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# The Evolution of the Biomedical Paradigm in Oncology: Implications for Cancer Therapy

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## 2.1 Introduction

According to the view of Harold Varmus, it is time for “changes in the culture of oncology” (Varmus 2006, 1165). The former NIH director and Nobel prize recipient for physiology and medicine for the discovery of oncogenes believes that “during most of the past 50 years, pharmaceutical chemistry continued to serve cancer patients much more effectively than did cancer biology.” He argues that, as a consequence of the strategy adopted, “laboratory-based investigations into the nature of cancer cells and clinical efforts to control cancer often seemed to inhabit separate worlds” (Varmus, 2006, 1162). So he points out that “the new era in cancer research” needs “stronger working relationships between bench scientists and their clinical colleagues, between oncologists in academia and those in community hospitals, and between oncologists and other physicians.” Moreover “new training programs” should “provide graduate students in the basic sciences with an opportunity to understand the dilemmas posed by cancer as a human disease” (Varmus 2006, 1165).

Varmus’ analysis joins the increasing attacks on cancer research policy inspired by the U.S. President Richard Nixon’s National Cancer Act of December 1971, declaring the “war on cancer”. In a recent issue of *Fortune* Clifton Leaflet, who personally experienced the condition of cancer patient, published a long article, “Why we are losing the war on cancer [and how to win it],” reporting statistical data and interviews with leading scientists. Among them, a very negative judgment about the methodological foundation of cancer research came from Robert Weinberg, who told the columnist that experimental oncologists cultivate the “illusion” of doing “something meaningful” just because they can manage straightforward experiments to accumulate a huge amount of reproducible data (Leaflet, 2004, 85).

The history of the “war on cancer” has been anatomized and declared a “failure” by an outstanding clinician and oncologist, Guy B. Faguet, who was in the forefront and now is retired. He demonstrates, in his very well received and reviewed book that “the three crucial measures of progress in the War on cancer, cure rates, prolongation of survival, and quality of life, remain stagnant despite enactment of the National

Cancer Act of 1971” (Faguet 2005, 52). He explains the failures as caused by “an unbalanced focus on treatment of operable cancer to the detriment of prevention and early detection, and adherence to the infectious disease model that has driven drug development towards the cancer cell-kill paradigm” (Faguet 2005).

In this paper we show that the existing main streams of cancer research and treatment reflect the schizophrenic epistemological status of scientific medicine. The field is prompted by two different, dissonant and incomplete philosophies – the bioexperimental and the clinical-epidemiological approaches – for the understanding and management of disease. We demonstrate that the “cancer cell-kill paradigm” that, according to Faguet, misrepresented the cancer problem embodies the epistemological essentialism of the bioexperimental tradition of medicine, which is no more maintainable. At the same time, the clinical-epidemiological approach is in some way threatening the scientific foundation of medical reasoning, as it spread among students the idea that statistical correlations can replace causal explanation (Thagard 1999). Then we argue that a new theoretical perspective is emerging in cancer biology, the evolutionary or Darwinian model of cancer progression, which indicates a more dynamic and realistic view of cancer, and highlights new paths of discovery for cancer therapy. Our original contribution, as historian and philosopher, is a reconstruction of the main conceptual steps that led to the understanding of cancerogenesis as a Darwinian process.

## 2.2 The Epistemological Evolution of Scientific Medicine

Let us introduce a very schematic view of the epistemological evolution of medicine. The main historical traditions of Western medicine are the clinical, the physiopathological or bioexperimental and the clinical-epidemiological (Corbellini, 2007). The clinical paradigm emerged with Hippocratic medicine and lasted until the beginning of the 20<sup>th</sup> Century. According to early and modern clinicians the knowledge of disease can be attained by observing and interpreting a patient’s natural or artificially induced symptoms and signs. From the late 17<sup>th</sup> Century a medical discipline called nosology emerged to classify symptoms and signs and to create specific patterns of disease entities, useful for making diagnoses (Porter 1997).

