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Nobel Prize in Chemistry 1958

Frederick Sanger

The Nobel Prize in Chemistry 1958 was awarded to Frederick Sanger *"for his work on the structure of proteins, especially that of insulin"*.

RESEARCH INFORMATION:

The proteins are among the most complicated and enigmatic substances in Nature and appear to be particularly closely related to all that we call Life. To this group of key substances belong for example all enzymes and many hormones, which control the chemical processes of Life, also the viruses and many toxins which cause disease, and antibodies, which are formed on vaccination, and are able to protect us against infection. In blood and in all tissues of the body, in muscles, nerves and skin, proteins form an essential and functional constituent. It is the chemical individuality of proteins which is responsible for the species' differences among all living things. The determination of the exact building-plan for these complicated giant molecules appears as one of the greatest problems in today's scientific research.

Even if some protein molecules are big enough to be observed in our most powerful electron microscopes it is not possible by any direct method to see the finer details in their structure. Here one must resort to the indirect methods which chemists use in studying the structure of complicated substances. Thus one has to break down the big molecules by

suitable methods and look for simpler and well-known substances among the fragments obtained. This procedure was used with proteins by the German chemist and Nobel laureate Emil Fischer in the beginning of this century. He found that protein molecules contain long chains of so-called amino acids. These are comparatively simple substances of which about 25 different kinds are found in Nature, and they are formed when proteins are boiled with strong acids. Thus we know that proteins contain a large number of different kinds of amino acids, but the composition and, above all, *the sequence* of the amino acids in the chains vary considerably. As a matter of fact it has long been assumed that it is this sequence which determines the individual chemical and physiological properties of different proteins.

That insulin is a physiologically important hormone which is used in the treatment of diabetes is well known to all. Insulin is also a protein and even if its molecules do not belong to the largest, they are sufficiently complicated to make the task of determining their structure appear a formidable one. It was this venture, however, which Frederick Sanger started fifteen years ago and which after zealous and persistent work gradually led him to a successful solution of the problem; namely the exact mode in which the 51 amino acids of the insulin molecule are linked together.

The start was promising. Sanger developed a method to "mark" at its free amino end the particular amino acid which sits at the end of a chain. For this purpose he used a dye reagent, dinitrofluorbenzene, which is bound comparatively firmly to the amino acid and will remain so even if the chain is broken and the terminal amino acid thus set free. In the complicated mixture of amino acids which results if insulin, "marked" in this fashion, is boiled with acids, one can thus isolate the coloured components, which must represent terminal groups. In this way Sanger could demonstrate that the insulin molecule contains two different chains with different end-groups, and he managed to isolate them after breaking the molecule by oxidation. Thus the problem was simplified: instead of one molecule with 51 amino acids Sanger now had two with 31 resp. 20.

If the chains are only partially broken down - for example by treatment with weak acids or enzymes - one obtains larger fragments of the chain, containing, 2, 3, 4, 5 or more amino acids in the very sequence in which they occur in the intact molecule. Sanger succeeded in isolating and identifying a large number of such fragments from the complicated mixtures obtained by such a treatment. In this work he combined in a very skilful manner different chromatographic and electrophoretic methods, especially paper chromatography as introduced by Martin and Synge, Nobel laureates in Chemistry 1952. Sanger managed to determine the sequence of amino acids in each bit of the chain thus isolated. In this work his "end-group" methods, already mentioned here, was of great help. Each piece represents a number of links in the chain and it now remained to fit all these pieces together in a correct way and thus to reconstruct - on paper at least - the original chain. This part of the work reminds one of laying a puzzle. It was a difficult and painstaking operation but it worked: it proved possible to make the puzzle fit. In other words, Sanger succeeded in reconstructing first one chain and then the other from all the pieces obtained, and particularly important - the result was the same, independent of the method used for breaking the chains.

Thus, Sanger could give the exact sequence of the 31 amino acids in one chain and the 20 in the other. Already earlier he had shown that the two chains are held together to form an insulin molecule with the aid of two bridges of sulphur atoms. The exact positions of these bridges were determined in a way similar to that used for determination of the structure of the chains.

The structure of insulin had thus been established - a remarkable achievement, indeed. Insulin is a protein, and this was the first time one had succeeded in determining the structure of a substance belonging to this very important group.

The significance of Sanger's work reaches, however, much further. The procedure he has used so successfully can be applied to proteins in general, in attempts to determine their structure. Already now, many research workers are engaged in such investigations, and

important results appear to be on the way in the exploration of how proteins play their role as key substances in the chemical processes of Life

Doctor Frederick Sanger. It sometimes happens that an important scientific discovery is made so to say "overnight" - if the time is ripe and the necessary background is there. Yours is not of that kind. The first successful determination of the structure of a protein is the result of many years of persistent and zealous work, in which the final solution of the problem has been approached step by step. You knew when you began to look into the structure of the insulin molecule 15 years ago that the problem was a formidable one. So did the whole scientific world. Those who knew you, were confident, however, that you would ultimately succeed, and each successive publication from your laboratory strengthened our confidence. Intelligence, knowledge and skill in the mastering of the methods required - we know you have them all - but in such a venture these are not enough. Without your wholehearted devotion to the task you had set before you, many obstacles on your way would have appeared insurmountable. Now that many years of work have been crowned with success you may look back and rejoice. You can also enjoy the satisfaction of seeing the roads you have broken and paved being used by many in their search for the building principles of the key substances of Life. However, very likely you are more apt to look ahead. It was Alfred Nobel's intention that his prizes should not only be considered as awards for achievements done but that they should also serve as encouragement for future work. We are confident that you are a worthy recipient of the Nobel award also in this sense. May we offer you our congratulations.

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