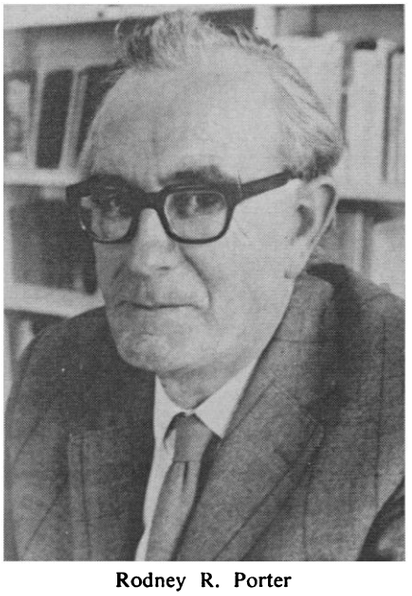
The 1972 Nobel Prize for Physiology or Medicine

The Nobel Prize for Physiology or Medicine for 1972 has been awarded jointly to Rodney R. Porter of Oxford University and Gerald M. Edelman of Rockefeller University for their separate research on the chemical structure of antibodies.

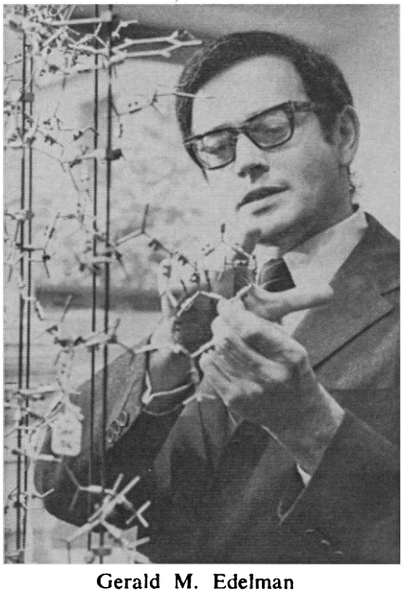
Porter was much influenced by the writings of a previous Nobel laureate, Karl Landsteiner, who advocated study of the chemical structures of antigens and antibodies in order to understand their interactions. Because antibody molecules were such large proteins, Porter sought to obtain "active fragments" from them by selective cleavage with enzymes. The hope was that such fragments, with antigen-binding specificity, would be amenable to primary structural analysis by the evolving methods used successfully by Porter's mentor, Fred Sanger of Cambridge University, in his Nobel-prizewinning determination of the chemical structure of insulin. Although Porter obtained active fragments from rabbit antibodies as early as 1950, it was not until 1958 that he was able to account for the whole antibody molecule in terms of three fragments of about the same size, which he recovered after antibodies were cleaved with the enzyme papain. Because two of these fragments (Fab) were alike and had antigen-binding activity whereas the third (Fc) readily crystallized and had quite different activities, it was clear that the cleavage occurred between functionally different parts and that the nature of the products accorded beautifully with the known bivalency of immunoglobulin G (IgG) antibodies. Ever since this simple separation of antibodies into functional fragments was announced, selective enzymic cleavage of immunoglobulins has been the starting point for diverse and innumerable studies in basic and clinical immunology and in cell biology in general. Applications of the Porter-type fragmentation procedure range from the preparation of highly specific "stains" consisting of modified Fab for use in electron microscopy to studies of the molecular mechanism of histamine release from mast cells whose plasma membranes are complexed with the Fc portion of human allergenic antibody.

Edelman undertook his doctoral thesis research with Henry Kunkel at Rockefeller, who recognized that human myeloma proteins, homogeneous products of plasmacytoma cell lines, were excellent models for antibody molecules. Structural studies of human immunoglobulins, including their enzymic fragmentation by Porter's procedures, were described in Edelman's thesis of 1960. However, he was aware from studies of Porter and others that these enzymatically produced fragments were not biosynthetic units of antibodies, and was dissatisfied with the notion that immunoglobulin molecules consisted of a single polypeptide chain of more than 1300 amino acid residues. Thus Edelman sought successfully to render immunoglobulin molecules into component polypeptide chains by reductive cleavage of all disulfide bonds in the presence of the dissociating reagent urea. His reports in 1959 and 1961 that immunoglobulins could be resolved into light polypeptide chains (L chains) and less well characterized larger polypeptides (H chains) by the likely cleavage of interchain disulfide bonds awakened his colleagues to the probability that antibodies, like insulin, were comprised of at least two qualitatively different polypeptides. Edelman, together with collaborators from New York University, then demonstrated that the L chains from guinea pig antibodies of different specificities yielded different characteristic patterns of electrophoretic mobilities. Thus it became likely that structural differences of L chains could eventually be related to different antigen-binding specificities. Another perceptive realization contributed by Edelman at this time was that the immunoglobulin-related proteins, called Bence-Jones proteins, often found in the urine of patients with multiple myeloma, were similar to L chains of antibodies. Thus structural studies of Bence-Jones proteins probably would yield information applicable to antibodies.

