PART THREE:

The Evolutionary Mechanisms of Change: Pathology

Many years ago I read a popular book from the "Eureka" series published in the former Soviet Union. Unfortunately, I do not remember the name of the author or the title or even what the book was about. But one thing I recall is my fascination with the author's approach to Parkinson's disease. As I recall, the author posed the question in the following way: what is the use of hand tremor under normal conditions? His answer hinged upon the way the hand operates under the conditions of uncertainty: tremor allows for greater flexibility, i.e., the ability to change the position of the hand quickly depending on the immediate circumstances. (Other examples of the same phenomenon - tennis players expecting a serve, goalkeepers in soccer waiting for a penalty shot, etc. - have confirmed the expediency of the hand tremor mechanism when it functions properly). The author then proceeds to discuss the pathology of the tremor mechanism which, he claims, manifests itself in Parkinson's disease.

CHAPTER 8

FIRST STEPS EN ROUTE TO A NEW CONCEPT OF CANCER

1. PATHOLOGY AS A DEVIATION OF AN OTHERWISE NORMAL MECHANISM

I found out afterwards that a number of the more creative biologists and medical scholars have stated this principle explicitly: a disease represents a pathology of some normal mechanism.

Let me quote the following passage from a book by Yury Vasiliev and Izrail Gelfand

> "In biology pathological disorders are frequently studied to probe into the respective normal mechanisms: the study of mutants suffering from metabolism disorders reveals normal stages of the metabolic process; the study of individuals with functional brain disorders pinpoints the location of certain functions in the healthy brain, etc. Similarly, by exploring the neoplastic cells we may come to understand normal interaction between the cells and the environment, normal mechanisms of morphogenesis, proliferation, and differentiation. This kind of research is very complex for it addresses the most intricate mechanisms of cell behavior. We are now just beginning to probe into the nature of cellular response and to develop an appropriate language to describe these interactions."[1] (p.3)

Having recognized this new approach to Parkinson's disease, I asked myself the following question: "Which normal mechanism, of which cancer is an extreme manifestation, is broken-down when the disease strikes?" Unlike Parkinson' disease or other diseases which affect specific

functions or parts of the body, cancer in the most developed forms envelops the entire organism.

Of course, cancer may be localized and destroy the organism by striking at individual organs without ever metastasizing (or before it has time to do so??). But to repeat myself, the developed form of cancer envelops the entire organism. This makes cancer a systems disease, a statement which I shall attempt to clarify later on.

Actually, some medical professionals purport that any serious illness is caused by the general state of the organism. This approach shifts the primary focus from the specific ailment to the "holistic" treatment of the body. An original view of holistic treatment has been proposed by Vladimir Dilman.

He attempts to link systemic internal disorders in the organism with the process of aging and specifies ten major non-infectious diseases which accompany aging, including arteriosclerosis, cancer, high blood pressure, and diabetes.

Dilman notes: "Thus, the same mechanisms are responsible for all of the ten major diseases of the middle-aged and elderly. These diseases are so closely interrelated that it is natural to ask the following question: are there really ten individual major diseases, or is there one integral disease with ten major symptoms?"[2] (pp.374-375)

Research on these ten major disorders should not compete with the study of each one individually. In other words, it takes a combination of general and specific factors, both being necessary conditions, for a major disease, or disease in general, to strike.

While Dilman's analysis of diseases is highly interesting, I would like to approach disease classification in terms of my ideas regarding the mechanism of change. One of my quasi-hypotheses regarding the biological mechanisms of change postulates two classes of diseases: one entails disorders in a normally reproducing cell and the other - disorders in the normal mechanism of change. The first group certainly includes such disorders as mechanical damage to the cell. The second class of diseases is more complicated. Based on my classification of the mechanisms of change as they perform over time (section 3, Chapter 3) it is quite plausible that mechanisms aimed at short term changes may cause problems that will manifest themselves in the form of various ailments, but ailments which the organism will be able to overcome. The best example of this case is seasonal virus infections caused by the need on the part of the organism to adapt to the new weather conditions. But even in this case, pathological phenomenon may flare up, e.g. when some dysfunction in the mechanism

of change is so severe relative to the organism's immune system as to cause its demise; flu epidemics accompanied by high fatality rates.

Mechanisms aimed at mid-term changes may produce painful side effects since the new things produced may hinder the organism's performance. For the most part these side effects are not fatal and are limited to specific organs, such as cysts or deformation of a single tissue. However, when these changes cause complete deterioration of a given organ or are fatal then we have a pathology of the mechanism of change.

Finally, mechanisms aimed at long term changes may cause severe problems because all kinds of inconsistencies arise as changes in different organs are being mutually adjusted. In the pathological case these changes may be so extreme relative to the immune system's capacity to resist as to lead to the organism's destruction.

We might conjecture that the various forms of cancer, in terms of the duration of the process, are linked with certain dysfunction in the mechanisms of change aimed at temporally different goals.

Whatever the source of ailment, one method for uncovering the specific causes of a disease is to investigate the function(s) performed by the damaged mechanism under normal circumstances. One could then try to eliminate abnormalities in these specific causes since even a temporary relief could be sufficient to ameliorate the disease.

So, I asked myself which specific functional failure could be linked to cancer? One feature peculiar to cancer is the change which takes place in the cells and the propensity of these cells to conquer the organism, including its reproductive system. This led me to hypothesize that cancer might represent a pathology of some mechanism which fulfills the function of change in an organism. By analogy with economics which encompasses the fast growing sphere of R&D with a multitude of respective mechanisms, I thought of an organism as also having various internal mechanisms of change. An organism, just like a society, integrates the sector of change with the production sector, the latter being directed at sustaining and reproducing a given entity. A break-down in the sector of change might cause great harm, even destruction, to society as a whole. Similarly, abnormalities in the organism's mechanism of change, whatever the state of its "production sector", perhaps, could be quite detrimental.

In exploring the various directions to develop my hypothesis, I decided to start by examining the normal operation of a rather intricate inner mechanism of change based on somatic cells. I soon realized that there was no relevant biological theory which would be acceptable to the scientific community and which would satisfy the rigid standards of empirical science. However, there is very little empirical material on the

somatic mechanism of change as it operates in the norm. I could summon a few works to corroborate certain isolated parts of my theory, but they would not add up to a coherent scientific hypothesis. In those rare instances when reputable scholars did voice their views on the subject, their ideas were rejected outright because they are associated with the heretical idea that somatic changes are heritable or beneficial in terms of adaptation. All these theories smell of obsolete Lamarckism, not to mention the fact that the aversion to any hint of somatic heredity was fueled by charlatans exploiting this idea.

Due to this deficit of scholarly material I saw no way to develop directly a coherent theory of a normal mechanism of change which I imagine to exist. Meanwhile, research in molecular biology has produced a vast amount of data describing a pathological mechanism of change.[1] So, sticking to my main hypothesis, I reversed the course of my investigation and corroborate the existence of the various components of the mechanism of change by showing their pathological expression. I realize this approach is controversial but it is not without merit. The general normal mechanism thus reenacted could provide clues in understanding the intricacies of its pathological manifestations. I shall illustrate this methodology with numerous examples dealing with cancer research.

So**,** cancer, as I define it, is basically an extreme form of a pathological attempt to restructure an organism using the mechanism of somatic change.

2. CONTEMPORARY VIEWS ON CANCER

2.1. Universality of Cancer

Assuming cancerous diseases derive from a pathology of the somatic mechanism of change then this class of disorders must encompass all developing life forms from plants to humans.[3]

Some scholars[4] deem that cancer is not universally intrinsic to all life, allegedly sparing plants. (Some reports[5] claim only limited similarity between plant and animal cancer). However, there is much evidence that points to the contrary. Noteworthy in this respect is the general overview of the subject containing the following passage (I left all references to demonstrate the interest generated by this topic).

