Linking the Laboratory and the Farm: Integrating Epidemiology and Biotechnology

Wayne Martin, Department of Population Medicine
Ontario Veterinary College, Guelph, Ontario, CANADA

Both holistic disciplines such as epidemiology, and reductionistic disciplines, typified herein under the category "biotechnology", have as a major goal the improvement of the health status of food animals, as well as the people and environment associated with the production of foods of animal origin. However the perspectives on how this goal should be attained differ widely between these groups. This paper describes, from the vantage of an epidemiologist, the merits of integrating epidemiologic and biotechnologic methods in the areas of ongoing disease control and food animal health research.

In opening this paper I would give strong support for the proposition that epidemiologists should work closely with biologists who are using and developing biotechnological (microbiologic, immunologic, cell biology, molecular biology, biochemistry, toxicologic) methodologies. However, as a cautionary note, although this linkage of holistic and reductionistic disciplines will be quite valuable, none of us, particularly epidemiologists, should become too fascinated with activities directed towards specific agents of disease (ie. individual toxic and/or living agents) to the detriment of our potentially more valuable role in identifying and controlling the causes (indirect risk factors) of health and disease. The latter, and its ramifications, has been discussed in some detail under the heading of Biology as Ideology by Lewinton, 1992.

One reason for my support of the integration of epidemiology and biotechnology is to maintain focus on biologic problems. Other epidemiologists (see Pettiti, Riemann and Gordis for examples) have noted that too often we have become fascinated with the hardware, mathematical and computer-usage techniques in our discipline and have (apparently) forgotten about the biologic problem we initially became involved in. Indeed, in a much more hard-hitting editorial Skrabanek, 1992, suggests that the discipline of epidemiology may be fundamentally flawed because its followers either don't know or don't care about the actual biology of the problem. As a result, according to Skrabanek, any statistical association becomes explainable, and quickly thereafter is equated with causation.

Lest the reader think that the misdirection of interest and activities is a problem peculiar to epidemiologists, Davies and others have levelled a major criticism at our profession; namely, that veterinary medicine itself often has been and continues to be technology driven rather than problem driven. As veterinary biologists we have developed new techniques with which to study specific agents or specific disease processes. Just as epidemiologists may become fascinated with hardware and software, reductionistic biologists may end up emphasizing parts of an agent, or their effects, not the "problem". In some instances there may be good evidence to suggest that the manifestational

problem, purportedly caused by that agent, is of such a small magnitude that it is of little concern to the industry or society. As Cal Schwabe has noted this might be an example of "agents" in search of "disease". There is a need to integrate reductionistic and holistic disciplines in the pursuit of solving "real" problems. For too long, interdisciplinary research has meant two "biologists" (or epidemiologists) from different departments/colleges, but with interests and perspectives at the same level of organization, agreeing to work on the same problem. Much hybrid vigour would be added by integrating scientists from diverse backgrounds in these efforts.

From my perspective an excellent way to remedy these problems (if true) is to have epidemiologists and "biotechnologists" collaborate in solving health problems; both at the practical everyday level and in research activities. One way of tying the field and the laboratory together is through joint participation of epidemiologists and biotechnologists in well designed prospective health monitoring systems (which by definition include measures of both disease and productivity). Biotechnologists could play a valuable role in such a system by the ongoing monitoring and identification and classification of selected microorganisms or toxins --- the activities of those involved would be driven by the problems identified, not by the tools they possess.

A list of the activities/skills that biotechnologists might usefully contribute is endless; Henderson in 1988, provided a brief overview of the possibilities, and previous congresses have included numerous presentations on this issue. In broad terms they include activities directed towards prevention, therapy, and diagnostics of disease, as well as towards the growth/survival of farm animals.

