crystallization of *Rh. viridis*, also appears in the most-cited list in Table 1, with approximately 140 citations.[6] This work is a core document in several fronts in Figure 1, beginning with "Photosynthetic reaction centers in bacteria," #84-2891, and continuing through front #88-0623.

As *Nature* noted in a wry postscript to its report on the 1988 Nobel Prizes, Michel originally submitted his 1982 paper to *Nature*. However, because no structural information had yet been obtained, the journal declined to publish it. The 1985 publication of the complete description of the reaction center in *Nature*, as the postscript concludes, brought a happy ending to the "editor's nightmare" of rejecting a Nobel Prize-winning paper.[12]

Biographical Notes

Robert Huber was born in 1937 in Munich, Germany, and received his doctorate from the Technical University in that city. He became a division head at the Max Planck Institute for Biochemistry in 1972 and was made director in 1987.

Johann Deisenhofer was born in Zusamaltheim, Bavaria, Germany, in 1943. He received his doctorate from the Max Planck Institute for Biochemistry. In 1988 he came to the US, accepting positions at the Howard Hughes Medical Institute, and the Department of Biochemistry, University of Texas Southwestern Medical Center.

Hartmut Michel was born in 1948 in Ludwigsburg, FRG, and took his doctoral degree from the University of Würzburg. He worked at the Max Planck Institute for Biochemistry from 1979 until 1987, when he became director at the Max Planck Institute for Biophysics.

This concludes our examination of the 1988 Nobel Prize in chemistry. In forthcoming essays, as is our custom, we will examine the 1988 Nobel laureates in physiology or medicine, physics, economics, and literature.

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