> "As just one example we want to concentrate on a kind of cancer which is observed in different kinds of plants (dicotyledonous), e.g. sunflower or tobacco [M. De Cleene and J. DeLey, *Bot. Rev*. 42, 389 (1976).], namely the crown galls. The interesting fact is that these oncogenes are of bacterial origin, i.e., they are a unique example of the expression of prokaryotic DNA sequences by eukaryotes. The bacterium which is able to transfer carcinogenic plasmid DNA into the genome of plants is called *Agrobacterium tumefaciens* [W. B. Gurley *et al*, in *Genome Organization and Expression in Plants*, C. J. Leaver (ed.), Plenum Press (New York, 1979), pp. 481.]. The plasmids which induce the cancer are ring shaped DNA molecules [Zatnen, I. *et al*, J. Mol. Biol. vol. 86, 1974, p.109.] and are different in different tumors, however, they contain as one part a special sequence of DNA which is the same in all cases and is called T-DNA [Chilton, M. *et al*, in *Genome Organization and Expression in Plants*, C. J. Leaver (ed.), Plenum Press (New York, 1979), pp. 471.]. Most probably this is the cancer causing sequence, i.e., the oncogene. The origin of cancer from the ring shaped so-called Ti-plasmids was proven by the observation that removal of this plasmid from oncogenic strains of *Agrobacterium tumefaciens* results in a loss of oncogenicity, while the introduction of this plasmid into the genome of non-oncogenic strains of the bacterium produces oncogenic forms [Van Larebeke, N. *et al*, *Nature* vol. 252, 1974, p.169 ; Watson, B. *et al*,*J. Bacteriol*. vol.123, 1975, p.255.]. Obviously we have here an example of an early discovered oncogene of non-viral but bacterial origin in plants. A review on this topic can be found in [Schell, J. and Van Montagu, M., in *Genome Organization and Expression in Plants*, C. J. Leaver (ed.), Plenum Press (New York, 1979),pp. 453 and other papers in this volume.][6]

Cancer has been discovered in animals living long before the advent of the human species. For instance, in the beginning of the 1920s bone tumor was discovered in a dinosaur skeleton found in Wyoming. Bone tumor was determined in a 1,500,000 year old human jaw and signs of malignant bone tumor were discovered in the septum hole of a human skeleton dating to the Neolithic period. Bone cancer was found in an Egyptian mummy. Papyrus and other documents unearthed in the Middle East allude to tumors of the various organs. Cancer is mentioned by Roman, Greek, and

Jewish sources. References to cancer have grown steadily reaching astronomical proportions with recent progress in medicine and biology.

It should be noted that animal and plant cancer are not completely unrelated. The work cited below presents comparative analysis of abnormal processes of growth in plants and animals examining neoplasmatic (epigenetic) and neoplastic transformation as well as hereditary differences in growth parameters of these two kingdoms. First proposed 80 years ago, the affinity between plant and animal cancer was subsequently rejected, but as a result of some recent findings is making a comeback.[2]

Cancer also encompasses a variety of inner structures at the level of individual organs as well as tissues and cells. More will be said concerning the problem of organs that are known to be susceptible to cancer. For now I will limit myself to a few preliminary remarks regarding cells and tissues.

Cancer is known to affect many different tissues and cells. This point is important since one facet of my hypothesis of cancer concerns the process of change as it unfolds in any tissue or cell unless its growth is halted. There is no need to dwell on the susceptibility of the various cells of the epithelium tissue to tumor. Just recall that muscle tissue (smooth and striated), although less prone to cancer, is susceptible to both primary and secondary tumors, some of which are malignant and can metastasize.[7-8,9,10,11]

2.2. Empirically-Driven Quest for the General Theory of Cancer

Today we have no general theory of cancer which would consolidate the latest discoveries in molecular biology. One indirect confirmation of this theoretical vacuum is the multitude of mainly descriptive definitions of cancer focusing upon some specific aspect of the disease or its causes. (These definitions are discussed in detail below.)

The rather simplistic empirical approach to cancer really goes hand in hand with the recent progress of the last three decades in molecular biology that has raised cancer research to a new level. It seems that most scholars believe that the only way to deal with this terrible disease is to uncover at the molecular level the underlying cellular mechanism.

Many biologists claim to understand the sequence underlying the malignant process. Moreover, in order to stop the disease they deem it sufficient to eliminate one necessary condition underlying tumor growth. In

other words, they think the process can be stopped at any stage before it destroys the organism. Outstanding achievements made in this branch of cancer research serve as a foundation for in-depth analysis and prevent superficial and unsubstantiated speculation.

Advanced research in this area has made it possible to fight cancer by impeding its progress at the various stages of the disease. This has lead to the idea entertained by many biologists of stopping cancer by thwarting telomerase activity which excites telomeres which, in turn, results in unchecked growth of cells. Other methods include revitalizing genes responsible for slowing down cell growth, stimulating repair mechanisms in the cell, and preventing the formation of tumor infrastructure, especially the blood supply system.

I would say, following the terminology used by John Wyke, that the recent advances in cancer research have evolved primarily from the "bottom up."[12] While there has been some progress in the "top down" approach, the main thrust of the research has been put at the intermediate levels of the hierarchy, for example, the structure of the tumor. So, in spite of this vacuum in general theoretical framework, outstanding experimental discoveries of recent decades have revealed the intricate workings of cancerous cells at the molecular level.

Considering the organism's physiological complexity, it might seem unreasonable to distract scientists from conducting new and valuable research into the operation and interaction of cells in favor of general theorizing about cancer. This attitude to practical vs. pure theoretical research implicitly presupposes that once the sea of empirical information becomes incomprehensible making further experimental data intractable, scholars would have no problem concocting the necessary theory to organize the data.

However, the history of science has proved otherwise. For example, in physics a leap into the subatomic realm was accompanied not only by pioneering developments in physics itself (such as quantum mechanics), but also have been preceded by new currents in philosophy, particularly the advent of positivism. Physics was one area where theory and practice worked in unison to complement each other.

I believe that the present day shortage of elaborate hypotheses regarding the nature of cancer as a systems phenomenon represents a major obstacle to further progress in this field. I hope the theory of cancer expounded here will help remedy the situation.

2.3. A Systems Approach to the Definitions of Cancer

Just like any definition, a definition of cancer is neither exclusive nor exhaustive.[13] Rather than try to come up with such an exclusive and exhaustive definition, a pluralistic mechanism of definition construction and selection is introduced in Chapter 3 of this book.[14] First and foremost in this mechanism is the construction of many definitions; we then proceed to select the definition which best serves our immediate pragmatic goals. The third step is to determine whether or not the selected definition is really expedient, and finally the selected definition is replaced by another definition in case the original one proves it is inefficient or inadequate in terms of the changing conditions.[3]

Definition of cancer from the systems perspective can be given in terms of function, structure, process, or genesis. All four dimensions are mutually complimentary.

From the functional point of view, the definition of cancer must specify its function. Some biologists hold that from the functional standpoint cancer plays the role of weeding out the weak; the mechanism is perhaps triggered automatically when a person reaches a certain stage. This would, for example, explain why cancer tends to strike older people. However, this approach raises a very reasonable question: why introduce such a complex internal mechanism of purging the old , a mechanism which not only destroys tissue where cancer originates (in itself sufficient to weed out the old), but does not direct the metastasis into organs whose quick failure would be lethal. We know that physical decline and death can result from a much less intricate internal process of degradation, not to speak of external factors such as viruses, microbes, and predators which are quick to strike the weaker and older organisms.

Even if we accept for the moment this functional definition of cancer, the question of the precise weeding out mechanism remains open. An interesting perspective on cancer from the functional point of view portrays it as a peculiar catalyst in the process of mutation.

> "The highly structured mechanisms of cancers, their tendency to occur as a response to environmental stress, and the existence of oncogenes, suggest that neoplasticity may represent more than a biological dysfunction. It is proposed that cancer exists as a phylogenetic mechanism serving to promote "hyperevolution", albeit at the expense of the ontogeny, that is similar to a process recently discovered in bacterial mutations. Cell-surface-associated nucleic acid in tumorigenic cells and

> sperm cell vectorization of foreign DNA indicate the existence of essential mechanisms necessary to the occurrence of cancer mediated hyperevolution. An analysis of the proposed mechanism indicates that for mutagenesis of chemical cytology, stress induced neoplasticity confers an evolutionary advantage of more than two orders of magnitude."[15]

I share the view espoused in the above passage that cancer is linked to the mechanism of generating new mutations. However, taken in isolation this factor obscures the more specific role of cancer as a pathology of the somatic mechanism of change.