The biotechnological advances can focus directly on the animal species of interest; for example on increasing the resistance of the animal species of interest based on results of DNA mapping, or the use BOLA antigens, to select or create more resistant animals. There will be better detection of agents through improved diagnostic tests (eg. DNA probes and PCR-aided tests to obtain faster, sensitive and specific diagnoses, fingerprinting techniques to specifically identify and follow the movements of members of a specific types of organisms, use of "lux" gene technology to identify potential pathogens, and the use of hydrophobic grid membrane technology to quantitate drug resistance, and the direct identification of antigens in tissue and body excretions. Efforts can also be directed against specific agents by enhancing the immune response with improved prophylactics (subunit vaccines, for example against foot-and-mouth disease using E coli as a carrier for the specific immunogenic antigens) as well as by using vaccines that stimulate immunity without interfering with standard diagnostic tests) In the same area, immunostimulants will be developed to combat cancerous cells. Undoubtedly, more effective and safe therapeutics (zero withdrawal broad spectrum drugs) will be developed. In terms of animal production, the advances can focus on growth promotants (somatotropins, somatomedians, B-adrenergic

agonists) which can increase production as well as productivity.

Biotechnological advances also hold the potential to detect disease (tissue damage) at an early stage and help forestall or prevent serious occult disease. For example, many biomarkers are more sensitive indicators of tissue damage than more traditional approaches. Thus they might be especially useful for detecting chemical exposures, or diseases with extended latent/incubation periods.

How can these activities be integrated with epidemiologic methods? I would suggest that in addition to providing a field oriented, problem-based context for biotechnologic work, epidemiologists can; assist directly with the evaluation of biotechnologic advances (the effects of embryo splitting/sexing, the evaluation of vaccine efficacy, and the study of pathogenesis); provide indirect assessment of the likely benefits and potential drawbacks to the use of these products before they are actually developed (eg. using simulation modelling to assess the likely impact of the "advance"); and third, epidemiologists can help design health promotion programs (programs which focus on management, behaviour, nutrition, etc -----the causes---, as well as activities directed towards specific agents) which incorporate those advances deemed to be useful. A major area for success from integrating biotechnology and epidemiology has been in our ability to track and identify specific microorganisms, and to better identify their possible role in causing diseases. This includes studies of verocytotoxigenic E coli, studies of Salmonella using plasmid profiles, studies of Haemophilus, using restriction endonuclease analysis, as well as distinguishing between vaccine and field strains of organisms as examples.

Despite the newness of biotechnologic advances per se, epidemiologists will need to continue to use traditional observational studies and field trials, and, for test evaluation, the epidemiologic principles of sensitivity and specificity. Observational studies, both retrospective and prospective, will continue to provide much useful information relating to biotechnologic advances. Although these studies produce measures of association, not causation, they remain valuable nonetheless. With regard to vaccine or biologic efficacy, it is likely that well-designed field trials will remain as a major tool for assessment of efficacy. Over the past decade, our profession has become much more accepting of the role of, and need for, well-designed clinical trials. Hopefully we are also maturing to the realization that despite the advantages of field trials, any one clinical trial is unlikely to provide the ultimate answer regarding efficacy. Further, despite their apparently superficial simplicity, the design of high quality field experiments is a science in and of itself.

With respect to the evaluation of biotechnologic tests (the development of which is an area of great activity and some potential) the principles of accuracy, precision, sensitivity and specificity continue to need to be applied. Again traditional concerns over within-individual and between-individual variation in biomarkers, the need for "blind techniques" and laboratory-to-laboratory standardization, remain. The National Research

Council has recently commented on biologic, statistical and laboratory-specific issues surrounding the usage of DNA typing. Misclassification, of either the health and/or the exposure status remains a problem, confounding of effect can be common and the statistical analyses of results must be as rigorous as in other studies -- in fact given repeated sampling of the same individual this aspect may deserve increased attention. A related aspect is the number of samples (cells?) per individual versus the number of individuals to be included in the study.

