COMMENTARY/

by Bernard Dixon

THE THIRD WORLD'S GREAT OPPORTUNITIES

The daftest observation one hears from otherwise intelligent people about recombinant DNA work is that it represents "frontier science" or "high technology," irrelevant to the problems of the Third World. Remarks of this calibre match those of excitable writers who go much too far in attacking the pharmaceutical industry and ignore the massive contributions that properly used drugs and vaccines make to health in less developed countries. Such commentators adopt a touchingly simplistic stance. They believe in clean water *instead of* drugs, land reform *instead of* pesticides, politics *instead of* science.

An excellent example is now emerging to show just how wrong-headed opinions of this sort really are. At long last, after decades of mediocre, short-lived, and risky immunization against infections like typhoid fever and cholera, we are due to see some highly effective vaccines to combat these diseases. Unlike conventional shots, which are given by injection, the new versions will be taken by mouth. This makes them potentially invaluable for widescale deployment in the Third World, where diarrheal maladies cause a horrendous burden of morbidity and mortality. And far from being fruits of so-called appropriate technology, they will be products of genetic manipulation, a vast improvement on the century-old tactics still exploited for making vaccines against many other common conditions.

Even without the full sophistication of modern gene splicing, one preparation has already been developed and shown remarkable results. Working at the Swiss Serum and Vaccine Institute in Berne, Switzerland, Professor Rene Germanier has evolved the genetically crippled Ty 21a strain of *Salmonella typhi*. This is a stable double mutant of the wild type typhoid bacillus which lacks a crucial enzyme, UDP-galactose-4-epimerase. After being swallowed, it undergoes only four or five cell divisions and then penetrates the small intestine wall before self-destructing. In other words, it persists long enough to induce immunity, but not sufficiently long enough to do any harm.

Writing earlier this year in *The Lancet* (1983, **1**:523) Drs. R. G. A. Sutton and M. H. Merson from the World Health Organization (WHO) in Geneva reported an efficacy rate for this vaccine of 96 percent, which is comparable with or better than most other vaccines in public health use. And no untoward side effects have come to light in a trial started last year among 85,000 young people in Santiago, Chile. A WHO committee is now hammering out international requirements for the vaccine—which, Sutton and Merson believe, "could contribute enormously to the worldwide effort to control typhoid fever."

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A rather different approach is paying dividends in the search for prophylaxis against cholera. It has been pioneered by Dr. Takeshi Honda, now working in the Research Institute for Microbial Disease in Osaka, Japan, together with Dr. Richard Finkelstein, now at the University of Missouri at Columbia. They have evolved a chemically mutated version of *Vibrio cholerae* called "Texas Star." It produces subunit B of the toxin molecule, which binds to the intestinal wall and induces immunity. But it lacks subunit A, which normally inactivates a key enzyme in epithelial cells, makes them secrete water, and thereby triggers off the appalling rice-water stools that characterize rampant cholera.

Results reported at a symposium held by WHO in Dublin show that a vaccine based on Texas Star provoked anti-cholera antibodies in 93 percent of volunteers vaccinated in tests organized by Dr. Myron Levine at the University of Maryland School of Medicine. When inoculated with pathogenic *V. cholerae* two months later, the volunteers showed "significant clinical protection." The vaccine did cause mild diarrhea in a quarter of the individuals, but was otherwise free of adverse effects.

There is, of course, a remote theoretical possibility that a bacterium of this sort could revert to its dangerous form. That anxiety has led Dr. James Kaper, head of the U.S. Center for Vaccine Development, to adopt an alternative strategy which makes reversion impossible. He has snipped out from a cholera vibrio the genes responsible for subunit A, and replaced them with an inactive gene. The resulting organism, which retains the subunit B genes, is due to be tested this year as a vaccine in animals. With at least two further candidates also under development, effective cholera immunization could be near at hand.

Intestinal diseases are not the only Third World scourges for which genetically engineered prophylactics are showing high promise. One of the most exciting reports during recent months has been that of the ingenious route taken by Dr. Geoffrey Smith and his associates at the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, towards a hepatitis B vaccine. They have contrived to make a recombinant of vaccinia (the virus used in the past to defeat smallpox) that carries the coding sequence for hepatitis B surface antigen. Unlike existing shots, which are expensive to prepare and relatively inefficient, a vaccine based on this novel virus could be made cheaply, and animal tests have shown it to be highly effective in triggering antibody production. Smith and his team believe (*Nature*, Apr. 13, 1983, p. 490) that it may well prove valuable in dealing with widespread, chronic hepatitis B infection in Africa and Asia.

There are many other diseases for which satisfactory preventive agents

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have never been developed or made available on a wide scale. For example, with the sole exception of yellow fever, no vaccines are in general use against any of the arboviruses. Technical difficulties plus a lack of adequate financial incentives have discouraged or defeated efforts in the development of this and many other types of vaccines. Today, the picture begins to look very different. Gene splicing could revolutionize our control of infectious diseases. And the greatest opportunities of all are undoubtedly in the Third World.

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appropriate scale: Who does what? How does the messy learning process advance, as know-how threatens to outrun "know-why"?

The answers are familiar, tedious, but recurrent: the need for transfers—of ideas and people, between institutions, between countries, between disciplines, and between sectors—to promote learning and understanding. Links are required between the developed world and the developing ones, demanding the institutional and infrastructural build-up to enhance the capacity to absorb, to adapt, and to implement: the global networks such as MIRCENs (Microbial Resource Centres: training and diffusion centers funded by UNESCO and other U.N. agencies) and CGIAR (Consultative Group for International Agricultural Research) are commended as models by FAST.

The FAST report has a lot of good ideas; the perceptions on the necessity of developing the bio-informatics infrastructure are particularly sound. The open question remains: can the old world really overcome its historical fragmentation, its cherished cultural diversity mapping into vested interests defended by administrative irrationality, to maintain or to win parity with the U.S. and Japan?