
Interferon by bacteria, on trial

The first clinical trial of human interferon produced by genetically engineered bacteria has begun at M. D. Anderson Hospital and Tumor Institute in Houston. Eight patients with advanced cancers are receiving injections of the material to determine its safety, patient tolerance and immune system effects. An additional trial is scheduled to begin in two weeks at Stanford University, to be followed by other clinical tests in cooperation with the National Cancer Institute. The initial trials will involve patients with a variety of viral diseases and cancers and physicians experienced in administering interferon.

The new technique for making the interferon, which is of the type produced by white blood cells, or leukocytes, was developed in a two-year collaboration between the pharmaceutical company Hoffman-La Roche and the genetic engineering firm Genentech. Another company, Biogen, was the first last year to announce bacterial production of interferon (SN: 1/26/80, p. 52). Until now the protein has been too rare and expensive to determine its usefulness in treating viral diseases and

tumors (SN: 6/7/80, p. 358).

Bacterially produced interferon is expected eventually to be the biggest product of genetic engineering technology, according to a report issued by a Norwalk, Conn., research firm called International Resource Development Inc. The report, which costs \$985 a copy, estimates the synthetic interferon market at \$375 million by 1985 and \$1.4 billion by 1990. Antibiotics are the next-largest potential market, according to the report. It predicts that \$1.14 billion of spliced-gene antibiotic products could be sold annually by 1990, according to the Wall Street Journal.

The genetic engineering product likely to reach the market first is human insulin, which is already well into clinical trials (SN: 1/3/80, p. 8). The IRD report predicts a \$2.2 million market in 1982 and \$235 million by 1990. Commercialization of recombinant DNA technology is expected to total more than \$3.6 million in 1982, \$520 million in 1985 and \$3 billion by 1990. The report predicts that the greatest benefits of the technology will result from new production processes for existing products. "Benefits from the technology for production of newly created substances will take longer. A greater amount of work in research and development will be required," the study says. □

Kidnapping: How kids handle trauma

On July 15, 1976, 26 children riding home on a school bus in Chowchilla, Calif., were kidnapped, and their plight commanded international attention. The children, ranging in age from 5 to 14 years, disappeared for 27 hours and eventually escaped from their abductors. After their return, the children reported that their bus had been stopped by a van blocking the road, and three masked men carrying guns had transferred them to two boarded-over vans. The children were driven about and eventually transferred into a buried truck-trailer that the kidnapers covered with dirt. Two of the oldest and strongest boys succeeded in digging out of the hole and releasing the others, but the kidnapers were long gone.

A psychiatrist at the University of California at San Francisco now reports that she has interviewed 23 of the child victims and one or both of their parents who have remained in Chowchilla, and finds several important differences between adult and child reactions to trauma. Lenore C. Terr, writing in the January *AMERICAN JOURNAL OF PSYCHIATRY*, says that every child showed the emotional effects of psychic trauma. Her interviews were conducted between December 1976 and August 1977. She concludes that, unlike adults, the children had no period of amnesia or haziness about the experience, did not use denial as a defense mechanism to deal with the kidnapping and had no involuntary flashbacks to the event. But 14

of the children continue to "play" out the trauma, either individually or in groups. Repetitive traumatic dreams, previously observed in adults, were also reported by these children. They had misperceptions, over-generalizations and time distortions about the incident. Twenty children fear being kidnapped again and remain on guard against such an occurrence. Despite good home environments, parental reassurances have gone largely unaccepted. Several children have linked a specific event before the kidnapping to the kidnapping itself. These types of "omens" may be a way for children to explain the incident to themselves, and figure out how they might have been warned before or soothed during the trauma.

Terr says that although adults have been reported to reenact traumatic incidents, the fantasies and reenactments of the Chowchilla youngsters are more literal than those of adults. The children's fears of another kidnapping have affected their attitudes toward their normal environment, and many items, such as motor vehicles, the dark, the wind and household objects, cause fear and avoidance.

The children in this group were at different developmental stages at the time of the kidnapping, but Terr's findings were consistent for the entire age range. Research and observations on childhood trauma are sparse, and Terr is not certain why this consistency was found. Further research may clarify the findings. □

Chlorine: On the water front

The drinking-water studies recently reviewed by the U.S. Council on Environmental Quality (SN: 11/1/80, p. 278) are now sharing the chlorination-controversy spotlight with a study promoted by the American Water Works Association.

