million Americans each year risk getting a tropical disease—but the risks for people elsewhere are staggering. In the tropics, the average life expectancy is reduced by an estimated 20 years for individuals, and something like 10% of an average person's life-span is "seriously disrupted by ill health." The problems are particularly acute for infants and children. "Worldwide, as many children die from diarrheal disease as there are total deaths from cancer," the report points out. By contrast, these diseases have been all but eliminated as major sources of death among children in the United States.

Improving the lot of children and adults in developing nations obviously requires more than changes in research programs. However, the scope of OTA's report is limited to evaluating the role that U.S. biomedical research might play in better understanding tropical diseases and thereby reducing their incidence and severity.

OTA found that much of the recent progress in this field is due to a "small but highly motivated corps of . . . researchers." A major reason the corps is so small is that the "U.S. government is spending relatively little money . . . [a fact that] appears to reflect choices in policy, whether implicit or explicit, and not a lack of promising avenues for research."

The current annual expenditure across several federal agencies for tropical disease research is about $100 million. Besides assembling a wealth of information about tropical diseases, the OTA report suggests several options for Congress to remedy this relative financial neglect. Another report, being prepared by the National Academy of Sciences, is expected to further delineate tropical disease research programs that might benefit from increased federal funding.

Despite the creative options the report lays out for Congress to consider, "There just is not a big U.S. constituency for this research," says one insider. "Nobody is setting priorities." Moreover, finding someone to champion the cause within the government is, so far, "like beating your head against the wall." □

Microbes Help Model Mammalian Metabolism

Margie Patlak

Microbes that transform compounds by the same biochemical reactions used by higher organisms soon will aid in evaluating drugs and various pollutants. A battery of bacteria, yeasts, and other fungi convert a wide range of chemicals into the same metabolites generated by humans, several research groups have found. "These microbes might serve as models for predicting the routes of metabolism a new compound will take in mammals," says the head of one such group, Patrick J. Davis, associate professor of medicinal and natural products chemistry at the University of Texas in Austin. A way of modeling mammalian metabolism with microbes was first suggested by Robert V. Smith and John P. Rosazza of the University of Iowa in the mid-'70s.

Microbial models are not expected to replace the higher-animal models used to evaluate new drugs and toxic compounds (ASM News, July 1985, p. 324). However, when used in concert with animal models, they can reduce the cost, time, and effort involved in such evaluations, Davis points out. "Also, we can use microorganisms to produce large quantities of drug metabolites . . . for studies on the compounds' biological activities, toxicities, and structures," Davis adds. "It's extremely difficult to get a sufficient amount of many mammalian metabolites, but you can easily scale up the production of metabolites with microbes."

If the mammalian metabolites of a compound are not known, microbes can indicate what those metabolites are likely to be, thereby better focusing the research that must be done on higher organisms. Microbes that use only one of several routes of metabolism of a compound also enable researchers to explore specific metabolic pathways that may be obscured in mammals. Sometimes, to develop an adequate model of mammalian metabolism, a "composite of several different microorganisms that each use an individual metabolic route" must be made, Davis says.

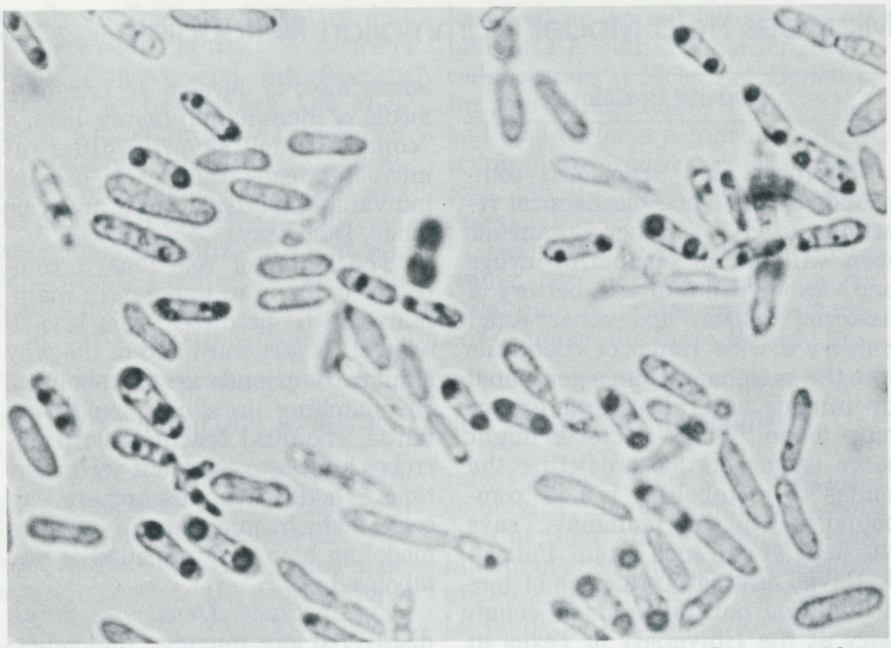
The types of reactions a compound is likely to undergo in mammals can be predicted from knowledge of its structure and of the way similar compounds are metabolized. By matching up a compound's potential chemical reactions with microbes known to carry out such reactions, Davis says, researchers can select which microbes to use for modeling how the compound is metabolized.

