# Bacteria synthesize brain hormone

Molecular geneticists at the University of California in San Francisco have just completed work that not only eclipses all previous gene-engineering research, but may mark the beginning of a new era in the biological sciences as well.

Scientists from three West Coast institutions (led by Herbert Boyer of UCSF) have succeeded in manipulating a colony of bacteria to produce a human brain hormone, thus delivering on a major promise of researchers who discovered a way to splice genes together more than five years ago. The successful study was announced by Philip Handler, president of the National Academy of Sciences, who testified before a Senate subcommittee that the experiment "was a scientific triumph of the first order."

Research teams led by Boyer, Arthur Riggs of the City of Hope Medical Center near Los Angeles and Wylie Vale of the Salk Institute in San Diego produced 5 mg of somatastatin, a mammalian protein neurohormone. They did it by inserting an engineered gene into about 100 mg of *Eschericia coli* suspended in 2 gallons of culture medium. The bacteria heeded the new "work orders" and, in Handler's phrase, like bustling factories "merrily engaged" in producing the hormone.

That the researchers chose to produce somatastatin was incidental, Handler said. Even though it took Roger C. L. Guillemin of the Salk Institute 500,000 sheep brains to accumulate the 5 mg of somatastatin he needed to decipher the hormone's structure—for which he shared the Nobel Prize in medicine this year (SN: 10/22/77, p. 260)—the hormone can now be produced in organic laboratories relatively cheaply. (Somatastatin, secreted by the hypothalamus in trace amounts, inhibits the pituitary gland's release of hormones that regulate body growth and glucagon and insulin production. It may be useful in the future treatment of diabetes, pancreatitis and acromegaly, a disease of abnormal bone growth.)

Nor was this the first time researchers have been able to introduce foreign genes into bacteria. Another team of UCSF researchers accomplished that earlier in the year by inserting a rat gene that codes for insulin production into *E. coli* (SN: 5/28/77, p. 340).

The insulin gene did not trigger the production of rat insulin by the bacteria, but the somatastatin researchers did induce the *E. coli* to ignore its own functions and, like a surrogate mother, mistakenly cultivate a metabolic process normally found only in mammals.

How the geneticists "tricked" the *E. coli* is not precisely known, but other workers in the field say it was a striking conceptual departure from earlier attempts at UCSF, which inserted natural genes into *E. coli*. (The rat gene researchers used messenger RNA, which carries genetic information from the cell nucleus to the protein-making machinery in the cytoplasm, as a "negative" to make a "positive" copy of the original gene.) Instead, Boyer and his co-workers constructed a gene from scratch, successively adding nucleotides like beads on a string. This artificial chain of nucleotides coded for the amino acid methionine as well as the amino acids which make up somatastatin.

According to a colleague from another department at UCSF, the researchers then linked a natural bacterial chain, the beta-galactosidase gene, and its control sequence to the artificial gene. Presumably, this natural gene sequence was added to "prime" the bacteria—while expressing the beta-galactosidase gene it would also express the artificial gene attached to it.

The next steps were relatively routine. This chain of "recombined" DNA, the nucleotides coding for methionine plus somatastatin plus beta-galactosidase, were spliced into either a virus or a bacterial plasmid, which was then introduced into some of the bacteria in the colony. After waiting for the bacteria to follow the new genetic blueprints, producing a large peptide chain containing both somatastatin and methionine, the researchers liberated the brain hormone with a chemical process that cleaved it from the methionine.

The researchers, however, refuse to confirm or deny this reported experimental design. According to a spokesman at UCSF, Boyer and his team are adhering to the traditional policy of withholding comment on a specific experiment until its methods and results have been "refereed" by a scientific journal, and then published. "Handler," the spokesman said, "must have heard of the research through the scientific grapevine. It was certainly not our idea—in fact, it caught us by surprise."

Handler's announcement probably also caught Genentech by surprise. Genentech is a California company Boyer organized two years ago to construct synthetic gene sequences that would be used to produce valuable medicinal drugs, such as insulin and possibly somatastatin. In testimony before the Senate subcommittee on science, technology and space, Boyer told Chairman Adlai E. Stevenson (Dem-Ill.) Genentech had paid for the somatastatin research through a contract with UCSF. UCSF, which is applying for federal patents protecting Boyer's new techniques is bound by the contract to award licensure to Genentech, would pay UCSF royalties on profits earned by such patents. A source familiar with the UCSF work said Boyer, worried that public discussion of the new techniques would prejudice chances for patent approval, had advised his fellow researchers to say nothing more about the experiment.

Handler may have preempted any later announcement of the experiment by Boyer in order to bolster his and other scientists' testimony before the same subcommittee (on Nov. 3) that not only was recombinant DNA research safe, but that it also (in the words of Paul Berg of Stanford University) "puts us at the threshold of new forms of medicine, industry and agriculture." □

# Methanogens: A third branch of life

The tree of evolution may need to be remodeled to reflect recent research results on the genealogy of microorganisms. A collection of twigs sometimes scattered on one side of the tree's major bifurcation may have to be regrouped into a third, and new, division of the trunk. It is suggested that members of this newly-proposed line of evolution changed little over the millenia and therefore resemble ancestral life forms dating back 3 to 4 billion years.

The newly-proposed evolutionary line contains all bacteria that produce methane, including *Methanobacteria, Methanospirillia* and *Methanosarcina*. But according to the researchers these groups should no longer be called bacteria. Carl R. Woese, leader of the team that is proposing the phylogenetic change, suggests they be renamed "archaebacteria" in deference to their proposed age.

Although they may have once dominated, methane-producing bacteria today fill only scattered, oxygen-free niches, such as hot springs in Yellowstone Park and the mud under the San Francisco Bay. They thrive on hydrogen and carbon dioxide and create methane gas ($CH_4$) as waste. Thus these microorganisms are called methanogens (methane producers).

Woese and his colleageues at the University of Illinois have been measuring the genealogies of organisms. They use a quantitative technique that Woese compares to the method one scholar used for dating cookbooks. The scholar determined which book was copied from which by tracing misspellings that crept in and were then included in later editions. Woese and co-workers charted the species differences among cellular macromolecules. The variations result