given phenotype. Nonetheless, this information will greatly improve our understanding of individual responses during disease and drug treatment, and enable new concepts in personalized drug therapy. The translation of DNA information to gene expression is the second source of molecular analysis and permits a correlation between the genomic information and tissue-specific gene expression at any given time point and in response to a wide range of conditions, including pathological processes and physical traumata. Thus, the states of a cell, cell population, and the whole organism are determined by the genetic makeup as well as by the epigenetic and environmental influences, leading to tissue-specific gene expression.

Until very recently, it has been literally impossible to simultaneously assess the gene expression of hundreds of genes, because of the complex and cumbersome methodologies in molecular biology. Thus, gene expression profiling in diseased tissue could not be performed. Much of our knowledge in molecular medicine is therefore based on single gene expression analysis. Though the one-gene–one-disease paradigm has helped explain a set of diseases, it soon became obvious that the great majority of pathogenic processes have a multigenic basis and that the outbreak of a disease also depends on epigenetic influences. Therefore, large-scale or even genome-wide gene expression profiles are needed for a better understanding of the molecular events leading to metabolic deregulation and toxicity Fig. 1, Fig. 3 and Fig. 4.

Since Southern introduced the blotting technique (1), the hybridization process has been used in a wide range of subsequently developed methods for the recognition and quantification of DNAs. In the beginning, a limited number of electrophoretically separated heterogeneous samples were immobilized on a membrane and tested with a single labeled cDNA probe—the classic northern blot—focusing on the expression of a distinct gene in different samples. Then, dot blots were used to enhance the number of addressable samples which were no longer separated. But only the reversal of this procedure—the arraying of multiple homogenous cDNAs and testing with a single heterogeneous labeled sample—made it possible to study the gene expression profile of thousands of genes in a given biological sample. With this procedure, a complex network of genes acting in concert can now be characterized, which permits a fundamental understanding of biological processes and fosters new concepts in molecular medicine and molecular toxicology Fig. 2.

The basic technology behind DNA arrays and its application to drug discovery and drug development processes are described below.

3. METHOLOGICAL CONSIDERATIONS

3.1. Sample Generation, Labeling and Hybridization

Essentially, the handling of microarrays starts with the isolation of RNA from any given tissue or cells. The sample is then labeled either