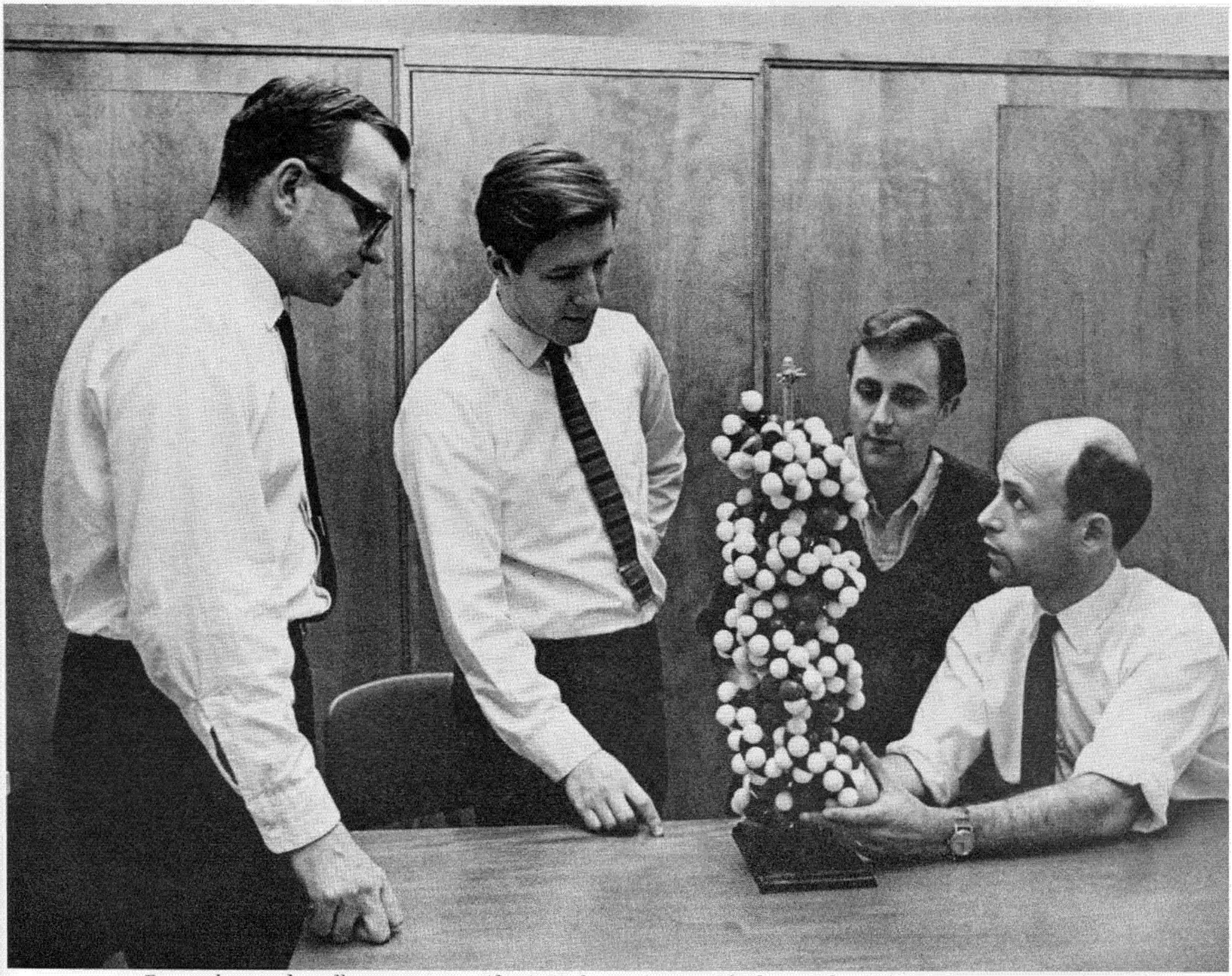


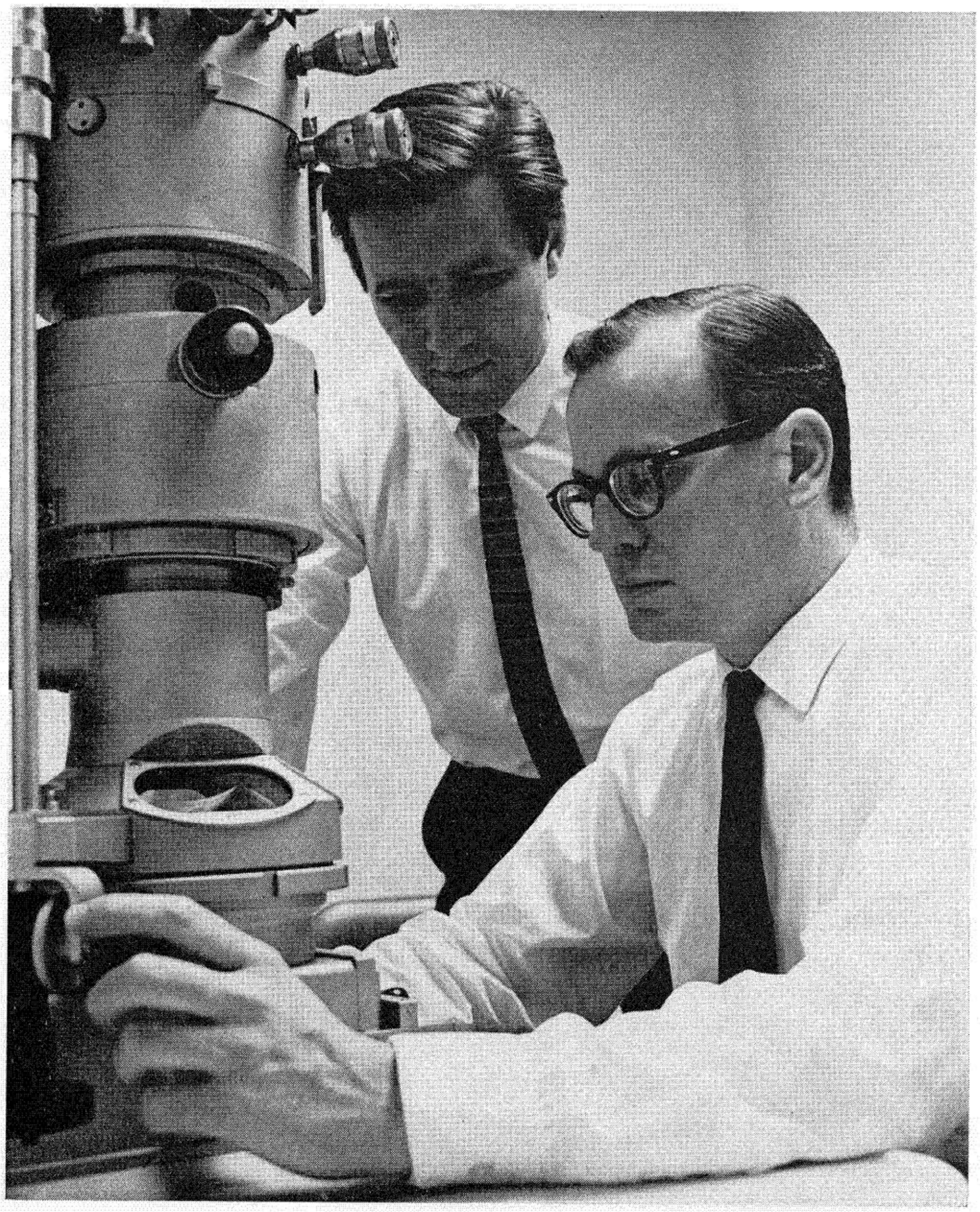
Researchers in the collagen project — Alan J. Hodge professor of biology; John A. Petruska, senior research fellow; Allen J. Bailey, research fellow; and John H. Fessler, senior research fellow — study a model of a small part of a collagen molecule, representing about 1/100th of the full molecule.

Collagen – A Masterpiece of Engineering Design

Caltech biologists work out the detailed subunit structure of the collagen molecule

Collagen is the most abundant protein in the body; it makes up about 30 percent of the protein in a human adult. It is the main constituent of connective and skeletal tissue. In bone it is like steel rods in reinforced concrete, in skin like pliable steel mesh, and in tendon like a steel cable.

