## EDITORIAL

## EPIDEMIOLOGIC AND ECONOMIC STRATEGY IN INFECTIOUS DISEASE RESEARCH

Communicable diseases represent the greatest challenge in health research for a variety of reasons. They are pervasive. Many are acutely dramatic in their presentation and rapid in their progression. Population movement acts as an amplifier by transmission from one place to another. Infectious agents mutate and are thus subject to selection pressure to accumulate new variants. Periodically previously unrecognized agents come to the fore in human or animal populations.

Molecular biology has revolutionized the classification and identification of causative viruses, bacteria, fungi, parasites, and of their derived mutants, giving rise to great accuracy of definitive diagnosis. It has given rise to the capacity for molecular epidemiology at local, regional and global levels. Potentially this facility lends itself to strategic planning of disease management and control with great precision on a global scale. Reality sees considerable limitations in the attainment of even a fraction of the benefit that can theoretically flow from these advances in technology.

When there is sufficient global concern, where an epidemic affects a sufficient number of people, where the disease is relatively long term and where mortality is high, then we may see the meticulous, widespread application of molecular epidemiology to useful purpose. Currently we see this in HIV/AIDS as it has reached crisis levels. However the enthusiasm for genomics has seen this information base swell to encompass an ever-growing list of infectious agents, so that the potential to implement the same sort of molecular strategy to the epidemiologic analysis of many diseases beckons.

Various characteristics of epidemics follow from these databases: identification of the causative agent group, specification of a particular mutant or multiple mutants, delineation of drug sensitive versus drug resistant strains, differential genetic susceptibility of hosts to particular organisms, and so forth. In turn, these molecular databases permit the building of geographic maps at local, regional or global levels that allow interpretation of the dynamics of disease spread and can help to interpret the process of disease transmission across small or large populations. Thus, for example, the mutational history of HIV in man has been traced, although not yet to the complete satisfaction concerning the ultimate origin of the virus group.

Molecular epidemiology has the potential, not yet fully realized, to guide the construction of vaccines targeted to specific molecules or epitopes of infectious agents, even in the face of substantial mutation rates. Possibly the theory of vaccine candidates is still somewhat rudimentary to cope adequately with the complexity of all high active site amino acid sequence variation but progress is encouraging. Certainly the molecular tools are critical ingredients in the equation.

Against this very positive molecular compendium must be seen the challenge represented by broader, more general epidemiologic theory in unraveling the environmental and human components of disease spread, exacerbation and recession, since this is the context in which attempts at control must operate. For example, regardless of molecular considerations of the viruses involved in etiology, explanation of the seasonal patterns of dengue hemorrhagic fever rests with description of mosquito vector habitat. This is dependent on water container distribution in the community. At the same time, it is well established that four viral serotypes can be involved, each comprised of many structural molecular subtypes. The serotypes determine the changing population herd immunity from time to time, while the accessibility of the vectors to water breeding sites determines the likelihood of mosquito transmission from host to host. Thus both environmental and host factors come into play against the molecular determinants concerned and these factors require consideration in relation to the feasibility of satisfactory vaccine development and application.

Similar considerations apply to many viruses, bacteria and parasites that give rise to endemic and/or epidemic transmission. The difficulties in the way of effective HIV vaccine development focus on both the molecular variability of the virus and on the modus operandi of transmission. The epidemiology of the disease is further complicated by the long lag period between infection and recognition of clinical symptoms. Malaria, on the other hand has a relatively shorter incubation period, although this is long enough to enable substantial travel of the infected individual. thereby compounding disease control efforts at community level. At the same time malaria shares the characteristic of molecular antigenic variation and mutation to drug resistance, which impinge on vaccine design. Mycobacterium tuberculosis mutates to drug resistance and its spread is enhanced by host immunosuppression such as that which is characteristic of HIV infection.