Porter—working in 1962–63 with students and fellows, among them his long-term colleague, Elizabeth Press—made a crucial contribution to the quaternary structure of IgG. With his legendary knack for both clean molecular surgery and separation of protein molecules, he was able to part the polypeptides of rabbit immunoglobulin by controlled reductive cleavage of interchain disulfide bonds, leaving the separated chains sufficiently native to permit antigenic analysis. Careful molecular weight determinations, the consequent recognition of the 1 to 1 stoichiometric relation of H to L chain, and amino acid and antigenic analysis led to the universally accepted four-chain model for IgG (Fig. 1). This model showed IgG antibody to be composed of two pairs of qualitatively different polypep-



Rodney R. Porter



Gerald M. Edelman

tides, H and L chains, and indicated the cleavage by papain at the middle of the heavy chains to yield Fab fragments containing antigen-binding sites. These Fab moieties were comprised of the NH_2-terminal half of the H chain and the whole L chain. Pairs of H and L chains, each forming one active site, have since been found by many workers to be the natural functional unit of all species and classes of antibody molecules.

During the 1960's, an extraordinary series of informal scientific meetings, called "Antibody Workshops," were held as often as twice a year at locations from California to Israel. These meetings were open to all who sought to contribute to molecular immunology and drew senior scientists from other fields and many young students into a study of antibody molecules. Porter and Edelman were dominant in stimulating contributors at these gatherings.

Now developments came rapidly and from many groups. The contributions of the H and L chains to the antigen-combining site intrigued many. Porter established the role of the H chain as perhaps the main repository of antigen-binding specificity. Edelman presented data complementary and supportive to those of Frantisek Franek of the Czech Academy of Sciences, leading to the conclusion that the H and L chains cooperated to form a site with an energy of antigen-binding characteristic of the intact parent molecule. Edelman's group, along with others, studied the propensity of immunoglobulin chains to self-assemble in vitro to yield molecules of the parent composition.

Much further understanding of antibody molecules came from continuing primary structural analyses. Norbert Hilschmann at Rockefeller and Frank Putnam at the University of Florida separately elucidated all or part of the amino acid sequences of L chains from several human Bence-Jones proteins. The striking conclusion was that L chains had a carboxyl COOH-terminal "constant" half (C_L) with the same primary structure and an NH_2-terminal variable half (V_L) that varied in sequence. Porter, knowing that rabbit Fc had no antigen-binding site, guessed that this crystallizable fragment of the COOH-terminal half of the H chain would be homogeneous and inspired Robert Hill of Duke University to determine its primary structure. In Porter's laboratory, the COOH-terminal half of Fc from rabbit H chain (C_H1) was also found to be homogeneous. From all this primary structural information, the segmental aspect of immunoglobulins stood out, and the repeating homologous sections of antibody (C_L, C_H1, C_H2, and C_H3) were apparent.

