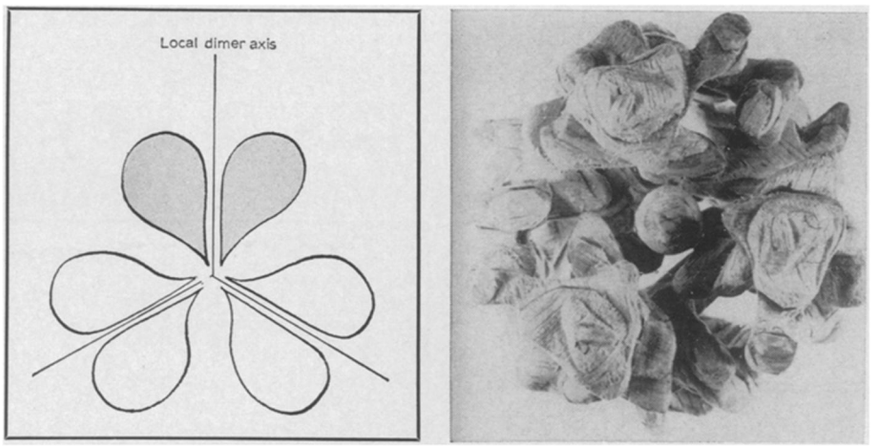
CRYSTALLOGRAPHY

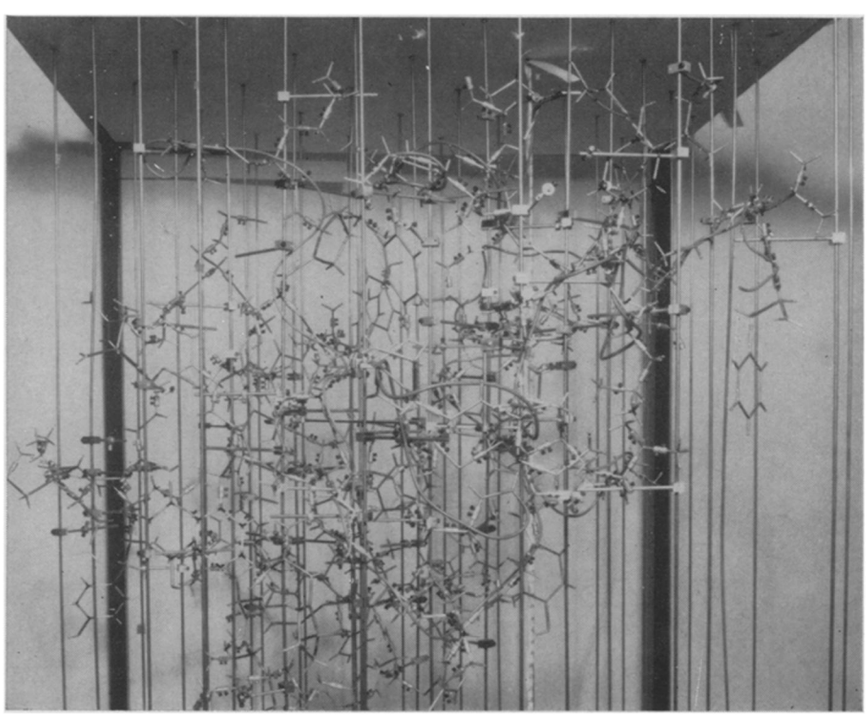
Insulin design traced

by David Fishlock



Photos: Oxford Univ.

Looking down the dimer axis (sketched l.), zinc atoms are at the center (r.).



Dr. Hodgkin built a detailed model of insulin showing each dimer in position.

As proteins go, insulin is among the smallest. Among research scientists concerned with the structure of molecules, and therefore their biochemical function, it is one of the most important. It is only 51 amino-acid molecules long; elucidating their sequence won a Nobel Prize for Dr. Frederick Sanger in 1958. Since then, animal and human insulins have been synthesized (SN: 10/23/65, p. 258), though the three-dimensional architecture of the molecule continued to remain elusive.

Now, that architecture has been mapped by another Nobel laureate, crystallographer Dr. Dorothy Crowfoot Hodgkin of Oxford University, England, and from this scientists may learn just how the indispensable hormone is manufactured in the body.

The structure was defined by X-ray crystallography, a technique that has gained renewed vigor in recent years (SN: 9/21/68, p. 298). By bombarding insulin crystals with X-rays and measuring the intensity and direction of scattered X-ray particles, Dr. Hodgkin mapped the molecular configuration of the molecule at a resolution of 2.8 angstroms. Further refinements at higher resolution will come next, then exploration of insulin's mechanism of action will follow.

Work on insulin structure dates back decades. In 1935, when Dr. Hodgkin first took an X-ray photograph of insulin, she speculated that it might be possible to resolve its structure by working with an isomorphous crystal—a derivative molecule in which a single atom is replaced by a heavier one. A zinc atom in natural insulin was suitable for such manipulation, and Dr. Hodgkin proceeded in the 1950's as crystallographic techniques improved and the advent of computers made their use more feasible.

Prof. J. D. Bernal, the British crystallographer who early in the 1930's had wooed Dr. Hodgkin to his science, once observed that successful analysis of a complex molecule depends essentially on the investigator's strategy. Of his brilliant pupil he says, "She was one of these masters whose method of work is as exciting and beautiful to follow as the results that flow from it."

In deciphering the molecular structure of insulin, Dr. Hodgkin replaced the zinc atoms in insulin from pigs with atoms of three different heavy metals: lead, uranium and mercury. By last July, she and her colleagues succeeded in mapping the electron density of the three insulin derivatives. They computed the outline of the molecule that is built of two amino acid chains: A, which is 21 amino acids long, and B, which is 30 amino acids long. The B chain comprises a misshaped U, one leg of which has doubled back. Within the bend, the shorter, more tightly coiled A chain snuggles.

Though key sites for molecular activity have yet to be identified on insulin molecules, the British work to date suggests that three residual amino acids on the A chain are not essential in determining the molecule's three-dimensional shape. Interestingly, these same three residues are the ones that vary most between the insulins produced by various species.

Insulin, Dr. Hodgkin's studies show, is, in fact, a six-part molecule, roughly triangular in shape, comprising three dimers or pairs of molecules enclosing two zinc atoms in the core. Bound together at the ends by groups of phenylalanine (a specific amino acid) and secured midway by hydrogen bonds, the six-part structure unites to form the natural hormone. ◇