During the second half of the 19<sup>th</sup> Century, the founders of scientific medicine were able to exploit the new physiological and microbiological knowledge by means of the systematic application of the experimental method. They created the physiopathological, or also so-called bioexperimental paradigm, based on the idea that the knowledge of disease must aim at developing explanatory theories and experimental models to identify the proximate causes producing functional alterations or disease. Physiopathologists assumed that heterogeneity and individual variations of data, that ancient clinicians explained assuming an individual constitution or diathesis for each patient, depended on some intrinsic limitations of the experimental models, and were a sort of noise. According to the followers of Claude Bernard (1865), disease is a deviation from functional homeostasis that can

be caused by several factors – internal and external to the organism. They defined health as absence of disease, establishing as a goal of medicine the treatment or prevention of diseases by rationally designed drugs and interventions, based on the understanding of the etiopathogenesis.

The bio-experimental paradigm has been at the origins of the greatest results of medicine, in terms of basic knowledge and of prevention and control of infectious, hereditary (monogenic) and chronic or degenerative diseases. However, the emerging complexity of the molecular, biochemical and cellular dynamics involved in etiopathology and the increasing frequency of chronic-degenerative diseases, with their multiple and statistically defined determinants, created a less favorable environment for the biomedical model, that suffered a decline of effectiveness (Corbellini 2007).

A new paradigm emerged, thanks to the improvement of statistical analysis of experimental design. The new perspective came out with the invention of the clinical trials, in the second half of the 1940s, that stimulate the rise of clinical epidemiology, and later the advent of the evidence-based medicine movement (Corbellini 2007). The implementation and success of clinical trials in assessing the effectiveness of drugs brought to the view that there is no need to know the functional mechanisms that cause the clinical phenomena: clinicians can just apply statistical methods to inductively establish causal correlations. Clinical trials based on frequentist statistics, has become the only reliable experimental design to test hypotheses and evaluate the effectiveness and efficiency of medical decisions.

This is not the seat to analyze the epistemological controversies between the bioexperimental and the clinical-epidemiological paradigms that live together in today's biomedical world, which means in medical faculties and literature (Corbellini 2007). They are both practically very useful. However, they are both based on an incomplete view of biomedical phenomena and seem not able to see their intrinsic epistemological limits, and they lack an historical or evolutionary perspective of diseases and health. In fact, they ignore the implications of the biological fact that, due to phylogenetic and ontogenetic causes, the phenotypic traits of an organism, including health and disease, result from individual histories (Corbellini 2007).

In the light of the previous picture we can now better understand how cancer therapy evolved.

### **2.3 From Magic Bullets to Targeted Therapies: Many Treatments but the Same Philosophy**

The origins of modern cancer therapy can be seen as one of the main instantiations of the biomedical paradigm. In fact, Paul Ehrlich's view (1906-9) of specific chemotherapy as a *therapia sterilisans magna* and of drugs as artificially designed antibodies or "magic bullets" has inspired the search for effective anticancer drugs since the beginnings. Cancer chemotherapy started in 1946 when Goodmann and

Gilman observed a dramatic reduction in tumor mass of a patient with non-Hodgkin lymphoma after the injection of a chemical derivate of nitrogen mustard (Goodmann and Gillman, 1946). Cancer chemotherapy has gone through several different phases, schematically listed in Fig. 2-1, characterized by important technical novelties, but not by any cultural change. According to Varmus (2006, 1162) “targeted therapy, in a sense, are not more targeted than the conventional chemotherapies,” while the classical assumptions of chemotherapy and drug discovery has been challenged by several new findings and concepts.

