

FEATURE REVIEW

Personalized Medicine Some Thoughts

Werner Kalow*

Medical practice has never been pure science; every physician automatically considers the patient's personality or circumstances when deciding to help him or her. Thus, to some extent, medical practice can be said to have always represented personal medicine. The current interest in, and emphasis on, personal medicine is based on the fact that regular drug treatment has sometimes very irregular responses, which cannot be explained by the patient's look and appearance; e.g. a generally safe drug may kill a patient, or a good drug may be ineffective in some patients. Such problems have led to the discovery that irregular drug responses in different people may be caused by differences between their genes, thereby creating the science of 'Pharmacogenetics'.

Pharmacogenetics has taught us that variations in gene structure may affect their dependent proteins, which may be pharmacologically important (e.g. drug-metabolizing enzymes, or the receptors whose occupation determines the drug's effect). By assessing a patient's crucial gene, one can often determine which drug, or which drug dose, is appropriate for that patient. Utilization of such search may rightly be called 'personalized medicine'. This is now sometimes done in a clinic, but so far, not often in medical practice. However, it turned out that such pharmacogenetic procedures could explain only a small proportion of abnormal drug responses. Thus, many investigators have looked for further explanations and for additional tests, as demonstrated by the 450 publications mentioned above.

The most important explanation for the occurrence of unexpected drug responses not-explainable by environmental factors or by classical pharmacogenetics lies in the fact that gene expression is variable. Variable gene expression means that the number of a given kind of gene may change, thereby affecting the gene's function. Gene expression can be altered by many internal and environmental factors. A classical example

is increased rate of metabolism of a drug after it has been given; the drug has increased the activity of the gene that controls its metabolizing enzyme. Another example: an alcoholic is a person whose original consumption of alcohol has affected a gene in the brain that affects the wish to drink more of it.

Since innumerable internal and environmental factors may affect gene expression, a person's set of genes is never constant but always more or less changing. This makes it impossible to exactly predict the activities of a person's genes. However, not all genes change their expression over a given time. There must be a likelihood that a set of genes studied a week apart is more similar than when studied a month or a year apart. We do not know whether a set of genes remains more constant over time within person A than within person B. Thus, at the present time, dealing with gene expression is usually a matter of probability, and perhaps never or rarely of certainty. Consequently, when dealing with gene expression and with future drug responses, one is dealing with matters of probability. By the same token, we can never precisely predict the effect of a drug on a person, although it often remains identical over reasonable periods; prediction of the effect of a drug is a matter of probability, and thus is 'personalized medicine'.

In short, there have been some steps made towards personalized medicine, but it will never be a reliable entity; it is an entity of probability.

Dr. Werner Kalow is Professor Emeritus in the Department of Pharmacology at the University of Toronto. His book entitled *Pharmacogenetics* (1962) represents the first book of its kind to provide a systematic study of this emerging subspecialty. He subsequently published over 300 scientific papers and several other books, making Dr. Kalow a world-renowned expert and pioneer in the field of pharmacogenetics. In 2001, Dr. Kalow received the Killam Prize for his outstanding work and lifetime contribution to science. He has also recently served as main editor of *Pharmacogenomics* (2001). Dr. Kalow was Chair of the Department of Pharmacology at the University of Toronto from 1966 to 1977. Retiring in 1982, Dr. Kalow remains an active member of the department.