CORRESPONDENCE

To the editor:

We have read with interest the Technology Report of Gatz et al. [BIO/TECHNOLOGY, 1983, **4**:337–341] describing the potential applications of monoclonal antibodies in food production. The applications as reported are all valid and may indeed identify commercial markets of the future. However, we would suggest another market for which monoclonal antibodies are presently being developed and are in some cases commercially available: diagnostic serology for detection of *antibody* to pathogenic agents.

A large portion of serology falls within the domain of various government laboratories that presently rely on procedures which measure secondary antigen antibody interaction such as agglutination, precipitation or complement fixation. With the advent of the development of primary binding assays such as the ELISA, RIA, and FA, a large investment of time and resources has been expended in their adaptation to veterinary purposes. Unfortunately, the unconditional acceptance of such technology rests with its interlaboratory standardization. This standardization would be greatly facilitated by the use of monoclonal antibodies as anti-species detection agents, conjugated with a desired marker. Monoclonal antibodies could thus be mass-produced, tested for specificity and conjugated by a given laboratory for distribution to other laboratories. Alternately, hybridoma lines producing antibody of an agreed-upon specificity could be distributed for processing by individual facilities. Either way, the monoclonal products would allow direct comparison of test results, a circumstance that would lead to better test evaluation/development and therefore optimizing diagnostic procedures.

Since several million tests are performed in North America for brucellosis alone there is little doubt of the economic feasibility of monoclonal antibodies in the context of the diagnosis of this disease. Of course, the same monoclonal antibodies would be applicable to any other serological procedure with that species.

In reading the report, a couple of questions arise. Six criteria for ranking production concepts are outlined in Table 2. However, seven criteria are evaluated in Table 3. Therefore, it is difficult to pair criteria with ranking. Another question arises with the use of the word "vaccines" in Tables 1 and 3. Presumably "passive immunization" would be the correct terminology as a vaccine is defined as a product from a living agent that elicits an active immune response as opposed to a serum (antibody) injection (Gell, Coombs and Lachmann. 1975. *Clinical Aspects of Immunology*, 3rd edition, pp. 1603. Blackwell Sci. Publ., Oxford.)

Sincerely yours,

Klaus Nielsen
Robert Duncan
Immunology Section
Animal Diseases Research Institute
801 Fallowfield Road
P.O. Box 11300, Station "H"
Nepean, Ontario,
Canada K2H 8P9

To the editor:

In his column, "Regulatory Trends for Biotechnology Products" [BIO/TECHNOLOGY, 1983, **1**:240-246], Dr. E. Korwek has misrepresented the sense and substance of the FDA's position on pharmaceuticals produced using recombinant DNA techniques. He takes the FDA to task for over-regulating, but he ignores the realities of our approach and of our statutory mandate.

Recombinant DNA technology has raised some interesting scientific issues for the FDA. First, the molecular structure of some products is different from that of the active molecule in nature. For example, the "human growth hormone" from recombinant organisms boasts an extra amino acid, an amino-terminal methionine; hence, it is actually an *analogue* of the native hormone. Second, despite some experience with drugs derived from micro-organisms such as vaccines, antibiotics, and L-asparaginase, there is meager, if any, experience with such substances employed as parenteral drugs in humans with continual administration over many months or years. Third, approval of the product application is also approval of the sponsor's processing techniques, and we will need to ensure that the quality assurance within the manufacturing process is adequate to detect the occurrence of mutations in the coding sequence of the cloned gene during fermentation. Such mutations could, of course, give rise to a subpopulation of molecules with an anomalous primary structure. One way we have dealt with this situation in the substances undergoing clinical trials is to require batch-by-batch testing with sophisticated techniques to ensure that the active drug substance is homogeneous and has the correct identity.

Because of these concerns, the Agency has recently decided that, where consistent with individual Center or Bureau policy, new applications will likely be required for products obtained via recombinant DNA technology. This will be true even if identity is demonstrated with the natural substance, or with a previously-approved substance produced in a conventional way. However, each instance will be handled on a case by case basis because of the wide spectrum of the products which we expect to be submitted for approval.

For the first such products, the requirement for new applications has been clear: human insulin has not previously been marketed; human growth hormone (hGH) is actually *methionyl*-hGH, an analogue of the approved substance; human leukocyte interferon preparations may contain a population of molecules which are *methionyl*-leukocyte interferon, an analogue of the natural substance.

