CHEMISTRY

The dialysis liver: Silicone seiged?

Tiny particles of silicone can flake off tubes in the kidney dialysis machinery and contaminate the blood it is purifying, researchers report in the Jan. 21 NEW ENGLAND JOURNAL OF MEDICINE. In addition, says Anthony S.-Y. Leong and colleagues of The Queen Elizabeth Hospital in Woodville, South Australia, the silicone accumulating in the body may be responsible for the liver disorders commonly seen among patients who also suffer chronic kidney failure.

Patients with chronic kidney failure depend on the life-saving dialysis process — a blood-filtering technique used by about 52,000 persons in the United States. To determine whether there is any link between that kidney treatment and liver dysfunction, the Australian researchers gathered, from 1973 to 1980, liver-biopsy specimens from 38 patients who had been treated with dialysis. All these patients were experiencing some degree of liver dysfunction. Leong, along with Alexander P.S. Disney and David W. Gove, also studied liver tissue obtained during autopsies of 31 patients who had undergone dialysis. Postmortem tissues from 10 patients with chronic kidney failure who had *not* had dialysis served as controls.

The tissue samples were examined by microscopic and other techniques. Those analyses revealed that of the 38 patients who had liver biopsies, 18 had various amounts of silicone in their specimens; of the 31 autopsies, 22 revealed the presence of silicone particles in the liver. The silicone particles were present in patients who had been on dialysis for six weeks to 85 months, the average period being 24 months. The patients who had undergone the longest period of dialysis had the largest accumulation of silicone in the liver, and no silicone was found in any of the liver samples or autopsy material from controls. The presence of silicone was associated with various degrees of inflammation and an abnormal increase in the amount of fibrous connective tissue in the liver, Leong and co-workers report.

The researchers also report their work on determining the source of silicone. "By passing 500 milliliters of whole blood through the silicone tubing in a [dialysis] roller pump at 250 to 300 milliliters per minute to simulate dialysis flow rates, we found silicone levels of 10, 35, 80 and 110 micrograms per 100 milliliters in the blood after five, 20, 48 and 96 hours of pumping, respectively," Leong and colleagues report. "Blood analyzed at the beginning of the experiment contained no detectable levels of silicone."

A preliminary announcement of such results drew similar reports from two other dialysis centers, Leong says. This indicates that "spallation of silicone from pump tubings is not a result of defective regional products and is a more common phenomenon than was previously recognized."

Moreover, says Leong, there already is ample evidence that silicone can evoke the types of responses they observed in the liver tissues. "The well-recognized 'silicone mastitis' is a chronic inflammatory response to the leakage or 'bleeding' of silicone from breast implants, and the injection of silicone into other subcutaneous sites has produced extensive chronic inflammation and a granulomatous foreign-body reaction," he says.

"The risk of introducing toxic substances through extracorporeal blood circuits is real," Leong and colleagues report. And the risk may not be limited to the use of silicone pump tubing; the use of polyvinyl chloride dialysis blood lines also may be harmful, Leong says. "Polyvinyl chloride and plasticizers used in the manufacture of dialysis tubings and other devices involved in the external circulation of blood are potentially toxic," he says. "Experiments have suggested that leachable products from polyvinyl chloride tubings can result in cardiotoxicity, and abnormalities of liver function and histologic features have been produced in the subhuman primate."

BIOLOGY

Sorting surface protein genes

Families of very similar genes on a chromosome present a difficult challenge to biologists. How can they determine which member of the family, which may contain both functional genes and nonfunctional "pseudogenes" (SN: 12/20 & 27, 80, p. 396), is responsible for a given protein? When the nucleotide sequence has been determined it often is not possible to match it with a protein, because the amino acid sequences of many large proteins have only been partially determined.

A successful solution to this problem now has been reported by Leroy Hood of California Institute of Technology and colleagues. They were looking for the gene encoding one of the mouse cell surface molecules (transplantation antigens) that mediate graft rejection. Among the genetic material of sperm of an inbred mouse strain, they found 30 to 40 DNA segments that appear to encode, or be related to the genes that encode, transplantation antigens or similar proteins. To distinguish among the DNA segments, Hood and collaborators transferred them into laboratory-grown cells of a different mouse strain. They identified cells that contained the gene product of interest, a surface molecule called L^d, by exposing the cells to a monoclonal antibody that binds to L^d but not to the natural surface molecules of the host cells.

The correlation between gene 27.5 and the L^d protein was substantiated by the nucleotide sequence of the gene. Although only a fifth of the amino acid sequence has been determined, it is identical to the translated nucleotide sequence at all the positions that can be compared. Gene 27.5 is divided by intervening noncoding sequences into eight coding regions, whose boundaries make a "striking correlation" with the structural domains of the surface protein. The first region encodes the signal protein that is clipped off during processing; others encode protein domains that lie outside the cell membrane, span membrane or lie inside the cell. The scientists conclude in the Feb. 5 SCIENCE, "Gene transfer and immunosuppression provide a powerful approach for identifying and characterizing the genes encoding transplantation antigens."

Enkephalin's multi-hormone precursor

Some hormones that function coordinately in the body are synthesized in concert, as parts of a single polypeptide chain, and then snipped into the active components. Two laboratories report in the Jan. 21 NATURE the nucleotide sequence of the precursor to a series of enkephalins, 5-amino acid molecules with opiate-like activity. The precursor protein is composed of about 300 amino acid subunits. The group led by Ueli Gubler of Hoffman-LaRoche, Inc. calls the precursor "proenkephalin"; the team led by Masaharu Noda of Kyoto University Faculty of Medicine in Japan calls it "preproenkephalin."

The precursor had been known to contain at least seven enkephalin molecules (SN: 11/7/81, p. 301). From the nucleotide sequence the scientists discovered that two of the met-enkephalins actually are slightly longer molecules, one with two and the other with three extra amino acids. Each of the enkephalin and extended enkephalin sequences are bounded by pairs of the two basic amino acids, lysine and arginine. The paired basic amino acids appear to be a hormone precursor processing signal. The precursor was also found to encode several larger enkephalin-containing peptides recently found in the adrenal gland. Proenkephalin is the only precursor known to contain several copies of a biologically active peptide, each in a different set of surrounding amino acids, says the Hoffman-LaRoche group. The precursor gene probably evolved by a series of duplications followed by substitutions, additions and deletions, suggest the Japanese scientists.