Many more common definitions of cancer are based on the structural or process-oriented outlook.

Structural definitions of cancer focus on the various components of cancer and their interaction. The common thread running through these definitions is the presence of radical tumor-forming cells and the immune system's ineptitude in restraining them. The following definition is an example of the structural approach: "Cancer is a malignant neoplasm." [16]

Process-oriented definitions emphasize the progress of cancer and its uncontrollability, i.e., the idea that cancer represents unorganized multiplication of cells. In keeping with our methodological device of uncovering the nature of the disease by reconstructing the respective normal but malfunctioning mechanism, cancer represents a break-down of the mechanism normally responsible for managing cell growth. However, these definitions fail to account for such typical phenomenon as metastasis. Biologists insist (see the hypothetical stages of somatic change described in the previous chapter) that the normal mechanism of cell growth does not exhibit migration of cells from one organ to another which would be reminiscent of the metastasizing process.

Here is a typical process-oriented definition of cancer: "**Cancer** a general term for more than 100 diseases characterized by the uncontrolled, abnormal growth of cells in different parts of the body that can spread to other parts of the body."[17] (p. 1)

Essentially similar definition is given in Webster New International Dictionary "Cancer. A malignant growth of tissue usually ulcerating, tending to spread by local invasion and also through the lymph and blood stream, associated with general ill health and progressive emaciation."

These definitions are not very precise. Jumping ahead I want to note that cancer cells are not necessarily uncontrollable nor is their growth unregulated. Reiterating my analogy with dissident radicals in society,

radicals include both anarchists as well as communists, fascists, etc., revolutionaries who try to impose their rigid program for governing a society - a relatively superficial program given the complexity of the issues.[4]

Another example of a process-oriented approach to cancer is the following descriptive definition which emphasizes the progress of the disease: "Cancer. A malignant growth of tissue usually ulcerating, tending to spread by local invasion and also through the lymph and blood stream, associated with general ill health and progressive emaciation."[18] (p. 55)

Consider the following definition of cancer from the process-oriented point of view: "Cancer...is a disease in which individual mutant cells begin by prospering [selfishly] at the expense of their neighbors but in the end destroy the whole cellular society and die."[19] (p. 188)

The above description encapsulates the idea that cancer cells behave as *egoists* who pursue their own interest ignoring the interests of other cells and eventually perishing themselves. I believe the definition would be more constructive if it made an attempt to distinguish between cancer cells and innovator cells; at first glance the latter exhibit similar behavior in pursuing their own interest and seizing additional resources. However, innovator cells are individualists, meaning they pursue their own interest while taking the needs of other cells into account.

In terms of genesis, definitions of cancer pinpoint its sources, such as carcinogenic substances, radiation, viruses, etc. as well as its general evolutionary origins.

All in all, in terms of etiology the predominant view today is that cancer is a result of external factors such as carcinogenic substances, radiation, etc.; as a result the thrust of the struggle against the disease is to eliminate these factors. However, an opposing theory that has been gaining momentum asserts that the primary cause of cancer is the organism's predisposition toward the aforementioned factors.[5] In other words, in the absence of other factors, carcinogenic substances are generally not sufficient to produce a cancer cell. Perhaps, these other factors are expressed as modified genes in the DNA program triggered by dysfunction in the higher-level program.

In introducing the agenda of the annual meeting of the American Society of Clinical Oncology that took place in Dallas in 1984 Sandra Blakeslee writes:

> "The new research shows that cancer is not primarily caused, as many Americans tend to think, by the poisons spewed into the air, water, and land by uncaring industrialists. Rather, each person is born with various genetic susceptibilities, essentially weak spots in their genetic makeup, that play a leading role in the cellular mayhem called cancer.
> For example, researchers have found that some people have genes that enable their bodies to detoxify chemicals rapidly, including the carcinogens found in cigarette smoke and natural carcinogens found in foods. Others are born with slow acting varieties of the same genes; their bodies are less efficient at getting rid of carcinogens. If exposed to large enough quantities of the chemicals, these slow detoxifiers are more likely to get cancer."[20]

In the light of the considerations expressed above, the role of heredity and the related germ cell mechanism in causing cancer. The heredity factor comes in if only because the mechanism of change in germ cells has turned pathological in parents. As a result the children inherit a damaged program of development (or the program that changes this program). Consequently, as the zygote develops the fetus assimilates a destructive program that is implemented via the fetus' somatic cells. This might be the reason why doctors administering preventive treatment try to find out about the history of the disease among the patient's blood relatives, the link between the somatic and germatic mechanisms of change in parents who never had cancer. In this case one can assume that the basically healthy predecessors have slowly, over the course of many generations, been accumulating some kind of predisposition toward pathological operation of their germ cell structure without these changes being physically expressed. However, at some point the pathological changes ripen sufficiently to produce a generation of children afflicted by cancer.

The following quotation is interesting from the standpoint of cancer's genesis :

> "If evolutionary theory is modified to include the assertion that cancer established, about 700-800 million years ago, the imperative that only those Bilaterian genotypes capable of extreme precision in the construction of multicellular organisms could possibly survive to participate in the struggle for existence and ruthlessly enforced that imperative ever since, then evolutionary theory is strengthened." [21]

This is an attempt to link cancer with the development of complex organisms. My hypothesis, however, that cancer represents a disturbance in the overall evolutionary process is equally applicable to complex as well as simple living creatures. In other words, if there exists, at the level of the organism, an orderly evolutionary mechanism of change susceptible to malfunctioning, there is a likelihood of cancer. Admittedly, the more complex the organism, the greater the likelihood of breakdowns in its evolutionary mechanism, and hence of cancer.

To sum up, disorders in the biological mechanisms of change are fraught with grave consequences. In a sense the most powerful constructive forces underlying development join with highly destructive forces also incorporated into the development process. The major threat stems from cancer dispersion when disorders are not localized to their place of origin. Naturally, the more important the given mechanism of change to the species' development the more grave the implications of its break-down. Disorders in these mechanisms in complex organisms having an intricate mechanism of change (especially if active) can lead to major diseases such as cancer.[22]

2. THE PROPOSED CONCEPT OF CANCER

2.1. Change and Cancer

The material in the previous chapters was designed to lead to the following general question as a starting point of our discussion of cancer: "What normal biological mechanism leads to this devastating disease?" It was suggested that the answer be sought in the break-down of the somatic mechanism of change instilled by evolution. It is upon this substrate of somatic cells that the tragedy called cancer is being staged. Somatic cells are sufficient for *cancer* to take root provided at least one or , in the spirit of the multi-factor concept of the etiology of cancer, a combination of the following conditions is satisfied.

First of all, damage in somatic cells is induced directly by external factors outside the organism (carcinogenic substances) as well factors inside the organism (viruses).

Secondly, the somatic cells possess internal mechanisms of change that are susceptible to pathological disorders.

Pursuing the latter venue leads me to hypothesize that the genetic structure of somatic cells, apart from carrying genes responsible for their own reproduction, includes genes responsible for change and that these genes can, under certain conditions, become oncogenes. One piece of evidence supporting this claim is the discovery of highly repetitive sequences of genes, called minisatellites, in the structure of the "selfish genes"; these mutations interfere with growth regulation and induce some forms of cancer[23]. In fact, assuming the internal mechanisms of change reside in the "selfish genes" (see chapter 5), the above hypothesis is further strengthened by the fact that the structure of "jumping" genes and certain cancer-causing viruses is identical.[24]

I will now try to conceptualize the phenomenon of cancer with the help of the systems approach.