**Fig. 2-1** An essential timeline of cancer therapy

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|-------------|--|
| 1946–1950   | Serendipitous discovery of anticancer activity of nitrogen mustard derivatives and of synthetic antifolates (MTX): cancer chemotherapy can be pursued.   |
| 1950–1960   | Methodological foundation of cancer chemotherapy, development of in vitro and in vivo model, and discovery of new anticancer drugs mainly by empirically testing natural and artificial products<br>6-mercaptopurine (6-MP)<br>vincristine<br>cyclophosphamide   |
| 1960–1970   | The first successes (Hodgkin’s lymphoma and ALL) resulted from clinical experiences, supported by new ideas on chemotherapy kinetics<br>MOMP<br>Taxanes<br>Cisplatin<br>adriamycin<br>“Remission induction therapy” or “total therapy” of ALL  |
| 1970 – 1980 | Adjuvant chemotherapy shows efficacy, endocrine treatment comes of age, but cancer cells hold genetic mechanism to acquire resistance to anticancer drugs<br>ABVD<br>Tamoxifen<br>Resistance of cancer cells to MTX  |
| 1980–1990   | Setting molecular biotechnology to fighting cancer: genes for target proteins are mapped and cloned, monoclonal antibodies and recombinant vaccines are developed (immunology enters the game)<br>Interferon therapy<br>Recombinant hepatitis B vaccines   |
| 1990 –      | The rise of targeted therapies (azacytidine, trastuzumab, imitinib mesylate, bevacizumab and gefitinib) and the bright hopes of tailored/personalized therapies<br>Colony stimulating factors<br>Interleukin-2<br>Azacytidine<br>Rituximab<br>Ontak® - recombinant Dna-derived cytotoxic protein<br>Trastuzumab - Herceptin®<br>Imitinib mesylate - Gleevec®<br>Bevacizumab (Avastin®)<br>Gefitinib (Iressa®)<br>Oncotype DX®<br>Gardasil® |

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The invention/discovery of magic bullets – with exclusive and absolute specificity – has constantly oriented the search for anticancer drugs from the beginning to targeted therapies. However, apart from monoclonal antibodies, the ideal of designing drugs *de novo* or synthesizing tailor-made chemicals that fulfill all requirements of efficacy, tolerance and absorption, distribution, metabolism and excretion characteristics has remained elusive (Drews, 2006). Moreover, the concept of absolute specificity doesn't make much sense from a biological viewpoint – physiological redundancies (degeneracy) and pleiotropy in cell signaling pathways have represented successful evolutionary strategies to develop the most adaptive traits (Searls 2003).

According to most oncologists the eradication of cancer cells, considered like a parasite extraneous to normal physiology of the body, as the final aim of cancer therapy inspired medical treatment of cancer for most of the past century (Faguet 2005). Such a view is no more tenable in the light of cancer molecular genetics, and a more pertinent philosophy should emerge (Reddy and Kaelin, 2002; Faguet, 2005). Paradoxically this view, that embodies the bioexperimental paradigm of medical research, can be maintained thanks to the prevailing influence of a clinical-epidemiological paradigm. In fact, the pivotal role played by the clinical trial to discriminate the levels of therapeutic efficacy of a new treatment scotomize the problem concerning the biological plausibility of drug pharmacological activity.

The new philosophy has to also take into account the expectations that inspire the drug designer, that the serendipitous discovery of new treatments was a temporary consequence of the lack of better knowledge and techniques, and that it is becoming possible to design an effective drug starting from the knowledge of the chemical property of the target, can be misleading (Horrobin 2003). Some experts think that because of the biological nature of the therapeutic targets, drug discovery will always rely on intuition, serendipity and luck, alongside rigorous science and rational thinking (Drews 2006).

## 2.4 The Darwinian paradigm in oncology

In our opinion, oncology is going through a theoretical revolution that challenges the dominant paradigms. Oncology – as with other branches of biomedicine like, in the past, immunology, medical microbiology and some aspects of neurobiology – is acquiring a more coherent biological way of thinking about the causal dynamics of adaptive physiological and pathological phenomena. This change may still support new therapeutic strategies, but certainly allows better integrating of basic and applied cancer research. It is foreseeable that in the near future the new paradigm will influence cancer therapy as well.