For instance, Davis and Smith discovered four microbes that collectively provide a particularly good model for the metabolism of pentoxifylline, a drug used to treat patients with vascular disorders. In their initial screening, they used 14 readily available microorganisms that studies showed can convert ketones to alcohols. Such conversions commonly occur in the processing of many drugs by higher organisms, and the ketone portions of pentoxifylline are known to undergo this transformation in mammals.

Of the 14 microbes, 13 generated an alcohol, the main metabolite of pentoxifylline in mammals. Of these 13 organisms, 2 (*Curvularia falcata* and *Streptomyces griseus*) also produced the same carboxylic acid metabolites of the drug that mammals generate. *Curvularia falcata* and *Cryptococcus macerans* converted more than 90% of pentoxifylline to its metabolites.

Further studies revealed that the three-dimensional orientation of the alcohol molecules generated by most of the microbes was identical to the primary orientation of the alcohol metabolite that is produced in humans. "This finding implies that the types of enzymes that metabolize pentoxifylline in humans have additional similarities to the enzymes that metabolize the drug in most of the microbes we tested—further evidence that these microorganisms can effectively model the mammalian metabolism of pentoxi-

Margie Patlak, a former staff writer for Research Resources Reporter, *is a free-lance writer based in Washington, D.C.*



Courtesy of the American Type Culture Collection

The yeast Cryptococcus macerans, *one of several microbes that can aid in the evaluation of drugs and various pollutants, transforms compounds via the same chemical reactions used by higher organisms.*

fylline," Davis says.

In another study, the use of microbes to model the metabolism of the antimalarial drug primaquine led to the discovery of a previously unknown mammalian metabolite. Charles D. Hufford and his colleagues at the University of Mississippi in University screened a number of microbes for their ability to metabolize primaquine; three *Streptomyces* and an *Aspergillus flavus* strain each produced one major metabolite. When the investigators searched for these compounds in the blood of rats and rhesus monkeys given primaquine, they discovered that the carboxylic acid metabolite generated by *A. flavus* is also the major metabolite in higher organisms. This metabolite was not predicted from studies of similar compounds. They are now studying *A. flavus*-generated carboxylic acid for its activity and potential toxicity.

The fungi *A. flavus* and *Cunninghamella elegans* are favorite microbes for mammalian metabolism models because they process a wide range of compounds via an expansive set of reactions. *Cunninghamella elegans* has a wealth of enzymes to carry out reactions, including those that produce some of the major metabolites found in the liver. Carl E. Cerniglia and his colleagues at the National Center for Toxicological Research of the Food and Drug Administration in Jefferson, Ark., have conducted extensive studies on *Cunninghamella elegans*'s ability to metabolize several types of carcinogens, including those found in car emissions and cigarette smoke. This fungus and others frequently generate carcinogenic metabolites like those shown to be toxic in higher organisms. "Although these fungi don't metabolize toxic compounds in the exact same way that mammals do," Cerniglia says, "there are enough similarities to make these microbes useful as models for mammalian metabolism of pollutants."

Most studies on microbial models have been done on compounds with fairly well-defined routes of metabolism in mammals. "Now investigators are starting to use microbial models prospectively to predict the metabolic pathways that drugs or pollutants follow in mammals or to study unexplored aspects of previously researched compounds," Davis says. "'In this way, microbial models will facilitate the study of drug metabolism in mammals." □

Plea for Better Use of Vaccines Renewed

Vaccines to protect against several serious, often life-threatening diseases are available but are not being fully exploited—particularly by the adult U.S. population, public health experts say. Too much reliance has been put on vaccination programs for children, and a comparable effort is being recommended to reach adults, especially those in high-risk categories for diseases such as influenza, pneumococcal pneumonia, and hepatitis.

"We take care of our children very well, but not our adults," says Richard J. Duma, who is president of the National Foundation for Infectious Diseases, as well as chairman of the division of infectious diseases at the Medical College of Virginia. "We almost instinctively rely on immunization of children," adds Frank Young, commissioner of the Food and Drug Administration. But we are "overlooking the same principles" of preventive medicine by failing to "vaccinate older people, despite having improved vaccines not available a decade ago." Both Young and Duma spoke at a National Adult Immunization Alert sponsored by the Foundation last November in Washington, D.C.

Comments and recommendations made by immunization experts about several vaccines available for adults include the following highlights:

- Influenza epidemics during the past 17 years have raised by 10,000 per year the number of expected influenza deaths in the United States. Despite this threat, only about 20% of the high-risk adult population, principally the elderly, receive influenza vaccinations, which are 60 to 80% effective.
- As many as half a million Americans suffer from pneumonia each year, and 60% of those who do not respond to antibiotic therapy die from damage incurred during the first few days of illness. Because the mechanism for that often-fatal damage remains unknown, the only way to prevent it is to guard against the disease. Although the vaccine is complex and more expensive than