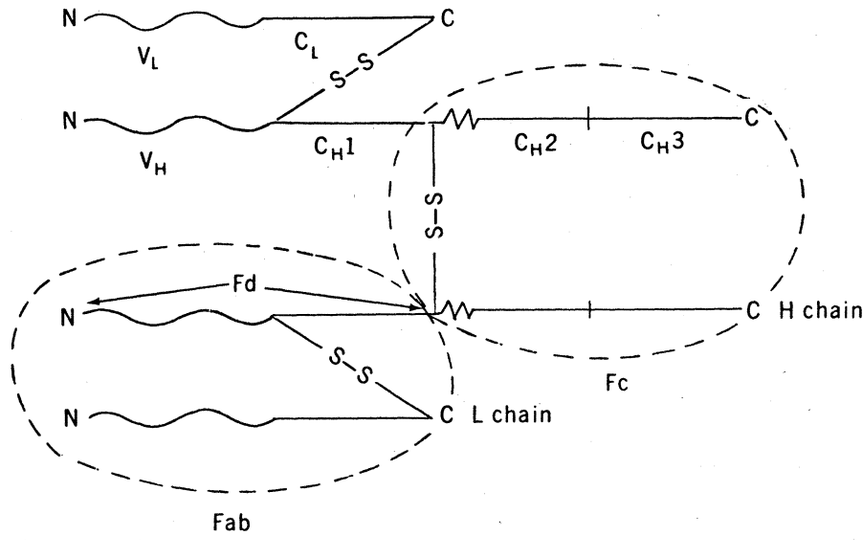


Fig. 1. The four-chain structure of immunoglobulin G. The diagram is based on the quaternary structural features proposed by Porter following Edelman's demonstration of the multichain nature of the molecule.

If "variable" regions were related to the antigen-binding site, the significant contribution of the H chain to binding specificity made it likely that this chain contained a "variable" region analogous to V_L. Porter's group made a dual approach to primary structural analysis of the H chain, concentrating on the NH_2 terminal halves of H chains from homogeneous human myeloma proteins and from pooled "normal" rabbit immunoglobulin, which is a vast mixture of antibodies. Press and her colleagues in Porter's group found evidence for a V_H region comprising about 110 residues at the NH_2-terminal end of the H chain when they compared the primary structures of IgG from several myelomas, including the one being elucidated in Edelman's laboratory. Porter's group also found the corresponding region from rabbit H chain of "normal" IgG to be heterogeneous and to contain alternate amino acids at many residue positions. At about this time Edelman had set for himself a formidable task, the determination of the primary structure of an entire human myeloma protein. With the help of William Konigsberg of Yale, who had been a principal contributor to the total primary structural analysis of human hemoglobin, the Edelman group achieved their goal in 1969. Their data permitted for the first time a comparison of V_H and V_L from the same molecule and formally established that a single antigen-binding site is comprised of two qualitatively different polypeptide regions. The completed structure also illustrated elegantly the known repetition of homologous sections within the IgG molecule. Edelman called these repeating sections "domains"—C_L, C_H1, C_H2, and C_H3—and suggested that each was a functional unit responsible for certain secondary biologic activities of antibodies. In the light of the x-ray crystallography data of Roberto Poljak (Johns Hopkins University) it is likely that the actual functional units are pairs of these domains intercollated to form globular units within the molecule.

Numerous primary structural analyses have been done on H and L chains from myeloma proteins and antibodies produced by immunization. Comparison of sequences and the use of affinity labels to chemically modify antibodies and mark residues in or near the antigen-binding site has led to the recognition in both V_H and V_L of three short (5- to 15-residue) "hypervariable" segments that may determine specificity. Porter's group has contributed a class of affinity labels, the nitrenes, which may come to be of great value for probing active sites because they can be photoactivated after they become bound specifically to the protein and react with almost any nearby amino acid residue.

Porter has championed the parallel analyses of model homogeneous myeloma proteins and specific antibodies in the belief that the whole process leading to an immune response can be better understood if we can more exact-

ly characterize the product antibodies. Edelman has evolved and refined theories to account for the presence of structural genes for particular antibodies at the time an organism is synthesizing them. He has advocated translocation of V_H and V_L genes to members of a group of corresponding C_H and C_L genes, respectively. Together with Joseph Gally (Meharry Medical College), he has also set forth possible mechanisms in support of the school which favors generation of some changes in immunoglobulin genes during somatic cell division.

Both Rod Porter and Gerry Edelman will be credited with inspiring the solution of remaining exciting problems in immunology, and in all likelihood will contribute to their solution. These problems include a correlation of primary structure with antigen-binding specificity, determination of the complete three-dimensional structure of IgG by x-ray crystallography, the synthesis of V_H and V_L regions with desired ligand-binding properties, a description of the genetic mechanisms leading to diverse antigen-binding specificities, and an understanding of the processes of lymphoid cell differentiation and cellular interactions that precede antibody synthesis.

