Researchers Isolate, Synthesize Growth Factor

A research team's 15-year search for an elusive brain chemical has ended in apparent success. The researchers report that they have isolated and chemically analyzed a molecule they believe is identical to growth hormone releasing factor (GRF), a substance responsible for regulating many of the body's growth and metabolic processes. The researchers also managed to reproduce the molecule synthetically, raising the possibility that manufactured copies might soon be made available for a wide array of applications in medical research and therapy. The team conducted the work at the Salk Institute for Biological Studies in La Jolla, Calif., and was led by Roger Guillemin, who shared the 1977 Nobel Prize for Physiology or Medicine.

Although GRF is normally produced by the brain's hypothalamus region, the researchers derived the newly reported molecule from a rare human pancreatic tumor. Certain tumors are known to produce hormones and other natural substances in unlikely parts of the body. "What can certainly be said is that the molecule we have now characterized has all the attributes expected from the long sought hypothalamic releasing factor," the researchers write in the Nov. 5 SCIENCE, where the findings were announced.

Scientists have long been aware that a chemical messenger from the hypothalamus stimulates the release of growth hormone from the pituitary gland. But the releasing factor, dubbed GRF, resisted study because it was normally present in only vanishingly small quantities. On several occasions various groups claimed to have isolated GRF, "but have never been able to establish its structure," says Nicholas Ling, a member of the Salk Institute team.

Guillemin and colleagues began their own quest for the structure in 1968, but the decisive step did not take place until two years ago. French physicians provided Guillemin with samples of a pancreatic tumor, removed from a patient, that was producing relatively large amounts of GRF. (Scientists think such abnormal production results from a breakdown of genetic controls in the tumor.) Guillemin and coworkers proceeded to extract and analyze the human pancreatic GRF, or "hpGRF." They have successfully identified its precise chemical structure — a short peptide of 44 amino acids — and have constructed replicas using an automated peptide synthesizer.

If synthetic hpGRF acts on the human pituitary the way natural hypothalamic GRF does, it could prove to be an invaluable pharmaceutical compound. Growth hormone (GH) has been implicated in a huge range of physiologic functions. And scientists have speculated that GRF, by correcting imbalances in growth hormone production, might be used to treat such GH-related disorders as pituitary dwarfism. Other possible applications that have been mentioned include speeding healing of wounds and burns, controlling gastrointestinal bleeding and even stimulating the growth of beef cattle.

Though growth hormone itself has been mass-produced by genetically engineered bacteria and has shown promise as a pharmaceutical agent in clinical trials, GRF may offer some advantages, according to Ling. GRF is a much smaller, possibly more stable, molecule than GH and might be manufactured at a lower cost, he says. Because GRF is small, scientists may also be able to produce large quantities through chemical, rather than bacterial, synthesis. This might permit structural modification of the peptide to yield analogs with different physiological effects or greater potency.

But many scientists are cautious in assessing hpGRF's potential value. Dorothy Krieger, director of endocrinology at Mount Sinai Hospital in New York, points out that "while there is some evidence that fragments of growth hormone are involved in wound and burn healing, it remains to be proven whether healing could be promoted by increasing the amount of circulating growth hormone." She adds that "before GRF could be used to treat pituitary dwarfism, it will have to be determined which cases are due to hypothalamic, rather than pituitary, dysfunction." GRF would be unable to trigger the release of growth hormone from a defective pituitary.

Perhaps the biggest question to be answered is whether the tumor-derived hpGRF is truly identical to the natural hypothalamic peptide. The effects of hpGRF on laboratory rats are virtually indistinguishable from those of rat hypothalamic GRF, according to Ling. But conclusive evidence won't come until researchers obtain sufficient hypothalamic GRF to analyze chemically — "and that may prove very difficult," he says. *—R. Pollie*

Aluminum linked with dialysis dementia

Aluminum, once thought to be a harmless environmental element, has been implicated during the past few years in two different types of dementia (mental deterioration) diseases — senile dementia and parkinsonism-dementia. And now it is being linked to a third dementia as well, that due to kidney dialysis, A. M. Davison and colleagues at St. James's University Hospital in Leeds, England, report in the Oct. 9 LANCET.

In part, Davison and his team have confirmed what other investigators reported between 1976 and 1978 — that dialysis dementia, which afflicts a surprisingly large number of kidney dialysis patients, seems to be due to aluminum in the water that helps comprise the dialysate (fluid) used to cleanse their blood. But Davison and his colleagues have gone further than previous researchers in that they have also shown that removing aluminum from the dialysate appears to lessen or even prevent dialysis dementia.

From 1968 to 1978, they studied 108 patients receiving kidney dialysis in the hospital and 150 receiving kidney dialysis at home. Of the total, 18 developed dialysis dementia, all of whom had been getting dialysis at home. Analysis of the 18 patients' domestic water supplies revealed that all had a high concentration of aluminum — greater than 80 μg/l (micrograms per liter). In contrast, those patients on hospital dialysis were being exposed to dialysate with deionized water, which contains virtually no aluminum.

After 1978, the researchers removed the high levels of aluminum from the domestic water of nine of the 150 home dialysis patients who had been dialyzed at home for one to four years and who had not yet succumbed to dementia. They wanted to see whether aluminum removal could prevent the development of dementia. They got mixed results. While aluminum removal appeared in varying degrees to benefit six of the nine patients — four developed no dementia at all, and two developed a mild dementia from which they are slowly recovering — it did not prevent two other patients from getting dementia and dying from complications related to it. (The remaining patient died from a kidney transplant complication unrelated to dialysis dementia.) In a second, more favorable, experiment, however, the researchers removed the high levels of aluminum from the water supplies of 24 other patients before they started home dialysis. The preventive measure seemed to work: none of the patients has developed dialysis dementia.

Thus aluminum appears to be causally related to dialysis dementia, Davison and his team conclude.

Arnold R. Brody of the National Institute of Environmental Health Science in Research Triangle Park, N.C., one of the scientists who linked aluminum to senile dementia (SN: 4/19/80, p. 246), says that the research by Davison and his team sub-