Researchers are conducting such studies in an attempt to determine whether disinfecting public drinking water with chlorine is linked to increased cancer risk. Chlorination first fell under suspicion when scientists discovered that chlorine reacts with natural substances in water to form trihalomethanes (THM's) — a family of compounds in which three of the four hydrogens in methane (CH₄) are substituted by chlorine, bromine or iodine. The major THM component — trichloromethane, or chloroform — causes cancer in laboratory animals.

The studies reviewed by the CEQ suggest that there also may be a link between THM's and cancer risk to humans. While the studies failed to establish a causal relationship between heavily chlorinated water and cancer, they did strengthen "the evidence for an association between rectal, colon and bladder cancer and drinking water quality." The results indicated, for example, that drinking chlorinated water was associated with increased risks — ranging from 13 to 93 percent — of rectal cancer.

But Robert W. Tuthill and Gary S. Moore of the University of Massachusetts at Amherst say it is "premature" to associate chlorinated water with cancer. Tuthill and Moore have compared present cancer rates in certain Massachusetts communities with past and present chlorine doses in the water supplies of those communities. While a portion of the study results showed an initial strong relationship between THM's and rectal cancer, that association disappeared after controlling for the percentage of foreign-born citizens in the study. Tuthill and Moore, whose study is reported in the *JOURNAL OF THE AMERICAN WATER WORKS ASSOCIATION*, believe that failure to control for social variables in previous studies may have led to "spurious associations of chlorination of drinking water with cancer."

CEQ member Robert Harris says "nonsense." He explains that certain of the CEQ-reviewed studies controlled for socioeconomic factors — taking into account, in one instance, the high content of fish and spices in the diet of Acadian descendants in Louisiana.

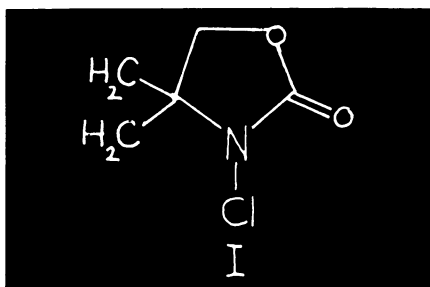
But Tuthill says his study raises other questions about the methodology of the CEQ-reviewed studies. "Most of the epidemiological studies to date have correlated current chlorination levels and current cancer mortality," ignoring the possibility that there is a latency period

between exposure to THM's and a resultant adverse effect. When Tuthill took this potential lag time into account by comparing the current cancer rates and chlorination procedures 20 years ago in the Massachusetts communities, he found no relationship.

Still, Tuthill admits that his study has its limitations — the examination of only a small number of communities and the study's ecologic approach (experimental and control groups are geographic areas rather than individuals). "The results from ecological studies are not nearly as definitive as those conducted on the individual level," Tuthill says. "The question [of chlorination safety] isn't answered yet."

Despite the uncertainties surrounding it, "The practice of chlorination," Tuthill and Moore conclude, "should not be phased out in preference to another method of disinfectant until there is stronger epidemiological and clinical evidence to support the charge that it produces serious health risks and until the potential health effects of substitute disinfectants are carefully explored."

One of those potential substitutes now under scrutiny is 3-chloro-4,4-dimethyl-2-oxazolidinone, or Agent I. At the recent American Chemical Society regional meeting in New Orleans, H.D. Burkett of Au-



The novel disinfectant compound Agent I.

H. D. Burkett et al.

burn University in Alabama reported that in addition to being as efficient as chlorine in eradicating bacteria, Agent I has certain advantages over the present method of chlorination:

- The current method involves storing chlorine as a gas before it is converted to its acidic disinfectant form. Agent I, says Burkett, is a nontoxic solid, much less hazardous to work with than toxic chlorine gas.

- Agent I is a "slow-releasing agent," liberating free chlorine as needed.

- Agent I is less likely than the conventional chlorine form to form THM's.