Researchers in the laboratory of Alan J. Hodge, *The electron microscope makes it possible to study molecular details in crystallites of collagen magnified more than 100,000 times.*



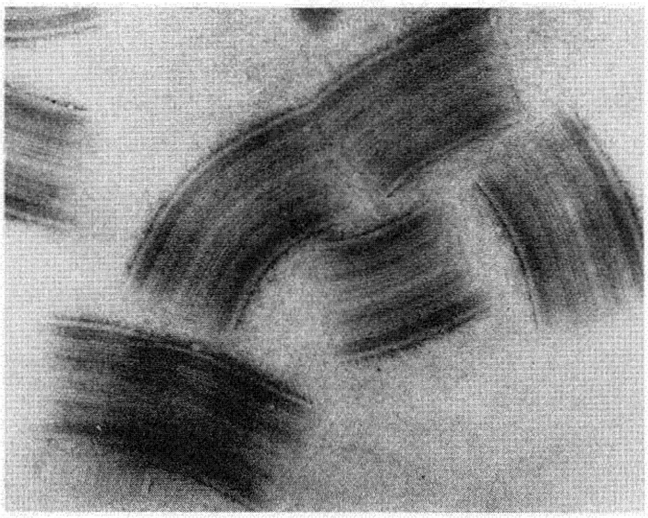
professor of biology at Caltech, have now worked out the detailed subunit structure, or architecture, of the collagen molecule. This is the first fibrous protein molecule to be so mapped. The research is supported by the National Institutes of Health, which is interested in the prevention and treatment of arthritis and other so-called "collagen diseases." Such basic structural research as this is an essential adjunct to medical studies and also may lead to a more fundamental understanding of the aging process in general.