Let us introduce this idea by quoting from two leading oncologists. According to Robert Weinberg and Douglas Hanahan, the six hallmarks of cancer (self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potentials, sustained angiogenesis, tissue invasion and

metastatic) are nothing but “acquired capabilities,” and “tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells” (Hanahan and Weinberg, 2000).

The heuristic role played by the evolutionary view of cancer progression has been testified by Bert Vogelstein’s fundamental contributions to the understanding of the genetic basis of tumor progression in colorectal cancer, that adopted the hypothesis that tumorigenesis is an evolutionary process (Fearon and Vogelstein 1990). Since then theoretical oncology deals with the concept of “cancer cell evolution.” Martin Nowak, who works out mathematical approaches to evolutionary dynamics, has transformed Vogelstein’s evolutionary view in a series of equations (Michor, Iwasa and Nowak 2004). Even epidemiologists are debating the usefulness of Darwinism as a theoretical framework to make sense of the role of environmental factors in carcinogenesis (Vines 2006).

So, the most advanced oncological research has reached the agreement that cancers are conventional Darwinian processes of repeated cycles of mutations and selections, and that Darwinian models of cancer progression can explain most tumor phenomenology. Environment contributes to cancer development with mutagenic chemicals and conditions that increase cell replications, thus creating the opportunity for mutations to occur and for the somatic selection of the advantageous ones to take place. Mutations that allow cancer cells to produce their own signals to stimulate mitosis, to suppress contact inhibition, to evade apoptosis, to attract the vascular system and to spread or metastasize can have a selective advantage. Somatic mutation and selection are very important for cancer treatment since that, as tumors, can evolve resistance to chemotherapy (Michor, Nowak, and Iwasa 2006).

Weinberg dedicated several pages to the Darwinian view of cancer in his recent and excellent textbook (Weinberg 2006). At the end of his analysis, Weinberg concluded that “the outlines of the model are undoubtedly true, but its details are very difficult to validate” because of the complexities involved in the multi-step tumorigenesis (Weinberg 2006, 423-4).

Well, but in which sense the Darwinian paradigm in oncology represents the natural outfall of the empirical and theoretical investigation on cancer biology? Which are the origins of the Darwinian view of cancer development? How basic research and clinical observations contributed to demonstrate its heuristic value? Which implications for the strategies of cancer therapies have predicted the founders of this new paradigm?

## 2.5 The Origins of Oncological Darwinism

Let us think to Darwin’s *Origins of Species* (1859). Which is the idea that he put forward and emphasized first? Darwin spent the first two chapters illustrating the reality of individual biological variations, under domestication and in natural

species. The discovery of a spontaneously occurring heterogeneity in somatic physiological systems with some kind of ability to change adaptively has also been the first step that led to the idea that some selective mechanisms could operate also to produce adaptive physiological responses to unexpected stimuli. The histories of immunology and neurobiology are the best examples of the successful heuristic role played by Darwinian thinking to explain the physiological dynamics that results in adaptive changes to memorize and learn through experience (Corbellini 2007).

In the history of cancer pathology, too, it was the recognition of the diversity of many properties of cancer cells that led to the view that the only unique property of cancer cells is their expression of multiple variables, and that cancer cells heterogeneity, is the biological prerequisite for tumor progression.

In the early and mid-19<sup>th</sup> Century, it was well recognized that at the macroscopic level, solid cancers had a heterogeneous appearance. Moreover, during the second half of the 19th Century, Virchow and most pathologists reached the view that any cancer cell is like a monad, invested with the potential to develop in any number of ways (Moss 2003). The first successful experiments to induce carcinogenesis by chemical stimulations of normal tissues, reported in 1915, were aimed at confirming Virchow's hypothesis that chronic irritation was the cause of cancer (Moss 2003).

