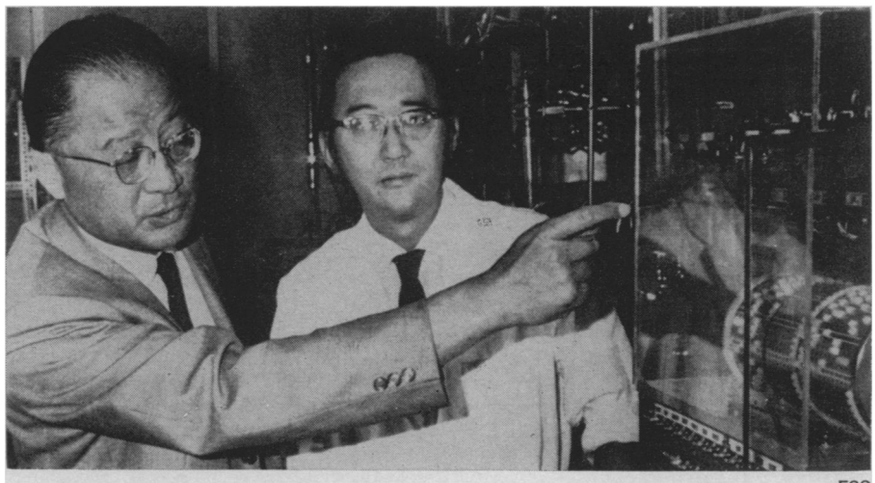
Diligence and luck pay off

Synthesis of human growth hormone opens many paths in medicine and biochemistry



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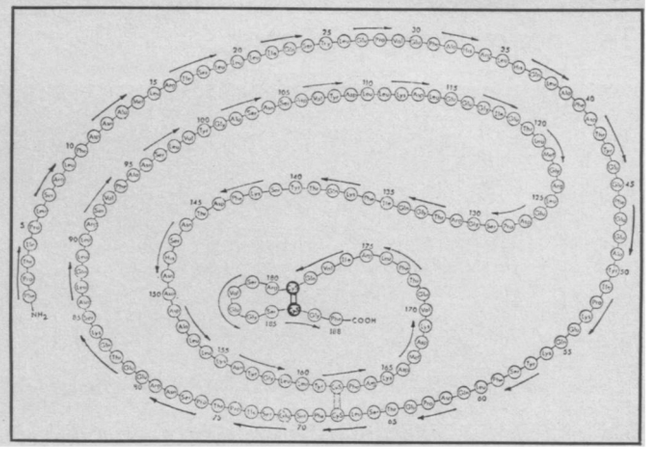

Drs. Li (left) and Yamashiro: Synthesis of human growth hormone, 188 amino acid molecules long.

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Four years of persistent research bore fruit this month with the announcement by two California scientists of the first synthesis of human growth hormone (HGH). The achievement paves the way for eventual clinical treatment of dwarfism, which afflicts some 7,000 children born in the United States every year, and should provide a tool for gaining insight into the biochemistry of phenomena ranging from the deadly uncontrolled growth of cancer cells to the dangerous accumulation of cholesterol in blood.

In 1966, Dr. Choh Hao Li, director of the Hormone Research Laboratory at the University of California Medical School in San Francisco, successfully determined the structure or sequence of the hormone, which is built of 188 amino acid molecules. Since then, he says, he and Dr. Donald H. Yamashiro have "lost sleep very often" as they struggled to reconstruct the hormone from laboratory chemicals.

The late 1960's were years during which protein chemistry moved into the forefront of research. Investigators reported the structure and synthesis of a number of proteins and hormones, feats that at one time were considered mere pipe dreams. Until now, the largest protein to have been manmade was ribonuclease, a 124-amino-acid molecule synthesized in 1969 by two independent research teams, one headed by Dr. Robert Bruce Merrifield of Rockefeller University and one by Dr. Robert G. Denkewalter of Merck & Co. in Rahway, N.J. (SN: 2/1/69, p. 112).