2.2. Systems Approach to the Theory of Cancer

Currently cancer is viewed as an event that takes place in an organism (total system) whose function in the norm is *survival*. Faithful to the guiding principles of the systems approach with its emphasis on the system (organism) as a whole, in which the target object is immersed, I have proposed a new paradigm for probing into the phenomenon of cancer. It is predicated upon the idea that the function of an organism is not limited to reproducing creatures in its own image. Organisms aim at *development* (change). I further surmised that complex systems, to which living creatures belong, ought to include more than one mechanism of change. Beside the widely eulogized mechanism of random mutations, I believe there exist diverse mechanisms of change that are ordered, to a greater or lesser extent.

To reiterate, I have focused on the somatic mechanism of change in multicellular organisms possessing rather advanced intercellular communication network. Molecular research into the structure and development of normal and cancer cells has shed much light on normal as well as malignant processes in the organism. As a result, the notion that genes present in the normal cells may, under certain conditions, turn into oncogenes has gained general recognition.[6]

What's more, this proposition holds with respect to not just the normal cells, that is cells that merely reproduce a given organism, but to innovator-cells as well.

Here I would like to remind the reader of James Shapiro's observation: most biologists regard as *normal* only those cells which

reproduce a given organism. They regard changes in the cell as a result of some kind of damage (break-down, mistake), i.e., changes in the genome are regarded as a deviation from the norm and always bear a negative connotation. This approach to genetic change agrees with the prevailing views on evolution as being driven by random mutations resulting primarily from external fluctuations. Accordingly, all afflictions of the genome are manifestations of these random mutations.[7]

Thus, any cell whose structure deviates from the norm is often labeled damaged, i.e., abnormal. Shapiro notes, however, that a change in the cell could be a normal phenomenon which serves to promote the cell's adaptation to its new environment.

> "Molecular genetic results have tremendously expanded our understanding of what living cells can do with their genome. The examples described above illustrate some of the many ways that different biochemical systems serve to restructure DNA molecules in organisms as diverse as bacteria and mammals. These DNA reorganization systems are subject to cellular regulation, and some of them serve specific adaptive functions in organismal life cycles. It is easier to understand how change can be regulated and used to meet adaptive needs if we think of it as a biochemical process rather than as a blind consequence of physico-chemical damage. Such damage does occur, of course, but it is anticipated, and the contribution of purely chemical events to genetic change is kept at a very low level by elaborate repair systems."[25]

It can further be surmised, and there is plenty of evidence to support the claim, that organisms possess special features to remedy various break-downs of some normal mechanism that is subject to failure. In other words, once the flaws in some functionally useful mechanism are uncovered, meaning we have determined the nature of the disease, the organism's own powers should be summoned to shield it from the disease.[26] Of course, if the organism's inner resources prove inadequate, thus creating a pathological situation the organism perishes unless it receives timely outside help.

All this leads us to an important distinction between *normal* and *pathological* break-downs. Both cases may lead to a disease, but normal flaws, unlike the pathological case, can be overcome by the organism itself.[27] Pathological disorders vary in time and in space in the extent of havoc they can wreak, progressing slowly or rapidly, attacking a single

organ (part) or many organs, changing or destroying them. For example, the simplest form of pathology entails degeneration when the cell (tissue, organ) begins to disintegrate, reverting to its early state that is unstable in the new environment. Of course, degeneration may assume extreme forms when the organ is ravaged completely. Another form of pathology with less severe consequences is transformation *(*reconstruction) of the cell manifested in benevolent tumors, deformities, etc. Still, there is a big gap between these changes in the cell and cancer.[8]

The more extreme expressions of pathology engulf many organs and destroy them very quickly relative to the life span of the organism.

Under certain conditions pathology can be treated by the rebirth of the cell, i.e., the cell's reversion to its original state. However, rebirth is not a universal remedy because the original state is predisposed toward all kinds of abnormal phenomenon. The other method is cell *rejuvenation* which entails elimination/introduction of certain elements.[9]

Particularly interesting in this connection is the relation between *apoptosis* and cancer. If we regard the former as a normal phenomenon then cancer could be deemed its pathology in the following sense: cancer leads to the rejuvenation of a cell that was about to die a normal death. Research conducted in the 1980s has proved that the oncogene *bcl-2* introduced in cells undergoing apoptosis results in cell survival.[28]

Correlation between apoptosis and cancer parallels in some respects that of telomeres and cancer. Typically cancer cells revitalize telomeres whose absence would otherwise be fatal (see section 2, Chapter 6). In my scheme of cancer, cancerous revival of a doomed cell is the work of the mechanism of change which must, before all else, ensure that cell's survival. Dysfunctions of this mechanism, which in itself are the cause of cancer, result in this paradoxical alliance between the cell's rejuvenation and such lethal agent as cancer.

Let us examine the behavior of normal and pathological cells in the light of our discussion of social systems in Chapter 2.

2.3. "Deviant" Cells and Cancer Cells

All cancer cells are deviants. They are characterized by 1) progressive multiplication, 2) mobility, 3) diminished adhesiveness (loss of cohesion), 4) phagocyte activity.

Generally speaking these features are shared by all innovator cells. Some characteristics of cancer cells may be missing in innovator cells, but these characteristics may not be universal for all cancer cells either. To

continue with the above list of features we could add 5) the output of these cells may contain poisons - tumor metabolites.[29]

The critical question is how to distinguish between innovator cells and cancer cells. It is important to recognize a cancer cell at an early stage of its development. Diagnosis based on the physical expression of the deviant cells may be too late in terms of stopping the cancer cell from destroying an organism. Is an early diagnosis possible?

The answer is not that simple. The astounding scientific and technological strides of seventeenth-eighteenth centuries made scientists and engineers believe that virtually everything is possible from perpetual motion machine to utopias (paradise on earth). The nineteenth century was more sober. It began with the discovery of the laws of thermodynamics proving the impossibility of perpetuum mobile. Soon after the great mathematician Evariste Galois proved that equations of the degree higher than four have no general analytical solutions. Other examples of impossibility abound. In the twentieth century this category of proofs extends beyond mathematics (Kurt Gödel's theorem) and physics into the realm of social sciences (Arrow's theorem proving that under certain conditions no solution to democratic voting procedure exists).

In solving complex problems modern science first attempts to prove that the solution exists and then proceeds to find it.

With respect to an early diagnosis of cancer the question is can we formulate sufficient conditions to distinguish a cancer cell from other deviant cells. Of course, at the present time the possibility can neither be proved nor refuted. I am rather skeptical; it is quite plausible that innovator and cancer cells are indistinguishable at an early stage of development. It may be discovered sometime into the process that an innovator cell has turned into a kind of "killer on the loose" which strikes haphazardly or "killer-robber" which kills selectively in pursuit of his own gain. Moreover, innovator cells may include various brands of "radicals" including "terrorists." Rather than invigorate a complex organism these cells try to subordinate it to their dictate based upon a superficial scheme with which the immune system is unable to cope.

It is especially difficult to stand up to the radicals in times of crises (in a sense similar to an organism under stress) when they promise to alleviate the current hardships. The tricky part is that the measures they propose may prove successful but only ... locally (in the short run). This was the case with fascists in Germany. Having gained power they reduced unemployment, raised the standard of living, returned Ruhr territories lost after WWI back to Germany, and so on. At the same time the fascist program contained seeds of the terrible things to come. Few were really

concerned because the majority focused on the current hardships and short run relief. It took American political culture not to succumb to communist or fascist (corporate socialism) ideologies at a time of crisis while borrowing certain ideas from these groups. Interestingly, Keynes was compared to Marx as far as augmenting government power, and Roosevelt was regarded by some as "pink."

By analogy with social systems it is not necessary for cancer cells to be unmanageable or exhibit profuse multiplication. Their behavior could be organized by being governed by their own destructive program. Coupled with the inability of the immune system to channel the resulting changes along a desirable course, the consequences of cancer are devastating.

My speculations, assuming they make any sense, lead to some practical, albeit remote, conclusions regarding our attitude toward cancer.

