Introduction

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"A geneticist's nightmare". This quote from the late James V. Neel, referred to diabetes mellitus, was meant to illustrate the extreme causal complexity of a multifactorial disorder due to a variable mix of genetic predisposition and environmental influences. The same concept can be extended to several other conditions, ranging from presenile dementia to the major psychoses, from asthma to ischemic heart disease. Neel's quote dates back to the 1970s, a time when there was very little a geneticist could do to convert the nightmare into a dream and the dream into reality. Essentially no genes were on hand at that time and the only tool that was factually available consisted of linkage studies between a disease and other phenotypic markers, the most popular being the leukocyte antigens of the HLA system, coded for by genes of the major histocompatibility complex (MHC).

Thirty years later, the picture has changed dramatically. The Human Genome Project (HGP) is a *fait accompli*, we know about 5000 genes, or one sixth to one tenth of the total, countless expressed sequence tags and an impressive number, estimated between 1.5 and 2.5 million, of single nucleotide polymorphisms (SNPs). This new knowledge is supported by new technology, the so-called microchip or microarray technology that allows the rapid screening of thousands of genes or polymorphisms all at the same time. The accompanying papers by Pollak et al. and Miertus and Amoroso are fine examples of how these miniaturized technologies (nanotechnologies) can be applied to the genetic analysis of cardiovascular disorders, specifically cardiac malformations and thrombotic diseases.

Pollak et al. provide a synthetic overview of SNP-based variability of the human genome and of how this variability can be explored by means of microarray technology, which has the capability of processing simultaneously a large number of polymorphisms from an even larger number of individuals. The authors suggest that such an approach would be applicable to a vast population study aimed at investigating predisposition to thrombotic disorders. They list five relevant genes within the arterial system and six relevant genes within the venous system, each one containing several polymorphisms. By multiplying the number of polymorphisms for a large number of individuals enrolled in the study, one can expect to generate an amount of data so big as to be necessarily informative. This is a reasonable prediction that still awaits experimental validation.

Miertus and Amoroso provide additional details on the functioning of the system and stress the importance of collecting all available data into easily accessible databases. They point to congenital heart defects as an approachable model system to test the power of the method. Congenital heart defects can occur as component manifestations of single-gene or chromosomal syndromes. More commonly, they are isolated defects with a multifactorial cause. In both cases, it is quite likely that their presence and level of severity also depend on several modifier genes, yet to be discovered. Thus, a genome-wide search using microarray technology is probably necessary in order to sort out all the possible genes involved.

The readers will appreciate the power and elegance of this new approach, as described in the articles of this minisymposium. However, they should not jump to conclusions. The road ahead is still long and difficult, and the understanding of complex diseases at a molecular level, not to mention their cure, continues to be a formidable task.

There are technical hurdles to overcome, like the collection of suitable material, e.g. RNA from diseased tissues, to estimate the expression of specific genes in those tissues, or the design of highly sophisticated computer programs capable of processing thousands and thousands of data in an ordered fashion. It would be useless to collect such a large amount of data if one did not have the tools to sort them out and make any sense out of them. But there are also clinical hurdles, that in fact may prove to be the most difficult to overcome. The Editor of this Journal contends that speaking today of ischemic heart disease without further specifications is as naïve as it would be speaking of anemia, without further specifications. His point is well taken and easy to prove.

If we were to try and sort out the genetic causes of anemia treating it as a single disorder, we could only expect a huge headache and eventual defeat. Two factors were instrumental in disentangling the causal complexities of anemia. One was the astuteness of clinicians who were able to construct a sufficiently accurate nosology of anemia, by dividing patients in clinically homogeneous groups that could be analyzed separately. The other factor was the availability of families in which the trait "anemia" segregated as a Mendelian character. Cardiologists today face the same challenge that hematologists faced 50 years ago, that of sorting out homogeneous groups of patients from among those presenting with ischemic heart disease and possibly recognizing at risk families where a single risk gene or polygene is likely to segregate.

The task is not at all an easy one. Possibly there is not enough clinical variability in the presentation of ischemic heart disease, to permit the formation of discrete groups of patients. Furthermore, familial clustering is a rare exception, with the added complications that a) affected individuals are at risk of dying suddenly under circumstances that would make it hard to collect valuable samples (e.g. DNA) for future tests; b) family members carrying risk genes are unrecognizable until they have an infarction, which may never happen in their lifetime. On the other hand, clinicians today can rely upon a stronger help from the geneticists. Their nosologic efforts can be supported and complemented by data obtained through the application of the new genetic nanotechnologies and significant progress can be expected as a result of a concerted action.

It is all too easy to predict that the way to understanding the genetic bases of ischemic heart disease is going to be long, difficult and expensive. Will it be worth the effort? Most likely yes, in view of a number of desirable consequences that can be reasonably expected, among which are the following:

• knowledge of risk genes for ischemic heart disease will make it possible to design genetic tests to assess individual predisposition;

• knowledge of individual genetic predisposition is likely to lead to more effective prevention of ischemic heart disease through the avoidance of exacerbating environments and adoption of a palliative lifestyle;

• understanding the molecular genetic bases of ischemic heart disease will lead to the design not only of more effective drugs but also of customized drugs, fitting the needs of individual patients or groups of patients;

• ultimately, and in a more distant future, there might even be the possibility of gene therapy, at least for those cases in whom genetic predisposition to ischemic heart disease was shown to be caused by the effect of a major gene.

Microchip and allied technologies will be instrumental in reaching these goals, although we should not delude ourselves by thinking that the technique itself will accomplish anything at all without a strategy where ample space should be allowed to basic research and to the freedom of testing innovative ideas.