Teacher-to-Teacher

GIFT—Gastrointestinal Function and Toxicology

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Human knowledge of toxicity probably began by accident when our ancient ancestors sampled the wrong plants for food and became ill or died. Later in history, knowledge about toxins was used with some sophistication in medieval royal court intrigues when rivals were poisoned and the fatal seizure passed off as sudden illness. In contrast, modern science has begun to look more closely at both overt and subtle toxicities, especially from long-term, low-dose occupational and environmental exposures that often produce chronic illness. Research relating to exposure through ingestion and especially the intestinal tissue itself has recently been eclipsed by investigations of exposure through skin and by inhalation. Even where laboratory animals are exposed through ingestion, as many are, the target organs studied are more often the liver, kidney, or nervous system rather than the intestine itself.

The Gastrointestinal Function and Toxicology Work Group within the Laboratory of Organ Function and Toxicology at the National Institute of Environmental Health Sciences is composed of scientists determined to redirect some attention to the intestine. The Group has devised an acronym for Gastrointestinal Function and Toxicology, GIFT, an optomistic-sounding short form that also means "poison" in German.

The mission of the GIFT Group and the NIEHS is not only to properly identify and describe the mechanisms of environmentally related diseases, but also to provide the knowledge to facilitate their prevention. NIEHS is the principal Federal agency for biomedical research on the health effects of environmental agents, both physical and chemical. Located in Research Triangle Park, North Carolina, it is the only one of the National Institutes of Health not located in Bethesda, Maryland.

When the Work Group first began intensive work on the intestine as a target organ for toxicity, scientists outside the Group kept suggesting that attention be redirected to other organs because the intestine is not as easy to work with as the liver and some other organ tissue and is difficult to prepare in subcellular fractions or as isolated cells.

The intestine has many different cell types, and the presence of mucus and the cells' tendency to aggregate further complicate studies; but these problems challenged rather than daunted GIFT investigators.

Misconceptions about the intestine dispelled by GIFT investigations include the notion that it is solely a barrier, absorptive in function, merely taking in nutrients and acting as a conduit for waste. This is an oversimplification. The physical transport provided by the intestine and its absorptive functions are accompanied by important metabolic functions. The GIFT laboratory has examined a number of intricate enzymatic interactions that occur in the intestine that differ markedly from those occurring in other organs including the liver.

Further, the intestine is not just a degradative organ that breaks food down into usable nutrients. It is also a synthesizing organ that acts as a transfer agent that allows certain nutrients to be absorbed into the blood and at the same time allows passage of non-absorbed material from the body as waste. GIFT researchers learned that metabolism in the intestine is to some degree anaerobic as opposed to the more general aerobic metabolism in most cells of the body. This anaerobic metabolism is similar to that in tumor cells, and may therefore have significance in considering the gut as a target organ for carcinogenicity.

An important finding of GIFT concerns the nutrient energy source used by the intestine for metabolic

and absorptive functions. Experiments with isolated intestinal absorptive cells and with isotope-marked nutrients revealed that the muscle cell waste produce glutamine, when it is available, is used in preference to glucose as a nutrient energy source.

GIFT research on normal intestine tissue is accompanied by investigations on the effects of various environmental agents. One such study revealed that the chemical 1, 2 dimethylhydrazine (DMH), structurally similar to a component of jet aircraft fuel, produced colon cancer in a single low oral dose in 80% of the exposed animals in the experiment. One important difference in the work done by the GIFT laboratory was that researchers waited 18 months to observe the carcinogenic effect of the single dose. This mimicked the human population where colon cancer tends to be an older person's disease. In terms of life span, a laboratory animal 18 months old is comparable to a person of retirement age. A separate experiment showed that administering a single dose of DMH to pregnant animals changed the enzymatic activity in the intestines of offspring. Other researchers have demonstrated that prenatal exposure to this compound induces tumors in the offspring in the brain and jejunum.

Another environmental agent investigated for its effect on the intestine is 2,3,7,8-tetrachloro-p-dibenzo-dioxin (TCDD) a by-product component of the herbicide included in Agent Orange and a toxin that was held responsible for human health effects in the widely publicized Seveso, Italy, chemical factory catastrophe. When the GIFT laboratory scientists looked at TCDD effects on intestinal cells, they observed that the less differentiated crypt cells were more susceptible to enzyme induction than were the highly differentiated absorptive cells (tip cells). This preferential induction may be an example of a more generalized susceptibility to toxins of the more undifferentiated cells.

Work with another environmental agent, acrylamide, a known neurotoxin, has suggested an approach to looking at a broad range of toxins that might act on the intestine as a target organ. Work by the behavior group at the NIEHS demonstrated that acrylamide has a diet-dependent effect on performance on certain behavior tests, and this work led GIFT scientists to develop baseline studies on absorption in normal intestine tissue to better understand the impact of other toxins and suspected toxins that may alter absorption of nutrients.

For too long, physicians have been more concerned with studying the intestine that have research scientists. When it comes to illnesses of the intestinal tract—many of which have environmental origins—medical doctors begin to look further than "nonspecific intestinal disease of unknown etiology" in describing these diseases.