Today the medical profession does its utmost to destroy cells deemed malignant or restore them to a "normal" state in the orthodox sense of the word, i.e., a conformist cell that reproduces a given organism. The last method is summoned to fight cancer by deactivating telomerase activity in cancer cells, i.e., restoring these cells to their normal cycle with a prescribed number of divisions and no side-affect on the healthy cells. "The paradigm is we have a new way of dealing with the tumor cell, not by killing it or poisoning it, but by reasoning with it."[30]

Since innovator cells may behave similarly to cancer cells, especially at an early stage, it is not advisable under early diagnosis to categorize all *innovator cells* as cancerous. This confusion in cell classification may hinder evolution by depriving innovator cells of opportunities under the guise of destroying cancer cells. I believe deviant cells should be approached in the following manner. Even if the subsequent course of development of radical cells is unknown and there is no guarantee that the immune system will be able to cope with radical cells if they turn out to be terrorists, it may still be advisable "to isolate these cells from society" rather than destroy them. By analogy with radicals in a democratic society, once this kind of group asserts its existence it can be "shadowed" or spied upon. Radicals may be kept away from classified work and their organizations infiltrated by agents. As soon as they turn to an armed conspiracy they can be isolated and tried in court. The most severe punishment is administered only if they initiate some kind of unlawful action.

Similarly, radical cells can be subjected to all sorts of isolation. Subsequently, if the organism proves capable of assimilating these cells they can be allowed to function on par with other cells. A number of oncologists have arrived at the same conclusion although for a different

reason. They realize that the destruction of cancer cells entails hazardous procedures including the possible disruption of healthy cells typical of chemotherapy.[31]

I realize full well that at the present time when cancer is still extremely lethal my comments sound rather frivolous (to put it mildly). It seems absurd to think of development when survival is on the line. As the saying goes, "Thank God just to be alive." But thinking of the future (at least occasionally) is bound to pay off. Indeed, destruction of all innovator cells could prove detrimental to the sources of change that give viability to the cell with all the ensuing consequences (such as the organism's life span). This statement is based on the role of telomeres discussed in the previous chapter.

The various "social" functions played by the cancer cells point to a connection between the function and the form of cancer.

Is not sarcoma a form of cancer in which the malignant cells resemble killer cells that simply take away nutrients or space from other cells by poisoning them with the waste they secrete? Less extreme forms of cancer that exhibit slower growth can affect change in the genetic structure of other cells; this resembles the way many radical groups operate. The creeping forms of cancer are akin to "revisionist" type cells (see typology of cell based on the analogy with deviants in society in Chapter 2).

Let us categorize all deviants that inflict harm as "traitors" since at first they all promise prosperity; cancer cells belong to this category.

> "Cancer is a kind of treachery from the interior of the body. Cells which have been "good citizens" so far obeying the laws exactly changing their nature, beginning to perform division and hyper plasia indifferent to the demand of the living body, intruding into adjacent normal tissue, besides spreading over other parts of the body, taking root there, and make the second base equally unlawful (metastasis). Such an unlawful castle can give rise to almost all organs in the body."[32]

Our discussion will focus on the "traitor" cells, meaning the general characteristics of cancer, and ignore the peculiarities of the various forms it assumes.

2.4. The Possible Usefulness of My Hypothesis on the Nature of Cancer

Giving in to vanity and fantasy, but only to illustrate the value of theory in cancer research, I would say that if a theory like mine was around in the 1960-70s it would have served as a catalyst in research on genetic changes that lead to cancer. It seems that for many years cancer research at the molecular level was focused on finding special cancer genes, or even one all-pervasive cancer gene. It was not until 1976 that M.Bishop and H. Varmus discovered that the gene which was thought to cause cancer in chicks was essentially identical to a normal gene. Thereafter, research shifted from one all-pervasive cancer gene to the underlying causes of disorders in the genetic mechanism at various stages of the disease.

Of course, who knows what could have been? I think a better way to bolster my case is to show the pertinence of my conceptual approach to future research. If nothing else, my optimism is based on the new vision afforded by my approach. It reveals the link between various stages of cancer, the nature of each stage, and the sources that might trigger the malignant process at each stage.

Possible evidence in support of my hypothesis concerning the nature of cancer may be found in the study of certain types of pathologies. Presently, biologists are at work looking for the links between arteriosclerosis and cancer: both conditions feature blockage of gene *p53* which is responsible for slowing down the rate of cell reproduction.[33] In case of arteriosclerosis, however, the rapidly multiplying cells impact the organism only *locally* by depositing themselves on arterial walls and interfering with blood flow. In case of cancer, the effect of rapidly multiplying cells is *globally* in that they gradually spread throughout the organism.

It is quite possible that local organ-specific diseases are pathological manifestations of the workings of stable reproductive mechanisms, whereas systemic diseases, such as cancer, are pathological manifestations of a cell changing its somatic mechanism.

It bears repeating that cells possess a mechanism to repair damage both as to the coding genes and as to the mechanism of change. In cancer cells genome damage is not repaired. One's conceptual framework guides one's search for causes that explain this type of behavior by the repair mechanism. Assuming some changes are of an innovative nature, the repair mechanism need not intervene. At some stages of cell development, cancer cells may behave just like or at least similarly to innovation-bearing cells so the repair mechanism remains idle. On the other hand, if any change in the cell is deemed abnormal - a deviation from

some states both as of normal reproduction and as of change, then this passivity on the part of the repair mechanism will always be regarded as a disorder.

It seems to me that the silence on the part of biologists regarding the function of the internal somatic cell-based mechanisms of change and the impact of these changes on heredity is rooted in the reigning doctrine which postulates a rigid chain linking change and heredity: the idea of an internal mechanism of directed change is rejected with positive change being implemented solely via selection among organisms that have undergone random damage to the genetic structure of the germ cells.

I should note that certain ideas presented here concerning the link between cancer and the process of evolution have been voiced independently, although in different and rather general terms, by a number of biologists.

For instance, I found a published report linking cancer and evolutionary change in the following context. The possible connection between cancer and certain genetic diseases such as Huntington's disease, myotonic dystrophy, fragile X syndrome, and spinal and bulbar muscle atrophy has generated some interesting questions. The impetus for research in this area was the discovery revealing similarities in the structure of the genes responsible for these diseases. Genetic affinity is manifested in the abnormal repetition or duplication of the same segment of DNA in the genome. Bert Vogelstein noted that this phenomenon of abnormal duplication is characterized by an instability of the genome as opposed to its stability as a norm. He speculates that "The expanding segments might speed genetic changes that allow an organism to evolve and in the case of cancer this mechanism goes awry." Vogelstein continues, "One way to think about tumors is as an evolutionary process in which evolution occurs fanatically."[34]

However, Vogelstein does not elaborate upon this point and fails to provide any explanation of how such a mechanism of evolutionary change might actually work.

One noteworthy exception to my criticism is the concept of cancer elaborated by Lev Meckler. (A word of warning. I would not venture to judge the validity of Meckler's concept so my criticism will be rather general. According to expert opinion, which is generally skeptical, the published account of Meckler's work represents a peculiar blend of plausible ideas corroborated by credible references, loose interpretation of certain facts, and axiomatic statements of dubious origin.)

According to Meckler, cancer can be viewed as a pathological manifestation of the mechanism of adaptation to changes in the

environment. It entails changes in the structure of the organism resembling the process of embryonic development.[35]

For me it is not necessary that the changes induced by the somatic mechanism be transmitted to germ cells; Meckler does cling to this point. The mere existence of this mechanism is sufficient. Perhaps the somatic mechanism is archaic and changes that it produces are not allowed to pass on. In fact, in higher organisms if changes in the somatic cells do reach a germ cell, it is more likely to occur in females.

My other point of contention with Meckler is the source of change. In my opinion, the impulse does not have to come from the environment. Meckler's emphasis is on the organism's immediate response to external demands, i.e., the passive nature of the mechanism of change. The importance of this response mode cannot be denied. At the same time, we should not underestimate the role of the mechanism of change that takes signals from inside itself and *actively* bears down on the environment. This mode is directed at conquering and modifying the world and in those cases where change can be initiated at the beginning it incorporates the tunnel process.