Drs. Li and Yamashiro followed Dr. Merrifield's synthesis method, assembling HGH amino acid by amino acid in linear succession, attaching each to polystyrene beads that anchor the amino acids in place during synthesis. At present, Dr. Li's synthetic HGH is only 10 percent as active as naturally occurring human growth hormone, a drawback he attributes to impurities in the synthetic molecule. He believes the impurities can be removed with further work.

As its name implies, human growth hormone, which comes from the pituitary gland at the base of the brain, regulates body growth, determining such characteristics as height and weight. Individuals with abnormally low HGH, for example, are dwarfs. Scientists have had some success in correcting this anomaly by administering natural HGH to such persons early in life, but its scarcity has precluded large-scale treatment. It must be extracted from the pituitary, a pea-sized gland, at death—a situation which poses obvious problems and which can be corrected by production of large quantities of the synthetic hormone.

Growth, however, is not the only process in which HGH plays a key role. According to Dr. Li, who has devoted his scientific career to the study of the 10 pituitary hormones, HGH also stimulates milk secretion by the mammary glands and promotes activity of sex hormones—androgen in the male and estrogen in the female.

He further reveals that animal studies show growth hormone speeds healing of bone fractures and acts to lower blood cholesterol levels. Whether these latter activities also occur in human beings remains to be proved, but Dr. Li predicts that experiments with synthetic HGH should shed light on mechanisms of cholesterol control.

A possible role for HGH in cancer has also been postulated by the 57-year-old chemist, who was born in Canton, China, and who immigrated to the United States in 1933. By some mechanism still imprecisely understood, HGH promotes growth by stimulating the rate of protein synthesis in cells.

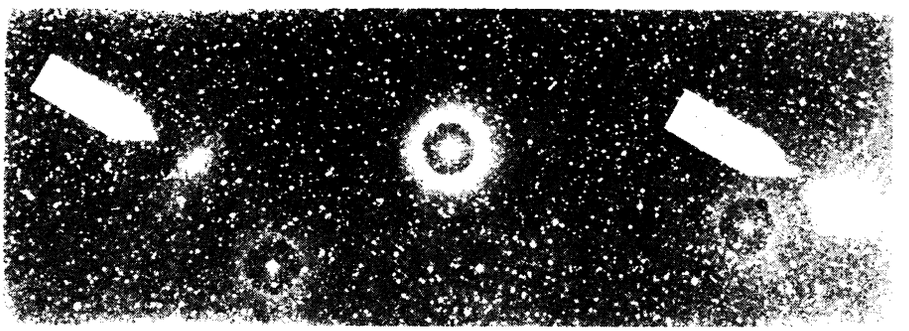
Although only theory, one explanation of its behavior holds that it surrounds a cell, changes the permeability of that cell's membrane and thereby creates an environment that allows amino acid molecules and other chemicals essential for protein manu-

facture to get inside. Thus cells produce more protein, grow and multiply. It is conceivable that some excess of this process is at work in tumor cells. Dr. Li suggests that if, from research on the synthetic HGH molecule, scientists could construct an antigrowth chemical that would be antagonistic to HGH activity, they may find a molecule that would halt the proliferation of cancer cells.

The synthesis of HGH marks the latest of a long series of accomplishments in Dr. Li's life as a chemist and endocrinologist. It began as a graduate student at the University of California at Berkeley, where, after graduation from the University of Nanking, he was assigned to study the pituitary, a gland about which little was known. In the course of time because of what he calls diligence ("For three decades I have worked almost 24 hours a day") and luck, Dr. Li and his associates isolated and purified 8 of the 10 hormones known to be secreted by the anterior pituitary—the front portion of the gland. They determined the structure of seven. Most recently, they reported the structure of ovine lactogenic hormone (from sheep), finding it remarkably similar in amino acid sequence to HGH (SN: 12/20/69, p. 570). □

NEARBY GALAXIES

Two newly found neighbors



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Maffei 1 and 2: On infrared plate they appear different from nearby stars.

Serendipity is a persistent characteristic of astronomical investigation. A new look at old data or a new method of observation often reveals the presence of objects that were there all the time but which no one was looking for and no one had found.

