EDITORIAL

FROM MOLECULAR MEDICINE TO PUBLIC HEALTH

Three papers in this issue on thalassemia in Myanmar serve to raise a challenge which pertains to substantial population groups in Southeast Asia. In countries such as Cambodia, southern China, Indonesia, Laos, Malaysia, Thailand, Vietnam a range of mutants affecting the structure and production of the globin chains of hemoglobin are associated with serious disease, particularly in children.

A great deal is known about the molecular basis of many of these mutants, as the result of global efforts targetting the globin genes, because they represented definable entities in molecular pathology even before the advent of DNA sequence analysis. The latter era of technology has given precise delineation of a wide range of mutations which represent sequence deletions, base replacements, etc which give rise to altered amino acid sequences with or without alteration of the kinetics of globin chain synthesis.

The catalog of mutant gene sequences has permitted the design of a range of oligonucleotide primers for gene segment amplification by polymerase chain reaction (PCR). This in turn has provided opportunity for pre-natal diagnosis of specific mutant offspring of known carrier parents, and for the gene typing of carriers themselves, so that risk can be ascertained (reviewed by Fucharoen *et al,* 1991). This precision game of molecular diagnostics is one to be played in major hospitals, with specialized laboratory facilities and skilled personnel. It is not a cheap game, in terms of capital or maintenance costs.

There is no doubt that PCR is a major step forward in this field, since it allows diagnosis on very small DNA samples compared with DNA mapping. For populations in which there is one or a few major mutants it is possible to use specific DNA probes with reasonable economic efficiency (Rosatelli *et al,* 1987) but in Southeast Asia there are many mutants in each population which makes for a much more complex analysis. PCR offers the greatest sensitivity but again the complexity is governed by the variety of mutants in a given population.

Detection of carriers represents another order of magnitude, since in this region their numbers are large and the majority do not show serious clinical symptoms. Older biochemical methods can detect the majority, albeit at a lower level of sophistication, since specific mutations require molecular definition in sequence terms. The propensity for genesis of clinically affected offspring depends on the precise nature of the traits carried by the parents, so that while simpler biochemical tests give broad indications they are less than optimal in information content.

Even the older biochemical assays, such as electrophoresis, chromatography and globin chain synthesis analysis require well equipped and funded laboratory facilities. The Burmese study addresses the issue of what is the minimal assay that can be used in a practical way to attempt to tackle the wider public health problem of screening large numbers. They suggest that the one tube osmotic fragility test may fill the bill to some extent. While it certainly is not optimal, it is a step in the direction of tackling this critical dilemma of moving from molecular medicine to the market place in poorer countries. The issue requires continuing reconsideration to arrive at the best compromise between large scale population screening and precise data delineation.

Even so, how to use the data base is not yet quite clear. High risk families are generally identified by affected offspring, allowing potential prevention of repetition but this begs the question of prediction of initial risk. The public health challenge is still wide open. Part of the question is a matter of attitudes in the community, something which the Burmese study also addresses. Here the issue is the acceptance of the fruits of diagnostic screening technology, whether it be DNA sequence analysis, osmotic fragility or a hierarchical referral system linking simple screening procedures with definitive endpoints. Coupling of technical consi-

derations with attitudinal analysis is a good start in the right direction.

Economics underscores the whole challenge. The Burmese study looks at the cost-effectiveness, cost-benefit and efficiency of present treatment schedules. Again, this is a start. It will be necessary to build on this beginning and extend the economic analysis to diagnostic screening at various levels of technical sophistication, so to move towards rational evaluation of alternative public health strategies for handling thalassemia at the population level. This is an exciting opportunity to link technology, clinical analysis, epidemiologic planning and economic moderation for a large disease problem.

Unlike strategy options in the control of some infectious diseases in tropical countries, modulation of large scale genetic disease public health problems requires that planning be geared to the very long term. The challenge may be less dramatic than containment of viral epidemics or the onward march of drug resistant malaria, but it confronts large population groups in this region, so it is here that the challenge should be met.

The studies in Myanmar address realistic issues in this regard and provide a starting point for the type of analyses that are needed in each country to provide a database on which to build evolving strategies. In the field of thalassemia we face the opportunities and the co-existent constraints presented by the triumphs of molecular medicine. This is a field in which the precision of molecular analysis is superb, the tools for application of this precision to preventive medicine are available but the translation to public health is underinvestigated at the level of technology choice in relation to economic feasibility. The challenge is not only economic, it also embraces selection of options for population screening and counselling which need to be developed into realizable strategies for public health planning.

Given the widespread distribution of a fascinating range of thalassemia mutants throughout this region an exciting opportunity exists for collaborative effort to bring the collective wisdom to bear on this major regional problem, in order to develop public health strategies that can be executed by countries of modest economic means.

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References

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