Others at this conference will discuss biotechnologic advances in genetics in some detail. Suffice it to say that to date, most of the biotechnologic advances have focused on problems with a Mendelian inheritance pattern. Studies of multilocus disorders are still in their infancy. Khouri et al discuss both indirect and direct approaches to the study of genetic factors. They stress the measurement of effect in terms of the relative increase in the rate of disease (relative risk) according to genetic status, as well as the proportion of the outcome attributable to the genetic factor (etiologic fraction).

The direct approach to the study of genetic factors initially focuses on identifying those with and without the genetic factor and then identifying the risk of disease in each of these groups. However, since more genetic sites are being identified as potential disease susceptibility factors, the chance of false positive associations will increase; hence, replication of findings is crucial. Also, if the frequency of the allele (or haplotype) differs within subgroups of the population, if these subgroups are pooled, confounding can/will occur. Therefore, analyses should be stratified on breed as one way to help control this confounding.

Indirect methods of study search for the susceptibility genes using indirect markers (eg. linked genes). At present, the commonest approach is to compare diseased and nondiseased individuals with respect to these markers. However, since these studies are, in essence, fishing trips to identify all possible marker differences, replication of findings is crucial.

For most studies, traditional epidemiologic methods will suffice. However, for genetic-epidemiologic studies, more very refined study designs will be needed. Two factors, misclassification and etiologic heterogeneity (ie. factors in addition to the susceptibility gene cause the disease) make it difficult to identify susceptibility genes in populations. The true relative risk is much greater than the observed risk, and the risk is confounded by allele frequency. In addition, it is wise to concentrate on related individuals and when possible to identify related individuals that are all exposed to environmental factors which may interact (synergistically) with the susceptibility gene. Thus, as the frequency of alleles increase, and as the frequency of "other causes" increases, very large studies will be required to retain a reasonable level of power. (This is true whether studying the risk of disease by apparent genotype, or the distribution of haplotypes in diseased individuals.)

Summary

There is little doubt that the biotechnologic revolution will change the nature of practice and research in medicine. However, the greatest economic and biologic payback is likely to arise if and when epidemiologists and biotechnologists actively collaborate in well designed problem-driven, not technology driven, field oriented projects. The new advances must be integrated with epidemiological concepts into ongoing health care delivery programs for maximum benefit.

REFERENCES

Blackall PJ Applying biotechnological advances to epidemiological work in Epidemiological skills in animal health. Proc 143, Oct 1-5, 1990, University of Sydney, ISSN 0814 6829, pp 177-194.

Davies G. Art, science and mathematics: New approaches to animal health problems in the agricultural industry. Vet. Rec. 117:263-267, 1985.

Gordis, L. Challenges to epidemiology in the next decade. Am. J. Epidemiol. 128:1-9, 1988.

Henderson WM. The potential of biotechnology for improving animal health and productivity. J Am Vet Med Assoc 193:1120-1123, 1988.

Kulka BS and Margolin BH. Methodological issues in epidemiologic studies using biologic markers. Am J Epidemiol 135:200-209, 1992.

Khouri MJ, Beaty TH and Flanders WD. Epidemiologic approaches to the use of DNA markers in the search for disease susceptibility genes. Epidemiol. Rev 12: 41-55, 1990.

Lewinton RC. Biology as Ideology: The doctrine of DNA. Anansi Press Ltd, Concord, Ontario, Canada. 1991.

National Research Council. Properly done, DNA typing can be "strong" evidence. Newsreport. Apr-May, 1992, pp 2-4.

Petitti, D.B., 1988. The implications of alternative views about causal inference for the work of the practicing epidemiologist. in: K.J. Rothman (Ed) Causal Inference, Epidemiological Resources, Inc. pp 149-151.

Riemann, H.P., 1988. The future of veterinary epidemiology and economics. Acta. Vet. Scand. Supp. 84, pp 85-88.

Skrabanek P The poverty of epidemiology in Perspectives in Biology and Medicine, University of Chicago, Winter, 1992, pp 182-185.