The cytological hypothesis of somatic mutations proposed by Theodor Boveri in 1914, based on previous observations of aberrant mitotic figures in carcinoma samples made by David von Hansemann in 1890, introduced a new interpretation of the process of experimentally induced carcinogenesis (Boveri 1914). Instead of being the product of the contingent interaction between cells and other cells and between cells and extracellular factors, cancer could rather be determined from within a cell.

In the 1940s several studies led to the idea that cancerogenesis was a "multistage process," involving two or more somatic mutations. Peyton Rous spoke of a "two stage process" involving the action of "provocative" and "actuating" carcinogens (Rous 1943, 581). Isaac Berenblum and Philippe Shubik, in a series of articles, suggested the existence of at least two different aspects of carcinogenesis: initiation and promotion. An event starts the carcinogenic process; another one accelerates it (1947, 1949). Finally, Peter Armitage and Richard Doll, looking for an explanation about the fact that cancer is mainly a disease of elderly, postulated the existence of six to seven stages for carcinogenesis (Armitage, Doll 1954).

The concept of somatic mutation was temporary obscured by the rise of cancer virology. Stimulated by the ideas of Amédée Borrel, who in 1907 discussed the viral origin cancer, and by the discovery of Peyton Rous, who in 1911 discovered the first cancer virus (Rous Sarcoma Virus, RSV) experimentally inducing tumors in chickens, tumor virologists for decades explored the hypothesis that viruses were the source of the stimuli which transform normal cells into tumor cells. According to Rous (1959, 578), "the somatic mutation hypothesis, after more than half a century, remains an analogy." The same conclusion was announced by other leading oncologists (Burdette 1955; Foulds 1969) until the "oncogene hypothesis" was put forward by Huebner and Todaro in 1969 (Huebner and Todaro 1969). The view that cancer transformation was determined by the expression of viral genes

(oncogenes) entered the genome of animals allowed to rescue the concept of somatic mutation. In 1971 Howard Temin reintroduced somatic mutation as a failure of normal cellular differentiation mediated by “protoviruses,” that become cancer causing viruses (Temin 1971). As we know, in 1976, out of the blue came the discovery that oncogenes are functional components of the animal genomes and the genetic explanation of cancer became definitively established (Stehelin, Varmus and Bishop 1976). Since then, molecular oncology became the leading area of cancer research, bringing to light the proximate causes that concur to produce the complex phenomenology of cancer progression.

The year 1971 was a crucial date for the advancement of cancer genetics. The geneticist Alfred Knudson wrote his landmark paper suggesting the “two-hit” model (completed by David Comings in the 1973 and by Knudson himself in 1985) in order to explain the puzzle of familial and sporadic forms of the retinoblastoma tumor (Knudson 1971; 1985; Cummings 1973). According to Knudson, “the origin of cancer by a process that involves more than one discreet stage is supported by experimental, clinical, and epidemiological disease” (p. 820). He pointed out that, usually, the mutation’s number varies “from 3 – 7” (p. 820), and that he wanted to support the hypothesis that “at least one cancer (the retinoblastoma observed in children) is caused by two mutational events” (p. 820). Knudson’s analysis of the age-specific incidence of retinoblastoma led him to propose that two “hits” or mutagenic events were necessary for retinoblastoma development. Retinoblastoma occurs sporadically in most cases but, in some families, it displays an autosomal dominant inheritance. In an individual with the inherited form of the disease, Knudson proposed that the first hit is present in the germ line, and thus in all cells of the body. However, the presence of a mutation at the susceptibility locus was argued to be insufficient for tumor formation. Given the high likelihood of a somatic mutation occurring in at least one retinal cell during development, the dominant inheritance pattern of retinoblastoma in some families could be explained. In the non-hereditary form of retinoblastoma, both mutations were proposed to arise somatically within the same cell. Although each of the two hits could theoretically have been in different genes, subsequent studies led to the conclusion that both hits were at the same locus, ultimately inactivating both alleles of the retinoblastoma (RB1) susceptibility gene.