The amount of data required to support such applications will vary widely, depending on a number of factors, including: whether the product is identical to a previously approved product; the projected length of time of administration to patients; the amount of previous clinical experience with the product produced via conventional technology; and the amount of previous clinical experience with recombinant DNA-derived substances [this latter variable refers to the *accumulated* experience with such substances, not simply the applicant's experience, as stated by Dr. Korwek].

The points above, which have been made earlier in several publications[1-3] belie such simplistic assertions as, "[T]he rDNA produced human growth hormone [sic] is now undergoing full clinical tests to obtain FDA approval . . . because the rDNA product differs by one amino acid from

Continued on page 706

IN THE NOVEMBER ISSUE

- **RESEARCH PAPERS:** Novel cloning systems for gram negative bacteria. Lactate-acrylate interconversion in *Clostridium propionicum*. Induction of aflatoxin synthesis in *Aspergillus flavus* by cyclohexamide.
- **REVIEW ARTICLE:** Industrial applications of some new microbial polysaccharides.
- **FEATURE:** Microbes for pollution control.
- **TECHNOLOGY REPORTS:** The emerging role of the U.S. Environmental Protection Agency in regulation of rDNA technology. Biotechnology and Canadian agriculture. Computer conferencing as a tool for international communication in biotechnology.
- **NEWS:** International meeting reports on biotechnology in food and drink. Enzymes for human therapy. The BIO/TECHNOLOGY stock index.

BIO/TECHNOLOGY

COMMENTARY (Continued from page 676)
tactics such as higher cell density and lower product inhibition is even greater than would be the case for an extremely efficient conversion.

Between 1940 and 1978, the percentage of the world's organic chemicals derived from coal fell from 95 to 3. The figures for petroleum boomed accordingly. Such are the possible dimensions of the *next* revolution, with all its unsolved problems, now being spearheaded by a resource-favored land in Latin America.

FINAL WORD (Continued from page 718)
whatsoever. The Commission considers developments in genetic engineering and provides advice, in the form of written reports, to the President, the Congress, and appropriate federal agencies. These reports will present the Commission's conclusions, as well as any recommendations for regulatory or legislative action. Because it is a purely advisory body, the impact of the Commission's conclusions and recommendations will depend upon the force and quality of the reasoning behind them.

It is a primary responsibility of government not only to promote science but to attempt to foresee the future of technology and any problems it might present. As the new genetic technology develops, it will be essential for our nation to be informed about both the positive and negative implications of it. Particularly for those of us in Congress, it will be important that we base our reactions to and decisions about the technology on objective, reasoned consideration of the issues and not on misunderstandings or exaggerations of the technology's potential for either good or evil. Biotechnology will unquestionably have a tremendous effect on our society in the years ahead. The challenge we face is how to ensure that those benefits are realized and any misuses are avoided. Accomplishment of these objectives will require public education and thoughtful debate about the complex issues that will confront us. The Commission that I have proposed is a first step in that process.

CORRESPONDENCE (Continued from page 675)
the conventionally-derived version . . ." and "[T]he effect of the new policy seems to be to require full clinical testing of all rDNA drugs . . . [T]he obvious effect of this policy is to increase the cost of marketing rDNA products." The term "full clinical tests" is a buzz-word intended to be pejorative; in fact, full clinical tests may consist of brief trials on five patients or lengthy trials on five thousand, depending on the particular circumstances. The record time in which human insulin moved through the regulatory review process demonstrates that regulation by FDA of recombinant DNA-derived products need not be debilitating nor Draconian.

We reiterate that the FDA will regulate each product according to the relevant statutes and regulations, and, as important, will attempt to do so intelligently and responsibly.

Henry I. Miller, M.D.
National Center for Drugs
and Biologics (HFN-823)
FDA
8800 Rockville Pike
Bethesda, MD 20205

1. Miller, H. I. 1981. The Impact of New Technology on Regulation by the FDA: Recombinant DNA Technology. Food, Drug, Cosmetic Law Journal **348**:351.
2. Miller, H. I. 1982. The Impact of New Technology on Government Regulation: Recombinant DNA Technology and the U.S. Food and Drug Administration. *In:* From Genetic Experimentation to Biotechnology—the Critical Transition, W. J. Whelan and S. Black (eds.) John Wiley and Sons, New York.
3. Miller, H. I. 1982. Recombinant DNA as a Paradigm of a New Technology: Its Impact on Regulation by the Food and Drug Administration. Journal of Parenteral Science and Technology **36**:248.