Meckler is very categorical about the affinity between cancer and embryonic cells. I believe he stretches the comparison between the two. The cancer cell transmits change to different organs while an embryonic cell carries the program of development of a given cell to a specific structure of an organism.

Furthermore, if the cancer cell was embryonic its development should not be limited to tumors, assuming the latter is a forerunner of organ formation. It should also start to form organs even if deformed ones.

This leads me to disagree with Meckler's claim that the migration of somatic cells is intrinsic only to pathological cells such as hybrid somatic cells and that information from normal organs is transmitted to other organs solely through the viruses. My concept, to put it boldly, does not rule out the migration of normal somatic cells, which include innovator cells. Therefore, in developed organisms cell migration is not the prerogative of cancer cells. As noted above since the process of somatic change requires cell coordination we should not rule out the possibility of a messenger somatic cell returning to its host organ; these considerations apply equally well to cancer cells. It seems that such reentry is not characteristic of embryonic cells.

Hopefully, the reader is convinced that the field of etiology of cancer leaves plenty of room for new ideas.

NOTES TO CHAPTER 8

[1]. Sometimes the situation is reversed. In discussing the suppressor genes one author notes: "While there is much to be learned about what the proteins encoded by the suppressor gene do, researchers are making progress toward understanding how these proteins normally function - and also how they may malfunction in cancer."[36]

[2]. "Tumorigenesis in eukaryotic organisms is based on the deregulation of normal cell growth and development. This deregulation may be elicited by external as well as endogenous factors. We distinguish between benign and malignant growths depending on the inducing tumorigenic agents and on the geneticmake-up of the affected organism. This review discusses similarities of neoplasmatic (epigenetic) and neoplastic transformations in plants and animals as well as inherent differences in the growth parameters between the two kingdoms. Examples given for neoplasmatic tissues are the hyperplasias and insect galls (zoocecidia) in plants and hypoplasia, aplasia and agenesis in animals (and man). Neoplastic transformation in plants is the result of either the incorporation of foreign nuclear material into the plant genome or an imbalance of inherited chromosomes (in hybrids). Examples for neoplasias are the crown gall disease and Kostoff's genetic tumors in plants, and the carcinomas and leukemias in animals. The more than 80 year old, but neglected, concept of a correlation between tumorigenesis in animals and plants has been revived through advances in molecular and cell biology and molecular genetics which will stimulate a new form of biological reasoning and thought, fueled by new insights into cellular regulatory processes."[37]

[3]. An extreme example of this approach is the definitive two-volume set on cancer.[38] It simply ignores the issue of definition of cancer. Some mathematicians who want to avoid scholastic arguments define mathematics as "anything that mathematicians deal with". Perhaps, the authors of the above publication had similar concerns.

[4]. Thus, communists-radicals (revolutionaries) were able to seize power in Russia and fascists to do the same in Germany. These groups then managed to impose their rule upon the entire country with various segments of society controlled by these groups evolving in a rather organized fashion. It is quite another matter that their primitive "genetic program" penetrated so deeply into the fabric of the social organism, it distorted the structure of the country and its mechanism of government, and it deformed people to such an extent as to lead the country within a relatively short historic time period to a virtual exhaustion with all the ensuing consequences.

[5]. The study of the regional aspects of cancer distribution has revealed a correlation between nutrition in various countries and different forms of cancer. Perhaps this is not a cause-effect relationship but merely a correlation: the genetic make-up of different peoples may create predisposition toward the various forms of cancer.

[6]. I do not know whether Meckler was the original exponent of the idea that genes present in the normal cells may, under certain conditions, turn into oncogenes, but certainly one of first.[39] In his later works, Meckler summed up his results: "It has finally been determined - contrary to the prevailing theories of oncogenesis - that there is no single transforming gene, or so called "sark" gene. Therefore, there is no single transforming protein capable of transforming any cell. Based on experimental results the theory of oncogenesis espoused here states that genes responsible for cell

transformation are the organism's normal genes which differ in terms of their organ or tissue characteristics. These genes are localized in specific sections of the genome that are no different from the sections housing its endogenous viruses, i.e., structures which, according to the present theory of oncogenesis, carry these genes from one type of cell to another."[40]

Whatever the priorities in this field are, in 1989 one of the few Nobel prizes awarded specifically for cancer research went to M. Bishop and H. Varmus. They discovered that normal cells carry genes which, if they malfunction, cause cancer. 13 years after this discovery made in 1976 almost 50 potential oncogenes have been uncovered. Under normal conditions, these genes are responsible for controlling the cells' growth and development..[41]

[7]. Typical in this respect is the views by Vladimir Dilman. He writes that "...damage to the genetic apparatus, first and foremost DNA, has great significance. Though this phenomenon lies on the basis of mutations, which is a necessary condition for evolutionary variability, it should be restricted as much as possible in the case of the sex cells as well as the somatic ones, because the accumulation of mutations in both the former and latter can lead to death of the cells and to changes in their vital activity, e.g., due to the development of auto-immune lesions."[42] (p.252)

[8]. "Recent research has revealed that children with certain innate developmental disorders have a high risk of developing malignant tumors. For instance, various forms of leukemia are frequently associated with chromosomal syndromes. Leukosis is 10-20 times more like under Down syndrome; Blum syndrome and Fankoni syndrome is combined with acute monocyte and myelosis leukosis in 10% of the cases. Children suffering from aniridia (lack of iris) are 1,000 times more likely to develop a Wilm's tumor [malignant kidney tumor A.K.]. Also linked with this disorder are congenital cataract, concha auriculae, microcephalia manifested in rued head circumference and mental retardation. Is has also been established that Wilm's tumor and hepatoblastoma are correlated with hemihypertrophy (hypertrophy of half or some part of the body), exophthalmos, macroglossia, and benevolent hamartoma (tuberous sclerosis, heart rhabdomyoma). It has been determined that dysgenesia of gonads is frequently correlated with dysgerminoma as well as with polypoid hamartoma, mucous membrane of the gastro-intestinal, respiratory, and pertaining to urination tracts. Malignant lymphoma are accompanied by developmental disorders of the immune system, growth disorders in long tubular bones, and skin appendixes (hair, nails). However, neuroblastomes are not generally accompanied by growth disorders.

So some tumors in children are correlated with certain growth anomalies while other are not. This attest to the selectivity on the part of these disorders with tumors of specific histogenesis.

All the data linking tumors with growth disorders suggest a common etiology. It is assumed that exposure to exogenous oncogenetic factors short term impact on the fetus results in developmental disorders and long exposure to the development of malignant tumors".[43] (p. 234)

[9]. My metaphorical terms *renaissance* and *renovation* are borrowed from Michail Sergeev's analysis of the development of religion in present-day Russia (source: private discussions).

CHAPTER 9

CHARACTERISTICS OF CANCER

1. CANCER STAGE BY STAGE

Let us examine the stages of cancer within the framework of the proposed definition of cancer as a pathology of the somatic mechanism of change. Our analysis will parallel previously described somatic mechanism operating in the norm; even the sequence of stages will be preserved.

The first thing to note is that cancer is a *multi-stage* process. It incorporates many diverse features that control the various levels of the genetic code (programs which govern the development of a new organism as well as programs that control the scope and depth of changes in the lower-ranking programs). The changes that ultimately prove to be pathological may be initiated at any stage of the process of somatic change.

Another scenario is that cancer cells mainly interact locally at each stage of development, meaning they interact within the framework of a horizontal mechanism.

So, what is the basic sequence of the malignant process?

1. Changes that transform a cell into a cancer cell may take place at various stages of this process starting from the creation of the organism's architecture during the embryogenesis when HOX genes (see section 2, Chapter 3) are active.[1]

We also observe changes that transform a cell into a cancer cell at various levels of the organism including the genetic level. Genes responsible for these changes may be the same ones that are present in a normal cell. It has been recognized that normal and oncogenes have identical nature.