Two years ago, Dr. Paolo Maffei of the Laboratory of Astrophysics at Frascati, Italy, made infrared photographs of the sky looking for members of a certain class of peculiar stars. On one of the plates he found two unusual objects that were definitely not stars, and he published a notice of their discovery.

Dr. Maffei's report aroused the interest of a graduate student at the University of California at Berkeley, Robert Landau, who suspected that the two strange objects might be unknown galaxies. His interest led a group of astronomers, including Drs. Hyron Spinrad, Ivan R. King and Nannielou H. Dieter of Berkeley, W. L. W. Sargent, J. B. Oke, Gerry Neugebauer and James E. Gunn of the Hale Observatories and Gordon Garmire of the California Institute of Technology, into an investigation of the Maffei objects. Their conclusion is that the two objects are indeed galaxies; that they are, as galaxies go, quite near our own Milky Way galaxy, and that they may be members of the local group or cluster of galaxies.

The two newly discovered galaxies lie about 40 minutes of arc apart in a location between the constellations Perseus and Cassiopeia. The main reason they were never noticed before is that this direction lies along the plane of the Milky Way, in which there are large concentrations of interstellar dust. The dust absorbs most of the light from objects beyond it.

Longer wavelengths get through the dust more easily. The dust transmits about one percent of visible light, six percent of infrared. On Palomar Sky Survey plates taken in visible light the Maffei objects are barely visible and do not look like galaxies, says Dr. Spinrad. They would have been ignored still if the infrared plates had not shown that they are brighter and more extended bodies than stars.

Most of the evidence published in the group's initial article, in the Jan. 1 ASTROPHYSICAL JOURNAL LETTERS, pertains to the object called Maffei 1. That object is a large, normal elliptical galaxy with a diameter between 50,000 and 100,000 light years lying about 3 million light years from our galaxy. Data relating to Maffei 2 will be published later, but Dr. Spinrad says they show conclusively that Maffei 2 is also nearby. Maffei 2 appears to be a spiral rather than an elliptical galaxy.

The identification of Maffei 1 was made with some of the largest telescopes available, including the 200-inch Hale telescope on Mt. Palomar. With these the spectrum of the light emitted by the object was studied and the variations in brightness of different frequencies over the extent of the object determined. These figures were then compared to those for known galaxies of various classes. Those for giant elliptical galaxies fit best.

The distance estimate varies within fairly wide limits between 1 million and 12 million light years depending on the method of determination. The estimate of 3 million light years, which the California astronomers believe accurate within a factor of two, comes from an argument based on the internal dynamics of Maffei 1 and the ratios of mass to luminosity in different regions of it.

Maffei 1 is by any estimate near enough to be a member of the local group or cluster of galaxies. The best distance estimate makes it twice as far away as the nearest galaxy to the Milky Way, the Andromeda galaxy. But if Maffei 1 is included in the local group, it raises questions regarding the long-range stability of the group.

Until now the known members of the local group were the Milky Way and its satellites (the two Magellanic Clouds), the Andromeda galaxy and the galaxy M31 and its satellites. Supposedly these were bound in a cluster by mutual gravitation. Such a group will be stable if the total kinetic energy engendered by the motions of the galaxies is less than the potential energy that represents the gravitational bonds.

One calculation indicates that without Maffei 1 the ratio of kinetic to potential energy in the local group is 1.1, which makes it marginally unstable. However, if there were enough unknown mass present, in the form of invisible intergalactic gas, that would tip the ratio in favor of stability. If Maffei 1 is included, however, the ratio becomes 10, definitely unstable unless enormous amounts of unseen mass are present. Thus, says Dr. Spinrad, "If you demand that it be a long-term member of the group, then the group is unstable." This means that over millions of years the members of the group would gradually drift apart.

Observations in both radio and light continue. So far Maffei 2 is known to be a weak and not particularly unusual radio source; no radio signal from Maffei 1 has yet been detected. The astronomers would also like to see more detail inside the Maffei galaxies, and Dr. Spinrad says they can do this if they can make a photograph in infrared of two microns wavelength. Other parts of the Milky Way are being checked on the chance of finding more such objects. □