Knudson’s hypothesis served not only for illustrating the mechanism through which inherited and somatic genetic changes might collaborate in cancerogenesis, but also to link the concept of recessive genetic determinants for human cancer to somatic cell genetic findings showing the recessive nature of tumorigenesis. In 1969 Harry Harris and his colleagues (Harris, Miller, Klein, Worst and Tachibana 1969), trying to understand whether tumorigenicity was a dominant or recessive trait, proposed that at least one of the chromosomes commonly lost in cases of cancer was a “suppressor” for tumorigenicity. Knudson, in 1983, points out for the first time that cancer might result, not only by activation of oncogenes, but also “through loss of appropriate anti-oncogenes.” In this way he was able to justify the retinoblastoma’s epidemiological data. Two years later Knudson wrote that “the hereditary cancers have revealed a new class of gene that is important in the pathogenesis of cancer.



The genes of this class, clearly different from oncogenes, have been called antioncogenes, because they produce cancer in a recessive mode, one normal allele being adequate to protect against a particular cancer” (Knudson 1985; 1438).

Physical evidence for the existence of antioncogenes came from the study of several types of tumors, including Wilms tumor, hepatoblastoma, uveal melanoma and bladder cell carcinoma (Koufos, Hansen, Copeland, Jenkins, Lampkin and Cavenee 1986). The RB1 gene was found in 1986 by Friend and his colleagues, which maps to human chromosome 13q14 (Friend, Bernards, Rogelj, et al. 1986).

In the meanwhile that cancer genetics came of age, something was changing in cancer pathology. In 1960, as a consequence of the discovery of cancer stem cells (Wicha, Suling, and Dontu 2006), a few pathologists and clinicians started to disagree with the reductive view of cancer as a disease of the cells. In early 1960s, the British radiologist and radiotherapist Sir David Smithers wrote a long paper in *Lancet* entitled *An attack on cytologism*. He appealed to Karl Popper’s falsificationism and criticized the idea that cancer is a defect of cells, suggesting that “cancer is no more a disease of cells than traffic jam is a disease of cars. Cancer is a disease of organization, not a disease of cells” (Smithers 1962; 495).

According to Smithers there is no such a thing as a cancer cell, but only cells behaving in a manner arbitrarily defined as being cancerous. Of course, he criticized somatic mutation hypothesis, as it focused on the idea of oncogenic mutation as an all-or-nothing event, while carcinogenesis is a gradual process. Smithers advanced the idea that an abnormal cell, particularly a stem cell, may produce a clone of cells reacting abnormally with the environment and so promoting the disorganization of the tissues (Smithers 1962).

During the first half of the 20th Century morphological, histological, cytological and physiological investigations on cancer showed that heterogeneity of cancer cells was a common and prominent feature of most human tumors. The number of parameters that could be used to describe cancer cell heterogeneity increased: morphology and function, biochemical markers (then differential expression of gene products), differential growth in vitro, tumorigenicity in vivo (including the number of injected cells required to generate tumors in animals), latency period, growth rate, antigenicity and ability to be affected by a host immune system, ability to invade and metastasize, sensitivity to chemotherapeutic agents and radiosensitivity (Weiss 2000).

The British pathologist Leslie Foulds was the first to interpret the heterogeneity of cancer cell populations in a dynamic perspective, and was instrumental in explaining tumor progression. In 1949, Foulds defined tumor progression as the “development of a tumor by way of permanent irreversible change in one or more characters of its cells” (Foulds 1949; 373). Actually, he suggested that progression brings the acquisition of new phenotypic traits. In 1958, Foulds described cancer as a “dynamic process advancing through stages that are qualitatively different,” progressing from precancerous stages to increasingly invasive and metastatic stages (Foulds 1958; 6). Finally, in a monograph of 1969, Foulds wrote that progression “is not the mere extension of a lesion in space and time but a revolutionary change in a portion of the old lesions establishing a new tumor having properties not formerly manifested” (Foulds 1969; 73).

