Labs tie for human growth hormone

Two teams of researchers — one private, one university — last week reported the genetically engineered bacterial production of human growth hormone (HGH), a hormone of more potential medical usefulness than previously engineered proteins.

The near-simultaneous success of the two groups differs in one aspect, however. David Goeddel, Peter Seeburg and co-workers from Genentech, Inc. — the San Francisco company that last year produced insulin (SN: 9/16/78, p. 195) — claim the first bacterial expression of a mammalian protein in its direct form — not as a precursor and not linked to any bacterial protein. The second group of researchers, Howard M. Goodman, John Baxter and co-workers — the University of California at San Francisco team that recently induced bacteria to produce the rat variety of growth hormone (SN: 1/20/79, p. 39) — succesfully coaxed the bacterial production of the natural precursor of HGH as a "fusion protein" — fused to a bacterial protein. The difference, though it represents an interesting variation of techniques, may only have meaning in terms of commercial production of the hormone, according to other researchers.

More significant, the laboratory production of HGH — normally produced by the pituitary gland at the base of the brain — represents the first contribution by recombinant genetic techniques of a hormone that is "really in medical need," according to UCSF's John Baxter. Unlike insulin, which can be obtained from other animals in sufficient amounts for medical use, the only source of HGH is human cadavers. (Though other animals can use human growth hormone, humans can only use the human variety.) The hormone has been used experimentally to treat children with the rare disease pituitary dwarfism (as many as 50 cadaver pituitaries are needed to treat a single child for one year) and has shown potential in controlling gastrointestinal bleeding and in healing burns. The promise of bacterial production of HGH may allow clinical trials of these uses.

Goeddel and co-workers achieved their unique success by using a gene for HGH that was partially chemically synthesized and partially copied from the natural gene. By chemically synthesizing the first section of the gene, the researchers were able to introduce their own chemical "start reading" signal and to eliminate the part of the gene that codes for the extra amino acids contained in the precursor of HGH. Other techniques, including the one used by the UCSF team, link the gene for the desired protein to a bacterial gene and introduce the hybrid plasmid into the bacteria. While these methods ensure that the mammalian gene is "read" in the proper sequence, the product is a fused protein — part or all of a bacterial protein is hooked to the mammalian protein. In Genentech's method, the HGH gene was the only gene in the plasmid, says Goeddel, therefore the hormone was a "clean" product. This first-time combination of naturally derived and synthetically derived DNA for use in a recombinant genetic experiment produces "under the best conditions" about 200,000 molecules of hormone per bacterium, says Goeddel.

By contrast, the approach used by Goodman and co-workers at UCSF produces "at least 250,000 molecules and as many as one million molecules" of HGH per cell, says Baxter. And, Goodman notes, their method — hooking the completely naturally derived HGH gene to the gene for the bacterial protein tryptophan and introducing the hybrid plasmid into the bacteria — allows the unique ability to control the HGH output of the cell. The production of tryptophan, like many other cell products, is controlled by the presence of "repressor" substances in the environment. Thus, the output of tryptophan and therefore the output of HGH can be controlled by varying the amount of the repressor substance. The next steps, separating the mammalian and bacterial protein and reducing the hormone from its precursor state, are "straightforward biochemistry," says Goodman, but still remain to be done.

In the meantime, both groups have shown that their products are very likely the real thing — they are the right molecular weight for HGH and they react with antibodies to HGH. The crucial test — whether or not the hormone will prove active in other animals — remains. If the hormone is biologically active, Genentech, under contract to the Swedish firm A. B. Kabi, will begin large-scale production, says Goeddel, pending a change in the National Institutes of Health guidelines, which limit size of the cultures used in recombinant DNA experiments.

(The NIH guidelines are binding only on federally funded facilities, but Genentech claims to adhere to them. Recently, however, a report in NATURE noted that Genentech had exceeded the NIH 10-liter limit in their production of the inactive protein strands that, when combined, make insulin. Genentech's exceeding of the limit highlights one of the sore points in the debate over the guidelines set for recombinant DNA experimentation — the unequal application of the restrictions to industry and federally financed researchers. Genentech president Robert Swanson said he notified NIH last fall of their plans to exceed the limit, but did not say how much was being made.)

The Genentech work on HGH, presented July 11 at the Miles Symposium on Polypeptide hormones at Johns Hopkins University, has been submitted to NATURE. The USCF research will be published in SCIENCE. □

Cures for cramps

Prostaglandins, the lipid-like chemicals that stimulate uterus contractions, have also been implicated in dysmenorrhea — severe menstrual cramps that can incapacitate 30 to 50 percent of women of childbearing age with nausea, vomiting, diarrhea, headache, fatigue and nervousness. Dysmenorrhea has been treated with narcotics, birth control pills, or aspirin. But now several drugs are being found to directly combat the cause itself — the overproduction of prostaglandins by dysmenorrheic women. These include ibuprofen, indomethacin, metamic acid and naproxen-sodium; they inhibit the synthesis of prostaglandins and are used currently to treat arthritis, according to an article in the July 13 SCIENCE. In Europe, South America, South Africa and Japan, metamic acid, for example, is sold without prescription as a painkiller. As an inhibitor of prostaglandins, however, it has an advantage that birth control pills (the only indirect inhibitor) do not. The pill must be taken 21 days a month to treat a condition lasting one or two days. Metamic acid, manufactured by Warner-Lambert under the brand name Ponstel, are to be taken only while the cramps last. □

Cancer in Smoky veterans

Along with 603 military personnel who basked in the glow of Shot Smoky — a 1957 nuclear weapons test in Nevada — were 22 rhesus monkeys. Eleven of those monkeys now have cancer, says Harold M. McClure of the Yerkes Regional Primate Center, where the monkeys have lived since 1960. McClure, who has been working with the monkeys since 1965, says that only 2 percent of a rhesus monkey colony should be expected to develop cancer. The bomb test monkeys suffered predominantly intestinal, kidney and skin cancers, McClure told SCIENCE NEWS.

Meanwhile, the Defense Nuclear Agency recently released a study of the cancer rate in the troops taking part in Smoky. The agency found twice as many cases of leukemia as would normally be expected in a group that size. The troops were exposed to about 970 millirems — less than the 3,000 millirems now permitted as a quarterly dose — largely from the residual radiation of previous tests. It was also far less than the monkeys' dose — 221 rems to 597 rems, at 3 miles away from the 44-kiloton explosion.

Other Yerkes radiation experiments involving monkeys were begun more than 20 years ago. One is showing neutron radiation to be more carcinogenic than any other. Three of four monkeys in that group have died of tumors, McClure said. Another test indicated that short repeated doses are less hazardous than is a single strong dose, he said. □