As we survey the horizons of the range of infectious diseases that affect humans, the dual importance of focus on both molecular and environmental epidemiology is self-evident. However, the laboratory base of the molecular biologist is geared to structural genetics and is often not in close touch with the mathematical and social streams of classical epidemiology. Both are frequently distant from the realities of economic planning. The academic molecular vaccinologist or pharmaceutical chemist too often passes on molecules to industrial companies to handle both work up and potential sales, thus to determine market price and market audience. Arguably the academic investigator should attempt to develop models or other means of looking ahead to the relevance, priority and cost-effectiveness long before molecular passage is contemplated. This argument goes way back to the basic purpose of the planned product: who are the most needy populations?, what price can they afford to pay?, how might this affect choice of targeted product and method of synthesis?

Thus molecular biology research in the health arena requires co-habitation with epidemiologic and economic planning from the drawing board phase onward, bearing in mind the global distribution of need, rather than orientation to the rich world, with aid-driven crumbs left over for the poor. There is a fundamental problem with this argument. Even in this era of commerce-driven research the basic scientist seeks kudos above profit, since recognition and promotion are still largely driven by discovery. Science tends to be rewarded by recognition of fundamental advance, regardless of practical application. Scientists tend to regard commercial objectives as suspect or at least as secondary, even where they now look more to industrial recompense. Further, few laboratory scientists have detailed understanding of epidemiology, even fewer of economic modeling. Thus it transpires that many of the drugs or vaccines emerging from academic laboratories end up as products geared for the top end of the market. We have seen this starkly in the recent controversy over the cost of producing anti-HIV drugs versus the market price, highlighted in the tentative offers by some pharmaceutical corporations to make them available in poor countries at the production cost level. That level is still way above affordability.

Quite apart from the humanitarian principle that medications should be affordable by all mankind, consideration of the epidemiological consequences of distribution limited to the wealthy (individuals or nations) highlights the absurdity of this separation of scientific endeavor from economic and epidemiologic reality. This places the onus back on to the planning phase of basic science: why go to all the intellectual effort and expenditure of grant funding for products that target trivial diseases, or lead to inordinately expensive production costs that can never be met by the majority of the world's people? Consideration of the classical epidemiologic patterns tell the story: infectious diseases are not generally confined to small groups in isolation but are subject to rapid spread on a wide base, so that effective modulation requires application of drugs or vaccines on the same scale. The required scale of planning is heavily dependent on the underlying economics.

It is evident that there is a need for combinations of skills that can uphold the freedom of operation of the bench molecular science to explore technical frontiers and at the same time ensure that economic pathways are addressed from the very first pre-experiment planning phase of the genesis of therapeutic or preventive products. This approach should safeguard the excitement of intellectual creativity and provide the satisfaction that the outcome will be applicable to the greatest number of people possible. Such a strategy places more decision power in the hands of the basic scientist in negotiations with companies potentially responsible for production and marketing, and thus also can help to protect the interests of the poor.

This strategy must ultimately encompass the currently inequitable issues involved in patent protection trade-related aspects of intellectual-property rights (TRIPS) ensconced in the World Trade Organization's regulations (Anonymous, 2001). This is a huge mountain to climb but it may be more scalable if the thinking is based on the academic laboratory rather than being handed over unadorned to the multinational corporations.

This approach to bringing together molecular biology, epidemiology and economics in the planning of research on vaccines and drugs for infectious disease control is part of the changing strategy required to re-structure public health globally (Garrett, 2000). Poverty is arguably the single largest contributor to inequity in health and consideration thereof thus needs to be an essential ingredient in the re-structuring process, not as an afterthought added later under political pressure. Infectious disease is a global concern, not something for which the solutions can be compartmentalized for the rich versus the poor. The economics of the game have a critical place at the molecular table from square one.

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## REFERENCES

- Anonymous, Special Report: Patents and the Poor. *The Economist.* June 23<sup>rd</sup>, 2001.
- Garrett L. Betrayal of Trust: The Collapse of Global Public Health. New York, Hyperion 2000.