Even though the increasing evidence of a monoclonal origin of cancer cells seemed to be in contradiction with the apparent heterogeneity, the time was right to reorganize the empirical data using an evolutionary model. Peter Nowell, who had discovered the Philadelphia chromosome, suggested the first explicit Darwinian model of tumor progression in 1976.

In his most quoted paper Nowell (1976) resumed the biological characteristics of tumor progression: a) acquisition by the neoplastic cells of the capacity to invade and to metastasize (malignancy); b) a tendency for neoplastic populations to increase their proliferative capacity (escape from normal growth control mechanisms); c) acquisition of morphologic and metabolic alteration generally interpreted as loss of differentiation; d) maximization of the efficiency in proliferation and invasive growth, and e) elaboration of products which aid the progression (tumor angiogenesis factor).

Finally Nowell suggested that these biological properties represent both the effect of acquired genetic instability in the neoplastic cells, and the sequential selection of variant subpopulations produced as a result of the genetic instability.

## **2.6 From Speculations to Reality and Beyond: Some Implications of a Darwinian View of Cancer Progression**

The confirmation of Nowell's model came from the discovery that the acquisition of the resistance of cancer cells to chemotherapy was similar to other well-known evolutionary phenomena described in medical therapy. In 1978, Robert Schimke discovered a genetic mechanism that provides the condition for a selection of cancer cells resistant to methotrexate (MTX). He showed that resistance of mouse cells to MTX results from a selection of cells of higher contents of a specific enzyme, due to an increase in the number of copies of the gene coding for this enzyme, that to gene amplification. "The properties of the resistance of cultured cells to MTX, including (i) a stepwise selection of progressively resistant cells; (ii) an increase in a specific protein present at low levels in sensitive cells, which, when present in larger amounts, results in resistance; and (iii) stable and unstable resistance in the absence of selection pressure, have analogies both in antibiotic and insecticide resistance" (Schimke 1978; 1055).

During the 1980s the concepts of genetic instability and clonal evolution were confirmed, and the possibility that epigenetic mechanisms could exert differential selection pressures on heterogeneous cancer cell populations widely discussed. In 1986 Barry Wolman suggested that genetic and chromosomal instability was the potential source of genetic heterogeneity in all tumors, and that variation in local environmental selective pressures and differential survival may contribute to cellular heterogeneity within an expanding tumor. In turn, heterogeneity itself might permit selection and increase in number of aberrant cells which are responsible for tumor progression and metastasis. Genic and chromosomal instability are potential sources for genetic diversity within all tumors. However, variations in local selective forces and differential survival within an expanding solid lesion may contribute to maintenance of a mixed cell population within the primary tumor (Wolman 1986).

Finally, Fearon and Vogelstein (1990) proposed the now historic model of successive genetic changes leading to genetic instability producing colorectal cancer (CRC), in which a number of genes are involved, including APC, k-Ras, DCC, and p53. With few modifications, the Vogelstein model still stands and knowledge on the function and interactions of the key molecules involved, which has been obtained since it was proposed more than 15 years ago, even strengthens the genetic cascade of events in the sequence originally proposed (Weinberg 2006).

According to Vogelstein's group "the genetic instability hypothesis can be viewed as a pessimistic one," as cancer cell heterogeneity should allow the tumors to face therapeutic challenges. However, they think that instability itself could be the Achilles's heel, providing a target for drugs killing unstable cells better than normal as it has been demonstrated in the case of yeast cells (Cahill, Kinzler, Vogelstein and Lengauer 1999).

