Preface

Although it may be scientifically unrespectable to make suppositions when there is no hard evidence to back them up, the history of unraveling the enigmas of the human existence has been full of unproven assumptions which were put to the test of time with the evidence emerging in due course, sometimes from the most improbable scientific corners. Archaeology is a good example of this.

The history of the science of heredity (also called classical genetics and by extension that of molecular genetics), or speaking more broadly the science of molecular biology, has very much in common with the science of archaeology.

When our ancestors started domesticating and breeding animals and cultivating plants thousands of years ago, they might have been using analytical cognition very similar to that of modern human beings. Current archaeological research dates the putative beginnings of this sort of human activity back to the prehistoric age of some 10,000 years ago.

Though humans may well have observed the outward appearances of plants and animals for centuries and used these observations in cultivating their crops and breeding their livestock, it was not until the mid-19th century that these observations were given a scientific foundation. The father of classical genetics happened to be an Augustinian monk living in the Moravian heartland of the then Austro-Hungarian Empire – the present-day Czech Republic – who taught natural science to high school students in the town of Brno and performed experiments with plants in his monastery garden. After more than

10,000 experiments into the inherited traits of plants he promulgated his theses at just about the same time as Charles Darwin (1809–1882) first publicized his views on evolution. The greatest insight of Gregor Mendel (1823–1884) was to focus on discrete clear-cut characteristics rather than measuring continuously variable properties. These clear-cut characteristics came to be known as Mendelian characters. Somewhat surprisingly, Mendelian discoveries fell into oblivion only to be ‘rediscovered’ at the beginning of the 20th century.

The 19th century saw many more discoveries in different scientific disciplines, which paved the way for the deciphering of the genetic code a century later.

From the first demonstration in 1828 by Friedrich Wöhler (1800–1882) – who converted an inorganic chemical compound (ammonium cyanate) in a test tube to urea (a molecule produced by animals), thereby showing that an inherent unity between the inorganic and living world existed and that there was nothing magical about the chemistry of living matter – another half a century passed before the actual extraction of DNA in 1869 (though it was not called DNA at the time). This was done by Friedrich Miescher (1844–1895) from the pus of infected wounds. However, it took yet another 70 years before Oswald Avery in 1944 recognized the true significance of the DNA extract as the substance of genetic information. After a quick succession of discoveries in radiation physics (X-ray crystallography) and chemistry (chemical analysis of DNA by Erwin Chargaff) in the first half of the 20th century, the now famous double helix structure of DNA was finally proposed by Francis Crick

and James Watson in 1953, partly based on the interpretation of data from the X-ray diffraction work of Maurice Wilkins, Raymond Gosling and Rosalind Franklin, all from the Cavendish Laboratory, Cambridge.

In spite of all of these truly historic achievements, deciphering of the complete sequence of the human genome in 2003 would not have been possible without a qualitative change in the methods used in the quest. The metaphor of a 'quantum' leap seems appropriate to describe the advent of new and powerful technologies in molecular biology in the past three decades which, coupled with advances in information technology, were driving the biotechnology revolution. Not so long ago one would never have imagined an array technology using chips (termed 'microarrays') with a surface as small as half of a square centimeter, where tens of thousands of single-stranded DNA species of known sequence could be placed in an ordered pattern and so provide a gene expression profile characteristic for a particular disease.

However, the function of most of a human's approximately 36,000 genes still remains to be defined. Yet more complex is the way in which the expression of these genes is controlled and coordinated. The trouble is, the deeper we get, the more complex things become. The frenzy of novel projects is dizzying – after genomics came transcriptomics, then proteomics, metabolomics, still further on epigenomics, structural genomics ... How many more 'omics' are there still to come? One may wonder.

At times we may feel real envy of the unsurpassed brilliance of the most famous example of code cracking in human history – when ancient Egyptian hieroglyphs were deciphered. The famous Rosetta Stone, which was first the symbol of the bitter rivalry between two great 18th century European powers, France and Britain, in their quest for dominance, went on to become the symbol for peaceful scientific competition between two linguistic giants, the British Thomas Young and the French Jean-Francois Champollion. Building on Young's correct assumptions and armed with the decisive advantage of his knowledge of the Coptic language (the only modern language remotely based on ancient Egyptian) Champollion finally worked the whole thing out in 1822. From then on

the world could put words to the great culture of the ancient civilization of Egypt.

Are we about to become witnesses to a similar breakthrough in molecular medicine on the bicentenary of the Champollion's achievement? We may well be.

The identification of mutations has already become part of clinical patient management in recent years, especially for patients with malignant disease. The targeted treatment of malignant tumors with monoclonal antibodies and low-molecular-weight tyrosine kinase inhibitors alone or in combination with conventional chemotherapeutics has resulted in a significantly improved overall or progression-free survival of patients with different tumors. Treatment with monoclonal antibodies has become part of standard treatment of patients with metastasized colorectal cancer. Due to advances in pharmacogenomics, it will become increasingly feasible to identify subgroups of patients with a defined disease for whom the efficacy of a drug can be predicted and fatal side effects averted. The aim of personalized medicine, elusive for so long – even resembling a *fata morgana* at times – is becoming reality.

But despite all the progress, there remains an important caveat to be remembered: by not taking a detailed personal medical and family history of a patient and not paying meticulous attention to the clinical routine, all of these promises may turn out to be merely a false prophecy. The term *molecular* has never been meant to be a substitute for sound *clinical* judgment – indispensable for centuries in medicine and archaeology alike. It may even be the only faculty to outlast all the others.

It is a great honor and pleasure to introduce the work of the contributing authors to the interested reader. This volume contains the lectures presented at the GOMB (Gastroenterology-Oncology-Molecular Biology) Meeting and EAGE Course in May 2011 in Budapest.

On behalf of the organizing committee we would like to thank all the authors for their participation in the meeting and for their contribution to this volume. We wish it good fortune.

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