While preliminary toxicity tests on white rats and chickens show no adverse effects of Agent I or its metabolites, its effect on humans is unknown. □

Attacking cancer after it has spread

Immune system stimulators, until now, have been a second string team in the cancer fight. "Immunotherapy" is very attractive in that it has no known side effects, but traditionally it has been used only after other therapies in attempts to fight residual cancer. At the recent meeting in Toronto of the American Association for the Advancement of Science, Robert S. Kerbel reported results from animal studies that suggest that in some vicious cancers the immune system, if cleverly manipulated, could be the best first line of defense.

The most difficult problem in treating many cancers is stopping or reversing their spread. Kerbel estimates that dispersed cancer cells, which initiate new tumors, are responsible for 85 percent of human cancer deaths. Kerbel and James W. Dennis have concentrated their work at Queen's University in Kingston, Ontario, on the most potent metastatic, or spreading, cancers.

One characteristic that distinguishes the cancers that spread most rampantly through the body is their ability to evade the immune system. But Kerbel and Dennis have developed a method to stimulate a reaction to such cancer cells. They take cells from the original tumor of a mouse cancer that spreads rapidly and widely and, in the laboratory, select cells with genetic mutations that result in altered membrane characteristics. A few of these variants have lost their disguise, the re-

searchers find. The variants still cause cancer in mice with deficient immune systems, but in mice with normal immune response, the variant cells are killed in a style resembling transplant rejection.

When the variant cancer cells were used in the laboratory to stimulate immune system cells called cytotoxic T-lymphocytes, Kerbel was surprised to discover that these "educated" cells are as effective at killing cells from the original tumor as at killing the variants. When injected into mice that had widespread metastases from the original tumors, the educated cells reduced dispersed tumors, although eventually the animals still died.

In a more effective procedure, the investigators surgically removed the original tumors in mice with widespread disease. They then irradiated the animals and injected killer cells previously stimulated by the selected cancer cell variants. After seven weeks almost all the control animals had died, but the six receiving the educated lymphocytes appeared healthy. Autopsies indicated that five of these mice were cured of their cancers.

Kerbel calls the results "interesting and encouraging." But the difficulty in providing therapy for patients with established, widespread disease will be in working out a reasonable protocol to select variants and stimulate a patient's own lymphocytes. Kerbel concludes that such therapy is now "still impractical, but not impossible." □

Cholesterol: You can't win

One of the toughest health questions facing Americans last year was how much cholesterol they should consume — authorities disagreed over whether lowering dietary intake of cholesterol protects against heart attacks and there was evidence that lowering blood levels of cholesterol, at least with drugs, increases a person's susceptibility to death from causes other than heart attacks (SN: 6/7/80, p. 357; 9/13/80, p. 165). And now it looks as if the question of how much cholesterol is good for you is going to be even more difficult to answer. Two new studies suggest that while a low-cholesterol diet *can* protect against heart attacks, it may increase vulnerability to cancer.

The first of the studies, reported in the Jan. 8 *NEW ENGLAND JOURNAL OF MEDICINE* by Richard B. Shekelle of Rush-Presbyterian-St. Luke's Medical Center in Chicago and his colleagues, started some 20 years ago. The investigators evaluated dietary cholesterol and blood levels of cholesterol in 1,900 middle-aged men working for the Western Electric Co. in Chicago. A positive association was found between the subjects' dietary intake of cholesterol and blood levels of cholesterol. The scientists then checked 20 years later to see which subjects had had fatal heart attacks and found that dietary intake of cholesterol appears to influence blood levels of cholesterol and in turn a person's susceptibility to heart attacks—as several previous studies have suggested. Other investigations, however, have failed to make these associations — hence the still-unresolved question of whether dietary cholesterol really influences blood cholesterol and in turn the risk of a heart attack.

The second of the new studies, reported in the Jan. 16 *JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION* by Roger R. Williams and colleagues at the National Heart, Lung and Blood Institute in Bethesda, Md., is part of the NHLBI's ongoing Framingham, Mass., heart study, which over the years has shed, and continues to shed, light on heart attack risk factors. Williams and his co-workers documented 691 cases of cancer in some 5,000 Framingham subjects and found that a low blood level of cholesterol was significantly associated with later susceptibility to cancer, particularly colon cancer, but only in men. Williams and his team admit that they do not know how a low blood level of cholesterol might predispose to cancer, especially since some studies have shown a link between high fat consumption (purportedly related to blood cholesterol) and colon cancer. Nor do they know why blood cholesterol was related to cancer in their male but not in their female subjects. □