Nowell was the first to put forward that the evolutionary model of cancer progression might induce a pessimistic view about the prospective of a definitive therapeutic success. If the cells within a tumor are so heterogeneous and ready to form variants in the face of therapeutic challenges, do we have a realistic chance of ever curing advanced cancer? According to Nowell (1976) "the fact that most human malignancies are aneuploid and individual in the cytogenetic alterations is somewhat discouraging with respect to the therapeutic considerations" (p. 27). Such a fact explained the failure to discover metabolic alterations sufficient to allow specific chemotherapy. "The same capacity for variation and selection, which permitted the evolution of a malignant population from the original aberrant cell, also provides the opportunity for the tumor to adapt successfully to the inimical environment of therapy, to the detriment of the patient" (p. 27).

Nowell pointed out a further consequence of the clonal evolution model of cancer, that is that each advanced malignancy has individual therapeutic problems, a view that has become adopted by the strategies aimed at developing tailored/personalized therapies (Hasegawa, Ando, Ando, Hashimoto, Imaizumi and Shimokata 2006).

A further implication of a Darwinian model has to do with the fact that any adaptive evolution is, by definition, context dependent. Anderson (2001) thinks that genomic instability should suggest that "instead of directly attacking the heterogeneous population of genomically unstable tumor cells, the invariant, genomically stable cells of the tumor vasculature become an especially appealing target." The idea role of environment was emphasized by Folkman, who saw that solid tumors are angiogenesis-dependent. That brought to the idea of fighting cancer by subtracting blood supply. These ideas have been developed in several lines, one of which brought to the invention of bevacizumab (Ferrara, Hillant, Gerber and Novotny 2004).

Nowell (1976) interpreted the concept of context dependence of cancer in terms of "potential reversibility of the neoplastic process." If the genetically unstable, highly individual malignancy is difficult to eradicate therapeutically, what is the likelihood of producing a "cure" by providing an environment which forces the tumor cell population to cease unlimited proliferation and move into a state of controlled differentiation?

Nowell quoted the experiment reported in 1975 by Beatrice Mintz and Karl Illmensee, who injected teratocarcinoma cells taken from embryoid bodies in vivo

into developing mouse blastocysts, and obtained normal mice with no evidence of tumors. They, however, found that tumor-derived cells were present in large numbers and contributed to several unrelated tissues. Mintz and Illmensee (1975) concluded that tumor cells were developmentally totipotent and could revert to normal behavior in the appropriate environment. In 1997 Mina Bissel has shown that blocking integrin function was sufficient to revert the malignant phenotype of human breast cancer both in culture and in vivo (Bissel 1997).

More recently, Rudolph Jaenisch and his group demonstrated by using nuclear transplantation that an oocyte's microenvironment can re-establish development pluripotency of malignant cancer cells. The nuclei of murine leukemia, lymphoma and breast cancer cells can support normal preimplantation development to the blastocyst stage, but fail to produce embryonic stem cells. A blastocyst cloned from a RAS-inducible melanoma nucleus develops into ES cells with the potential to differentiate into multiple types in vivo. These findings are in some way paradigmatic for studying the tumorigenic effect of a given cancer genome in the context of the whole animal, and demonstrate that "the malignant phenotype of at least some cancer cells can be reversed to a pluripotent state despite the presence of irreversible genetic alterations and allow apparently normal differentiation. It is now important to define the epigenetic factors that influence the malignant phenotype to help establish therapeutic strategies for cancer patients" (Hochedlinger, Belloch, Brennan, Yamada, Kim, Chin and Jaenisch 2004).

In the light of this theoretical perspective it would be wise to overtly recognize that there will not be "the cure" of cancer, as cancer is not a single disease. There certainly will be many small successes that will steadily reduce the overall death rates from various types of cancer, including the invention of strategies that will exploit body's inherent capacity to prevent the growth of the in situ tumors naturally developing along organisms' lifetimes (Folkman and Kalluri 2004).

## 2.7 Epilogue

The small lesson to take home from the history of 20<sup>th</sup> Century oncology could be illustrated by slightly modifying the famous dictum of Theodosius Dobzhansky: "nothing in biology [and medicine] makes sense except in the light of evolution[ary thinking]" (Dobzhansky 1971).

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