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Magnetohydrodynamic Power: More Efficient Use of Coal

Coal is the largest source of energy which is available now in the United States, but research into methods of improving the use of coal as a fuel has languished for lack of support. In recent years, however, more attention has been given to cleaning up coal-burning power plants, which despite their disadvantages are likely to continue as the mainstay of the utility industry for the rest of the century. Magnetohydrodynamic (MHD) generators that convert heat from combustion gases directly into electricity constitute one possible alternative, in that the high efficiency attainable with this technology would lead to reduced consumption of fossil fuels and markedly reduced thermal pollution. Perhaps surprisingly, it now appears that MHD generators also offer one of the best methods of eliminating sulfur oxide and reducing nitrogen oxide emissions from coal-fired power plants.

Despite its promise, MHD has yet to be demonstrated as a practical technology, in part because support for construction of large-scale experimental facilities has not been available. Substantial technical problems associated with the endurance of the equipment remain to be resolved—MHD generators operate at elevated temperatures, typically 2400°C in the gas entering the generator, and the hot residues from coal combustion are extremely corrosive—although most scientists in the field are confident that these will not present serious obstacles. Because the technology has not been demonstrated, its economic prospects are still uncertain, but preliminary estimates are favorable.

Research on MHD is becoming worldwide, with active efforts in Japan and several European countries. Several laboratories in this country are working on MHD with support from the U.S. Department of Interior and the utility industry. A more ambitious effort is being conducted in the U.S.S.R., which is already testing an experimental 75 megawatt power plant incorporating an MHD generator. Recent U.S. visitors report that the plant has so far produced up to 4 Mw for brief periods and seems to be operating successfully. The Russian program is primarily oriented toward the use of natural gas as the fuel—a choice that makes design of the generator not as difficult as for ash-laden fuels such as coal.

The MHD generator is basically an expansion engine in which hot, partially ionized gases flow down a duct lined with electrodes and surrounded by coils that produce a magnetic field across the duct. Unlike the gas in a turbine, the expanding gas propels only itself, and the movement of the electrically conducting gas through the magnetic field generates a current in the gas that is collected at the electrodes. Thus MHD generators are compact, have no moving parts, and can potentially accommodate temperatures and corrosive gases that would destroy conventional turbines. Very high temperatures would be necessary to ionize combustion gases; but with the addition of small amounts of potassium or other alkali metals, temperatures in the range 2000° to 2500°C provide sufficient ionization to allow the process to work.

Power plants incorporating MHD generators would include, in addition to the generator itself, pressurized combustion chambers for burning the fuel and heat exchangers or other equipment for preliminary heating of the air fed to the combustor. The preliminary heating appears to be necessary to reach the required temperatures, unless oxygen in large quantity is added to the fuel mixture, a procedure that would be uneconomical at present. Exhaust gases from the MHD generators themselves would be used, in full scale power plants, to generate additional electricity with conventional steam turbines; in most designs, MHD would provide about half of the electricity from the combined plant. The overall efficiency of the combined generating facility is expected to reach about 50 percent in the first full-scale MHD plant, as compared to 40 percent for the best conventional or nuclear power plants; and with more sophisticated MHD designs the efficiency could reach 60 percent.

MHD generators need stronger magnets than ordinary generators do because of the lower conductivity of gases as compared to copper, and superconducting magnets will probably be used in commercial plants. Large superconducting magnets have been built for applications in high energy physics, but relatively few have been built for MHD purposes and they are still very expensive. Research with the field strengths equivalent to those that will probably be used in MHD power plants (50,000 gauss) is only beginning. The electricity produced from MHD generators is inherently direct current, which must be converted before transmission over existing networks.

Endurance of the generator remains the most substantial problem facing those working on MHD. Only limited experience with long-term operation has been gained—a few-kilowatt generator at the Avco Corporation in Everett, Massachusetts, has been operated for several hundred hours and a 70-kw generator has been run for 500 hours in the U.S.S.R. The major question about long-term durability is whether leakage of current and arcing between electrodes due to condensation and penetration of the seed material into the