With great interest I have reread Francis Crick’s paper written in 1970. This was prior to the second revolution in molecular biology and genetics, which had finally led to the emergence of genetic engineering, total sequencing of various genomes, and unraveling of a multiplicity of mechanisms of cellular processes whose distortion results in diverse pathologies. Here follow only some of the events that occurred after Crick’s paper had been published.

1970. The most exciting event of this year was the discovery of reverse transcriptase, the enzyme synthesizing DNA using complementary RNA as a template, made independently by two future Nobel laureates: Howard Temin (he died a few years ago) and David Baltimore. The enzyme was found in viral particles (virions) of RNA-containing viruses. This discovery explained how these viruses can function in the animal genome and cause malignant tumors. Another outstanding result of this year was the description of a restriction endonuclease, which later was also marked with a Nobel prize. In the same year it was shown that the Raus sarcoma virus contains a transforming gene src. That was the beginning of real genetics of cancer.

1972. Prior to this year, all studies, however important, had been run along the lines of classic genetic, biochemical, and molecular-biological research and made use of the traditional methods of investigation. That was the case even with such epochal discoveries as the unraveling of the DNA spatial structure and the isolation of reverse transcriptase. In the same year it was shown that the Raus sarcoma virus contains a transforming gene src. That was the beginning of real genetics of cancer.

1973. Important improvements of methodology of parasexual genetics occur, and restriction endonucleases in combination with DNA ligases start to be employed in constructing recombinant DNA.


1975. Tonegawa and coworkers revealed the different location of genes encoding the variable and constant parts of immunoglobulins in DNA of the embryonal and myeloma cells, which led to conclusion on rearrangements of the immunoglobulin genes in formation of cells of the immune system. A first cDNA is cloned. Genetic engineering begins to contribute to the basic science: cDNA of the rabbit β-globin gene is cloned. In the same year, recombinant DNA methods are first used in prenatal diagnostics of a hereditary disease, α-thalassemia, and the paper, by Sanger and Coulson appears where a real method of express DNA sequencing, the precursor of the current method, is proposed.

1976. A homologue of the viral src gene is found in the cellular genome.

1977. Published are express methods of DNA sequencing (W. Gilbert and A. Maxam; F. Sanger et al.) to give a real tool for analysis of the gene structure as a basis for understanding their functioning. Another extraordinary event of this year has a fundamental rather that methodical character: the mosaic exon-intron structure of the adenoviral genes is discovered (R. Roberts, P. Sharp). Subsequently, it turns out to be the general property of eukaryotic genes.

1978. A eukaryotic gene was introduced into the bacterial cell, where the encoded protein, proinsulin, was synthesized. In the ensuing years, recombinat insulins and numerous other genetic engineering products became part of clinical practice. It was shown that genetic engineering enables mutations to be introduced into a predetermined site of the gene. This technique becomes a key component of reverse genetics. Protooncogene src was shown to encode a protein kinase.

1979. An epochal event in the theory of cancer: it is shown that chemically transformed cells harbor the activated oncogene ras. It is established that RAS protein binds guanine nucleotides. Later, it turned out that this protein participates in numerous processes of signal transduction from the cell surface to the nucleus.

1981. First transgenic mouse appears. The thymidine kinase gene of the Herpes simplex virus is introduced by microinjection into the pronucleus of a fertil
ized monocellular embryo, and this gene is shown to function in the mouse somatic cells. Ever since, transgenesis has become a key tool in basic research and an important approach to solving practical problems of agriculture and medicine. Insertion of a virus is shown to activate the \textit{myc} protooncogene.

1982. It is found that a point mutation activates gene \textit{ras} in human bladder tumors, and a chromosomal translocation activates protooncogene \textit{myc}. These are two more epochal events in development of insights into the nature of tumor transformation of the cell.

1983. The emerging resource of bioinformatics is used for the first time: by comparing the structures of growth factor PDGF with the known protein structures, homology was found to the oncoprotein encoded by oncogene \textit{sis}, which revealed that this oncogene encodes a growth factor. It is shown that different oncogenes cooperate on the tumor transformation of cells.

1984. Still another important stage: it is shown that oncogene \textit{erbB} encodes the truncated receptor of a growth factor.

1985. Still another revolutionalizing technique—polymerase chain reaction (PCR)—is described. This has become indispensable in studies on molecular genetics.

1986. Gene \textit{RB}, first tumor suppressor, is cloned. The advent of the massive cloning of tumorigenic genes.

1987. Yeast artificial chromosomes (YAC) turn up to play an important role in cloning large genomic fragments. Oncogenes are shown to relate to the developmental control.

Of course, a multitude of other events occurred that are impossible to cover in this brief comment—studied were oncogenes; genes of the immune system, receptors, and various regulatory proteins; mechanisms of replication, transcription, translation, repair, etc. I selected the events that were basal for the development of the modern genetics, that is, revolutionized the methodical basis and enabled studies that could not even be imagined by the outstanding geneticists of the earlier generations.

Such was the history up to 1988. And what thereafter? A new epoch of molecular genetics began—the epoch of integral studies of genomes.

In 1988, the National Research Council of the United States explicitly formulated the national project \textit{Human Genome}. This was a large-scale project, which planned, first by 2005 and then by 2003, to completely determine the sequence of the total of three billion nucleotides encoding the entire genetic information that makes a human the human resembling his or her forbears. The launching of this project meant that the development of molecular genetics had reached a qualitatively new level allowing fundamentally new problems to be solved. This project showed that science had changed its face ideologically and technologically and come up to transitions:

from studies of separate genes to studies of entire genomes, from genetics of crosses to parasexual genetics (studies based on the introduction of genetic material into the cell or whole organism in an asexual fashion and ensuring conditions for its subsequent inheriting);

from classic direct genetics, moving to the gene identification from the traits encoded by these genes, to reverse genetics, which first identifies a fragment of the genome and then finds out which trait is determined by this fragment;

from the work with isolated genes or their expression products to the study of their effects on the level of the whole organism, where the role of these products is interpreted in the context of the complex of their interconnections.

The improvements of advanced methods and technologies enabled:

directed effect on the genetic apparatus of the cell or whole organism, resulting in a hereditary alteration;

structural study of single molecules through their specific amplification;

directed systematic change of properties of the interacting molecules promoting their maximal interaction, in other words, leading to evolution \textit{in vitro};

use, along with traditional protein enzymes, of artificial enzymes of polynucleotide nature;

total automation and robotization of experiments and maximal transfer of the burden of analysis of the experimental results onto computer;

creation of integral databases, allowing the express comparison of the structure of new products with the known ones and, on the basis of homologies, preliminary conclusions on their possible functional roles.

The epoch of integral studies of genomes has begun to form a special section of molecular genetics—genomics. Nowadays, genomics deals with analysis of the structures and functions of genomes as an integral functional massif of genes, their regulatory elements, and other sequences required for the genome functioning. It also includes analysis of parasitic selfish elements evolved and fixed in the genome, whose role in the existence and evolution of genomes still remains to understand. Genomics, having begun from studies of the human genome, considerably widened the range of its interests and encompassed many model organisms such as bacteria, yeast, nematode, fruit fly, and mouse, whose genomes are being compared for unraveling the structural bases of their functional organization. A united space of genomic information has emerged, which rapidly enhances its potential. The comparative analysis of genomes of various organisms is the starting point for functional genomics, which is supposed to determine the functional significance of newly found