The collagen molecule proves to be a masterpiece of engineering design. The strength of the collagen fiber results from both the design of the individual molecule and the overall pattern in which the molecules are linked together into a unified structure. The pattern appears to be the same in all animals.

Collagen is composed of protein threads, or polypeptide chains, each about 1/85,000th of an inch long. These are twisted, overlapped, and bonded together in such a manner as to take the greatest possible strains.

The Caltech model of the collagen molecule emerged after extensive mathematical analyses of data obtained with the electron microscope, x-ray crystallography, and biochemical techniques. John A. Petruska, senior research fellow in biology, collaborated with Dr. Hodge in the mathematical phases of the work, while Allen J. Bailey, Commonwealth Fund fellow, has been primarily responsible for the chemical investigations. John H. Fessler, senior research fellow, has been doing research designed to detect the subunits of collagen in early stages of biosynthesis. The Caltech model rests on many major contributions from laboratories at other institutions, also.

The collagen modecule consists of three chains



Electronmicrograph of a particular crystalline form of collagen in which the molecules lie side by side with no longitudinal displacement. The band pattern in each of the crystallites shown is a map or "fingerprint" of the molecular details. Magnification is 90,000 diameters.

of amino acids, which are the building blocks of proteins. Each chain is fashioned into a left-handed helix, or spiral. The three chains are wrapped together, right-handedly, to form a super helix of 35 turns about 1/85,000th of an inch long.

In addition to being wrapped around each other, the chains are linked together by hydrogen bonds whose attachments are sideways instead of end to end. Nature uses similar hydrogen bonding to produce tough fibers of silk.

Not only is the individual molecule designed for tensile strength; so also is the arrangement of the molecules in a fiber. The fiber has neighboring molecules systematically displaced to form a pattern like a wall of offset brick or stone, with a small space between each brick or stone on the horizontal plane. Each space is some one and a half millionths of an inch long, or about one-seventh the length of the three-stranded molecules (as shown in the diagram below). In bone, these spaces are filled with calcium phosphate, which provides rigidity and is the equivalent of cement in reinforced concrete.

Dr. Hodge began his investigation of collagen eight years ago at the Massachusetts Institute of Technology with Dr. F. O. Schmitt, professor of biology there. Because the molecule is too small to observe directly in the desired detail, the problem was attacked indirectly.

The biologists grew crystallites of the molecule in which all the molecules were aligned side by side instead of being offset like bricks. In these crystallites the like molecular features were in register and could be seen as bands in the electron microscope, as shown above. Staining with heavy metal ions served to further intensify these bands. Up to 90 bands could be resolved for certain types of staining.

Detailed analysis disclosed that the band pattern could be explained in terms of a subunit model like that shown below. Two of the molecule's three polypeptide chains consist of five identical subunits joined end to end, while the third chain consists of seven subunits. All three chains are the same length. Detailed computer refinement of the pattern by Dr. Petruska lends strong support to this concept.

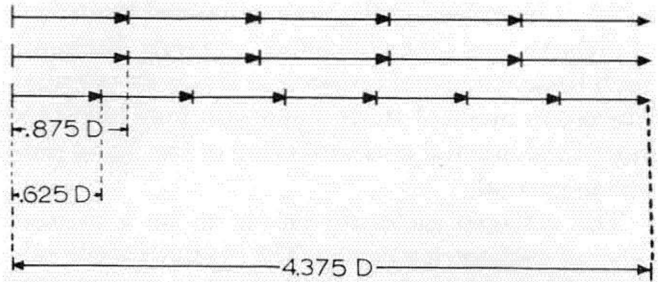
Although the sequence of the amino acid building blocks has not yet been worked out in detail, it is known that two of the chains are chemically very similar, or identical, while the third is distinctly different. In each chain, glycine, the smallest of the 20 amino acids used in building proteins, comprises 33 percent of the amino acid units. The presence of the small glycine units in every third position enables the three fibers to fit snugly together and to be maximally hydrogen-bonded.

The new model of the collagen molecule has these advantages, according to Dr. Hodge:

Relatively little genetic information is required for assembling it – only that needed to form the two types of polypeptides, the shorter one and the longer one.

The unequal lengths of these subunits suggest mechanisms of growth assuring the assembly of very large molecules which are homogeneous with respect to length, thus insuring their capacity to form highly ordered structures.

The next step is to map the sequence in which the amino acids are strung together in the two subunits. This will further increase the understanding of the important molecule. Preliminary work indicates that the same kind of unequal subunit structure may explain the lengths and properties of other important large molecules, such as myosin, which is the major protein component of muscle.



Schematic representation of the subunit model of the collagen molecule. Two of the three chains contain five subunits each, while the third contains seven. The molecular length is 4.375D (where D is the systematic displacement of the neighboring molecules in the native fiber). It is because this length is not integral in respect to D that "holes" occur in the fiber.