The sources of change that lead to cancer can be internal to the genome, i.e., driven by its inner mechanism of change (the program which changes the program which changes the program that forms the organism). These internal sources of change are least explored and this whole notion

raises skepticism on the part of most biologists. Meanwhile, we know that certain elements of the program for changing the program that shapes an organism are identical for both normal and pathological mechanisms of change. This applies to transposons and certain viruses and perhaps proviruses[44] that tend to induce malignancy. The work of Howard Temin has revealed the role of retroviruses in the malignant process by tracking the DNA environment under which the cancerous retrovirus (RNA segment) is able to infiltrate successfully.[45]

At the chromosome level, changes that lead to cancer reflect chromosome damage or pathological recombination.[46] [2]

At cell level sources of change that induce cancer may not be limited to the genome. Mitochondria and other structures in the cell that contribute to its development may play a role.

At the intercellular level, beside nucleotides, for instance, viruses, cancer can be triggered by oncoproteins.[47]

At the level of the organism cancer is associated with the failure of the immune system to halt the development of the cancer cell.

Causes of cancer external to the organism are many and diverse. They may be rooted in the mechanism of sexual crossing or the environment. Crossing may produce inferior combinations of germ cells meaning one of the cells (perhaps the carrier of the predisposition in latent form) or their combination creates a predisposition to cancer. External sources of cancer believed to exert the greatest impact are carcinogenic substances and high levels of radiation. I would like to reiterate that there is too much emphasis on the link between cancer and various environmental factors at the expense of the less explored dysfunction in the internal mechanism of change.[3]

2. Generally speaking, cancer cells are less differentiated although the spectrum is quite wide.[4] A mature epithelial cell turned malignant reduces its level of differentiation substantially (so called negative differentiation) while immature, meaning less differentiated epithelial cells, can turn cancerous in a more straightforward fashion. Cancer cells generally exhibit a reversion back to lower forms[48] appearing even during reversion to ancient forms[49], for instance from eukaryots to prokaryotes.[50]

3. Having become less differentiated the cancer cell changes its behavior not only because some genes are suppressed, this occurs in normally changing cells as well, but also because some of its genes are damaged by exposure to chemicals or radiation. Cancer cells also behave differently when new genes in the form of viruses penetrate its genetic structure.

4. As a rule, cancer cells becomes more autonomous in terms of acquiring nutrients and excreting byproducts of their metabolism; they fail to follow normal "input/output" processes regulated by the organism. This drastic change in cancer cells' metabolism is expressed, among many other changes, in the reduced number of receptors linking it to other cells. As opposed to normal cells of complex organisms that consume glucose and oxygen the cancer cells' oxygen supply is upset and a switch is made to a highly simplified form of anaerobic metabolism which only requires glucose from the outside. This characteristic of cancer cells was first pointed out in 1923 by Otto Warburg and became a pivotal element of his general theory of cancer.[51] However this mode of metabolism produces greater amount of lactic acid.[5] In a normal cell operating under anaerobic metabolism lactic acid is eventually discharged and, in fact, it gives back some useful substances in exchange for glucose received from the host. Essentially the cancer cell turns into a criminal. It consumes glucose and excretes waste in the form of lactic acid which the host must somehow utilize [6]; being less differentiated and lacking many receptors the cancer cell is not only oblivious to the needs of the host but is unable to produce many substances needed by the host. In the view of Zinovy Chereisky what makes cancer cells especially dangerous is their pathological metabolic process resulting in excessive concentration of lactic acid coupled with a clogged membrane that prevents its discharge.[52]

5. The threat posed by changes in cells that have turned malignant varies. Cancer cells may result in benevolent tumors. Some tumors are localized to a single spot and stay confined to that organ; there are tumors which move from tissue to tissue within a given organ. These relatively mild forms of cancer interfere with the organism's performance but they are not lethal.

Another feature of cancer cells is piling up of malignant cells that do not exhibit frantic growth.[53] Here, the organ housing the malignant tumor disintegrates.

It would be interesting in this connection to look at tumors from the standpoint of developmental biology and organ deformities. Presumably, tumors represent either an atavism of the mechanism of reproduction via the somatic cells (this incorporates the process of change) or an unregulated embryonic development.

Finally, when the changed cells attain a certain level of maturity they may attempt to leave a given organ, that is begin to metastasize.

6. The cancer cell undergoes change at various stages of its development, including M1 and M2, induced by telomerase activation and resulting telomere renewal.[7]

7. The mechanism of repair of modified DNA segments fails to engage or does so too slowly. "The Beckman team does have a handle on the relationship between slow DNA repair and genetic mutations found in skin cancer."[54] It is to be expected that the repair mechanism does not respond to innovative changes since if it did, it would be like a repairman who, seeing a modernized piece of machinery, disassembles the newly added parts thus reverting to the original state. The dysfunction in the repair mechanism is actually its inability to address harmful changes in the genome which sidetrack the normal course of innovation. This flaw may stem from some defect in the repair mechanism or in the mechanism of change incorporated into a higher-level program.

Another plausible scenario is that the aroused mechanism of change in the cancer cell halts the process of apoptosis thus replacing definite death under apoptosis with possible death resulting from cancer.

8. Growth of the cancer cells is made possible by the activation of telomerase and the resulting change in telomeres (see above paragraph 5).

9. Cancer cells multiply faster than normal cells. There is plenty of literature on the mechanism of rapid growth of cancer cells so I need not dwell on it.

10. Cancer research has been probing into genes responsible for the accelerated rate of cell growth. In the recent years more research has been focused on the reasons for the deactivation of the so called "tumor suppressor genes" that control the process of normal growth.[55] Interesting in this connection is the mutation of the *p16* gene found in many kinds of tumors including skin, urinary bladder, breast, and kidney cancers. The forms of cancer in which the mutated *p16* gene is present exceed considerably the mutations of another recently discovered suppressor gene, *p53* (it was found in rectal and some other types of cancer).[56] The *p53* gene is semifunctional. It is geared toward halting cell division or even directing the cell to self-destruct if its DNA is damaged and the repair mechanism is unable to fix the problem.[57]

11. Cancer cells grow to form tumors which require an internal infrastructure. One of its components is the blood supply system. The same growth/inhibitory factors that contribute to the formation of a new vascular system in normal tissue support the formation of the blood supply system in tumors. What is pathological in this case is that this blood supply system contributes to the destruction of the organism.[58] (p. 124). It is still unclear whether organisms possess special mechanisms that prevent the formation of a blood supply system around dangerous growths.

12. Most tumors are not localized to a given organ. Cancer cells are capable of transmitting information to cells in other organs through the viruses they produce.[59,60]

Cells contain genes that turn on the mechanism which allows a cancer cell to leave the tissue and invade other organs via the blood/lymph stream.[61]

13. Metastasizing does exhibit certain patterns. Some forms of malignant tumors metastasize very selectively. Metastases are not blown around passively through the blood stream but take root only in receptive organs.[62] Reasons for settling in some tissues and not in others were discussed above in connection with the migration of "innovator" cells. With regards to metastases, it seem they take root in those organs that: 1) consume/supply ingredients to the organ where cancer originated and/or 2) are morphologically connected and/or 3) are formed sequentially as the genetic program unfolds. These considerations are purely speculative since I have no experimental evidence to support these hypotheses regarding the logic of the metastasizing process.

Finally, the presumably iterative nature of the process of coordination of changes induced by the somatic hereditary mechanism would cause metastasis to return to the original organ in the form of cells "enriched" with the newly acquired information or as cells of other organs that have been changed.

