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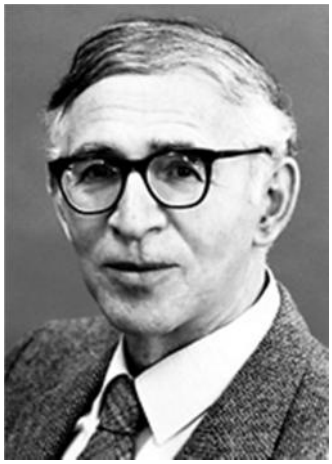
Nobel Prize in Chemistry 1982



Aaron Klug

The Nobel Prize in Chemistry 1982 was awarded to Aaron Klug *"for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes"*.

Information about winners:

Aaron Klug, MRC Laboratory of Molecular Biology, Cambridge, England,

RESEARCH INFORMATION:

DEPICTING THE BUILDING BLOCKS OF LIFE

Life is a chemical phenomenon. Living organisms are the most complicated of all chemical systems in the universe. In contrast to the dead matter which surrounds us, life is characterized by a high degree of order and organization. The building blocks of the cell are to a large extent giant molecules (macromolecules) in which thousands of atoms occupy a unique arrangement in space specific for each substance. The cell also contains ordered structures, organelles, which are large aggregates of different macromolecules, and many important biochemical functions are associated with such molecular aggregates. As examples may be mentioned that the chemical machinery of heridity is localized in the cell

nucleus, and other organelles, mitochondria, are the power stations of the cell, producing energy by combustion.

The goal of biochemistry is to explain a biological function on the basis of chemical structure. An important step in biochemical research is consequently the isolation and structure determination of the macromolecular components of the cell and of the functional aggregates formed from them. Pure chemical substances can often be obtained in the form of crystals, in which the position of the constituent atoms and molecules is repeated in a periodic fashion, and in this case there is a general method available for determination of structure. This method is based on an interpretation of the specific pattern which is created, when X-rays are scattered from atoms in a periodic arrangement. The principle of X-ray diffraction is old and was awarded with the Nobel Prize in physics already in 1915. Not until much later was the method sufficiently developed for the determination of the structure of biological macromolecules. Max Perutz and John Kendrew were awarded the 1962 Nobel Prize in chemistry for their investigations on the structure of proteins by X-ray diffraction.

Complicated molecular aggregates, such as membranes, muscle fibres and chromosomes, can generally not be obtained as highly ordered, three-dimensional crystals suitable for structural determination by X-ray diffraction. Aaron Klug, who has been awarded this year's Nobel Prize in chemistry, has developed a method for the structural determination of biologically functional molecular aggregates. His technique is based on an ingenious combination of electron microscopy with principles from diffraction methods.

Electron microscopy has long been used to obtain a two-dimensional picture of biological objects. The power of the method to give a clear picture of the structure is, however, limited by several factors. The molecules of life consist mainly of light atoms, which makes the picture lacking in contrast. Increased contrast can be achieved with long exposure times, but this entails the danger that the structure is destroyed by radiation damage. Instead the contrast is generally improved by "staining" with heavy metals, which can also lead to a distortion of the structure.

Klug has shown that pictures of biological objects seemingly lacking in contrast often contain a large amount of structural information, which can be made available by a mathematical manipulation of the original picture. His method allows electron microscope pictures of high quality to be obtained with very low radiation doses and without the use of heavy metal stains. In this way changes in the sample are minimized, so that the electron microscope picture at high resolution is a true representation of the original biological structure. The method gives a two-dimensional projection of the sample only, but Klug has shown that a three-dimensional reconstruction of the object can be obtained by collecting pictures in several different directions of projection.

The method of Klug makes it possible to determine structures at high resolution of functionally important molecular aggregates. Klug himself has chiefly investigated complexes between nucleic acids and proteins, the key substances of life. One nucleic acid, DNA, is carrier of the traits of heredity in the chromosome of the cell nucleus, and it forms giant complexes with specific proteins, histones. Less complicated nucleic acid-protein complexes are found in viruses, which can be said to be genetic material without a cell of its own. Klug has used the whole arsenal of structural chemistry, including his own method, to investigate the structure of several viruses, e.g. tobacco mosaic virus (TMV). His structural investigations snow that TMV contains a long thread of nucleic acid which is arranged in the form of a helix through interaction with as many as 2130 identical protein molecules. Klug's structural investigations have also given a detailed picture of the formation of the virus particle from a mixture of its nucleic acid and protein constituents. In this way he has illuminated a very important biochemical principle, namely the spontaneous formation of complicated functional molecular aggregates from the molecular components.

The DNA-protein complex of cell nuclei, chromatin, is condensed to chromosomes during cell division. In a given cell only a part of the genetic message in DNA is transcribed, a fact which must also be related to structural changes in the chromatin. Knowledge of chromatin structure is consequently of great importance for an understanding of the control functions of the cell.

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Chromatin is too large a molecular aggregate to allow a direct structural determination even by the method of Klug. With his co-workers, Klug has, however, succeeded in breaking down chromatin to fragments which are small enough to be studied by X-ray diffraction and electron microscopy. Klug has then been able to construct a model for the chromosomes based on his knowledge of the structure of the fragment.

Klug's investigations of biochemical structures have yielded a detailed picture of the functional arrangements in biologically important nucleic acid-protein complexes. They have already provided clues to the problem of cell differentiation, since the transcription of the genetic message in a cell is under structural control. Continued structural investigations of chromatin will, in a long-term perspective, undoubtedly be of crucial importance for our understanding of the nature of cancer, in which the control of the growth and division of cells by the genetic material no longer functions.

For more details please visit:

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1982/press.html