BIOLOGY

Joseph Alper reports from Madison, Wisc., at the 7th American Peptide Symposium

Hormone fragment makes good drug

Scientists are experimenting with several thymic peptide hormones as treatments for severe immune diseases (SN: 1/26/80, p. 61). These tests have generally been successful (SN: 1/18/75, p. 43) but have been restricted by the limited availability of the peptides. Help is now at hand. George Heavner of the Ortho Pharmaceuticals Corp. in Raritan, N.J., reports that a 5 amino acid peptide corresponding to amino acids 32 through 36 of the 49 amino acid hormone thymopoietan is being used to successfully treat patients with rheumatoid arthritis, de George's syndrome and severe combined immune deficiency disease. In all three of these illnesses there is an improper balance of different types of T cells responsible for cellular immunity. The drug, called TP5, works by altering the ratio of helper T cells to suppressor T cells regardless of whether the ratio is too high or too low. Furthermore, once the balance is restored to normal, the peptide has no further effect. In fact, researchers at Ortho have not been able to establish a dose at which the compound becomes toxic. The compound is completely degraded in 30 seconds to a simple nontoxic amino acid, but its effects last long after it is gone. Ortho plans to begin clinical tests soon on other T cell-related immune diseases.

More on biosynthetically made insulin

Two Eli Lilly scientists reported on several aspects of their processes for making human insulin using recombinant DNA (SN: 9/16/78, p. 195). Robert Chance notes that methods have been greatly improved for chemically coupling the insulin A- and B-chains, which are made separately by different bacteria. He also says that they are getting more insulin by hooking the insulin gene to a bacterial tryptophan-E gene instead of to the beta-galactosidase gene previously used. William Frank reported that he has successfully produced insulin from bacterially made human proinsulin (SN: 3/15/80, p. 166), by first forming the correct disulfide bonds and then enzymatically producing insulin and the insulin C-peptide.

The two researchers agreed that clinical trials were progressing rapidly with only one minor surprise: It appears that human insulin is absorbed slightly faster after under-the-skin injections than either beef or pork insulin. Chance estimated that biosynthetic human insulin would replace beef insulin by 1990 and supplement pork insulin, which is expected to be in short supply within 20 years.

Sequencing peptides gets easier

As isolation methods become more and more sensitive, new peptide hormones are popping out with novel biological activity. One problem, though, is that scientists often have less material than is needed to determine the peptide's sequence. But now, Michael Hunkapillar and Leroy Hood of the California Institute of Technology have built an instrument that can sequence less material than can now be isolated by the most sensitive method. The new instrument is called a Gas-Liquid Solid Phase Peptide Sequenator, and it uses gaseous reagents to remove one amino acid at a time from a peptide chain. Using reagents dissolved in argon gas, instead of organic solvents, means that less peptide will be washed out of the machine as sequencing progresses; this is the limiting factor in determining the sensitivity of a peptide sequencing instrument. Overall this machine is 1,000 times more sensitive than the previous best instrument (SN: 1/26/80, p. 52). The researchers have already used the new sequenator to partially determine the sequence of T cell interferon, which may be more potent against cancer than other forms of interferon currently being investigated.

Substance P transmits pain

Evidence has been mounting that Substance P, an 11 amino acid peptide that is found throughout the nervous system, is either a neurotransmitter or that it works to control the action of other neurotransmitters. Now it seems that it does both. Susan Leeman of the Massachusetts Medical Center in Worcester has found Substance P in the same neurons as the known neurotransmitter acetylcholine. By treating spinal cord nerve cells with antibodies to either an acetylcholine or Substance P she found exact cell locations for these two compounds. Acetylcholine resides very close to the nerve cell synapse with another nerve cell. Substance P, however, congregates in special vesicles far away from the nerve ending. Leeman believes that acetylcholine actually transmits the nerve signal, and that Substance P regulates how strong the signal is. Meanwhile, Michael Piercey of the Upjohn Co. in Kalamazoo, Mich., has found that Substance P works at other neurons to transmit pain signals through the spinal cord. When he applied capsaicin, a compound that produces severe inflammation and pain, to a mouse's skin, the mouse vigorously scratched and bit the painful site. Simultaneously, nerves coming into the spinal cord released Substance P. This experiment alone would also support Leeman's hypothesis, but when Piercey injected Substance P directly into the spinal cord, without applying capsaicin, the mouse exhibited the same biting and scratching behavior. Injecting Substance P just below the skin did not produce this response. This suggests that Substance P alone transmitted pain signals through the spinal cord. Both Leeman and Piercey believe that Substance P probably plays both roles in the nervous system, depending on the particular function of the nerve cell.

Hormones have many sequences

It is well known that peptide hormones are made as part of a larger peptide and are then snipped from this precursor by cellular enzymes. Part of the extra sequence helps package the hormone for export from the cell. Sometimes, biologically active peptides are found in the throw-away part (SN: 11/17/79, p. 342) but still there are usually parts of the precursor, called prosequences, that do not seem to have any purpose, although the cell uses a lot of energy to make these extra bits of peptide. Now, the role of these prosequences is further muddied by the discovery that there can be many different prosequences for the same hormone. Dennis Shields at the Albert Einstein College of Medicine in the Bronx has found multiple precursors for pancreatic hormones somatostatin and glucagon. He isolated messenger RNA from the islets of Langerhans of the angler fish and then used a cell-free protein synthesizing system to make all the corresponding precursor molecules. He separated these according to size and charge and located the somatostatin and glucagon precursors using antibodies specific for the two hormones themselves. When he examined the chromatographic gels, however, he found not one precursor for each hormone but 14 somatostatin precursors and at least three glucagon precursors. Sequence analysis of the somatostatin precursors showed they all contained the same somatostatin molecule and a common sequence close to the hormone. However, the prohormone length and amino acid content differed greatly in the different prohormone molecules. Shields says that each precursor must come from a different gene and that possibly the sequences help regulate gene expression. He is now raising antibodies to the prosequences to answer this question and to search for biologically active peptides that may come from them. In fact, Joel Habener from the Harvard Medical School reported finding a peptide in one of glucagon's prosequences that resembles the biologically active peptides VIP and GIP.