14. Another crucial variable is the ability (or rather inability) of the immune system to combat cancer, to check its devastating activity. Presumably there is a certain mechanism that weakens the effectiveness of the immune system, at least in so far as not to impede the emergence of dissident cells, including cancerous ones. Viewed in this light, the problem of combating cancer by strengthening the immune system takes on an added complexity. In the case of AIDS, it is possible to argue that the suppressers of the immune response have gained enough strength to make the organism helpless in resisting various pathogens. A correlation of AIDS and cancer points to a similar progress of immune deficiency with respect to cancer cells allowing them a chance to grow uncontrollably.[8] It cannot be ruled out that ultimately the immune system does not differentiate at all between cancer cells and innovator cells, although it is rather effective in recognizing foreign organisms based not only on the telltale features of their protein coats but also, as we now know, their DNA pattern (so far this feature is found limited to microbes and viruses). These results are based on the specific features of bacterial DNA and their impact on the immune system.[63]

Whatever the reasons for immune deficiency in combating cancer, many researchers have proposed strengthening the immune system with various drugs. Of speci al interest here is the pharmacological research conducted in the U.S by Steven Rosenberg at the National Cancer Institute and Hilary Koprowski at the Wistar Institute in Philadelphia.

The link between cancer and the immune system calls for further investigation. I have found it beyond me to enter the highly complex field of immunology. But I certainly hope to attempt this incursion in a not too distant future for in this book I have already sown the seeds of this investigation by presenting the analogy between society and the immune system.

To sum up our discussion I would reiterate that cancer represents a systemic disease that embodies the striving by all living creatures for change. The phenomenon involves radical deviants and the inability of the immune system to address them, i.e., to assimilate innovation. In other words, the damage is not caused by the appearance of newly formed radical cells but by the inability of the organism to assimilate them, i.e., to gradually integrate the cells' innovativeness, making it part of the general process of biological development. By analogy with social systems introduced in the previous chapters (hopefully it has helped elucidate the point) political systems incorporate a variety of programs including radical ones. The power of the extremists lies in their ability to propose new ways of development, to create ideals to be aspired toward, even if these ideals are unattainable. The weakness of the extremists is attempting to immediately achieve the set goals, perhaps unattainable altogether, and bypassing all the intermediate stages.[9] The development of a system as a whole requires that no extremist group be allowed to seize power. So the danger stems from the inability of the system to deal with radicals rather than their presence.[10]

General arguments aside, assuming that cancer represents a pathological manifestation of the somatic mechanism of change I have put together in the following table all the alleged stages of development of a normally changing, i.e., innovator cell, contrasting these stages with experimentally confirmed stages of cancer.

TABLE 9.1. Stages governing normal and pathological change in somatic cells.

Stages of change in the norm	Stages of cancer
1. The sources of change range from external factors such as chemicals, radiation, viruses to internal self-inducing processes.	1. The sources of change range from external factors such as chemicals, radiation, viruses to internal self-inducing processes.
2. It seems that the more pervasive the changes affecting the cell the less differentiated the cell must be in order to free itself of the forces suppressing the development of its diverse genetic capacities.	2. As a rule cancer cells are less differentiated although the spectrum is quite wide and includes regression to ancient forms.
3. The less differentiated cell alters its performance due to changes within its genetic structure or via the inclusion of new components into its genome.	3. The main reason for lesser differentiation of the cancer cell is the suppression of some of its genes. Cancer cells also form by incorporating new genetic elements, such as viruses, into their genetic structure.
4. The innovator cell strives for greater autonomy by simplifying its metabolism (anaerobic process supersedes oxygen intake), reducing the number of receptors linking it to other cells, etc.	4. Typically, the cancer cell becomes more autonomous in its consumption of nutrients and discharge of byproducts, radically simplifying its metabolism, reducing the number of receptors, etc.
5. The scope of changes in the cell is quite wide. Roughly we can distinguish three phases: minor changes, significant changes, and major changes.	5. The devastation caused by changes in the cell turned cancerous varies from benevolent tumors to metastasis.
6. Changes are implemented by different mechanisms, including telomeres, depending on the stage of cell development.	6. At the various stages of its development, including M1 and M2, the cancer cell undergoes change induced by the activation of telomerase and the resulting change in telomeres

7. The repair mechanism in a cell is possibly turned off when it encounters an innovation.	7. In cancer cells the repair mechanism fails to address, or is slow in doing so, the damaged segments of the DNA; it seems that the apoptosis mechanism also fails to perform.
8. Following its newly acquired specialization the cell begins to reproduce owing to telomere renewal.	8. Cancer cell growth is made possible by activation of telomerase and the resulting changes in telomeres.
9. The specialized cell must grow faster in order to affect the development of related cells.	9. Cancer cells also multiply faster than normal cells.
10. The presence of growth accelerating genes suggests the presence of growth-arresting genes.	10. In cancer cells the genetic growth-arresting mechanism malfunctions.
11. The changed cells begin to form new structures that require an infrastructure including the blood supply system.	11. Cancer cells form a malignant tumor with own infrastructure.
12. Methods of transmitting information to other cells include secretio*n* of genetic information as well as migration of the entire cell into other organs. In order for a cell to invade other organs there must be a mechanism of cessation from the living tissue of the host organ.	12. Most cancer cells are not localized to a given organ. They can transfer information to cells of other organs. There are genes in the cell that allow cancer cells to disengage from the host tissue and intrude into other organs through the blood or lymph stream.
13. The settlement pattern of a cell in other organs is probably not random.	13. There is method to the process of metastasizing.
14. In order for an innovator cell to fulfill its role each one must be to some extent "politically" independent, i.e., the immune system should not interfere too much with its development. Possibly, this task is fulfilled by special regulatory genes.	14. Disparity between the potency of the cancer cell and the immune system allows the former to develop. Purportedly AIDS involves intensified activity by the genes that block the immune system thus making an organism defenseless against all kinds of deviants.

Assuming the overall approach makes sense, I would conclude that the same process of change can be directed at creating new more perfect organisms as well as at destroying the existing ones. The implications in terms of program hierarchy (see Introduction) are the following: the first-level genetic programs (that change the zero-level program that forms an organism) for creating innovation are quite identical to the ones that destroy by means of cancer what is already there. The fact that normal genes and oncogenes responsible for change (that is belonging to the second-level program) are quite similar indirectly corroborates this speculative idea that has become commonplace in the biological establishment. Nonetheless, the mechanism underlying the interaction at various stages between the genes belonging to the first-level program and genes of the zero-level program is still obscure.[11]

Perhaps the difference in the genes responsible for the development of cells bearing constructive innovations or malignancies resides in the second-level program, the program which changes the first level program. The second level program is the main sanctuary for genes that cause excessive behavior on the part of cancer cells both in isolated instances of change (excessive loss of differentiation, rapid growth, propensity to invade other organs) as well as their general aggressiveness.

2. CANCER AS A PATHOLOGY OF THE MECHANISM OF CHANGE: SOME IMPLICATIONS OF THIS APPROACH

2.1. Cancer and Age

Strictly speaking cancer should be associated with the state of an organism rather than its age. Each particular case is different but a sufficiently large set of individuals will exhibit statistical patterns since age is strongly correlated with the state of an organism.[12]

Disorders in the mechanism of change vary depending on the stage of life.

During the embryonic stage when the focus is on the formation of an organism and there is much room for variation on organs, pathological changes in the genetic code are manifest, primarily in deformed fetuses, still-born babies, etc., rather than cancer.

During the stage of development but prior to puberty when growth is the characteristic feature, negative deviations in the mechanism of

change lead to deformities, but in much smaller quantities than at the previous stage.

The frequency of cancer may rise as the organism matures. This may be correlated with increased activity of the mechanism of change (under a very strong assumption that changes that have been initiated may be slowly getting ready to transform to the progeny via the germ cells). This process could be more pronounced in females; these observations agree with the fact that in girls cancer occurs at an earlier age than in boys.

At the stage of sexual maturity but prior to aging cancer is on the rise but disorders in the mechanism of change at this stage of one's life are not that common since both the mechanism of change and the immune system are still rather stable.

Old age predisposes toward break-downs of the still active mechanism of change associated with the organism's reproductive capacity as well as weakness of the immune system. As Vladimir Dilman mentioned, "... it has been statistically noted that frequently the reproductive function has been switched off later than usual in women who fall ill with breast cancer after menopause."[64] (pp.120-121)

In deep old age when sexual activity and its companion the mechanism of change decline rapidly, the frequency of cancer declines in spite of decreased robustness of the immune system. For instance, we observe a decrease in such widespread form of cancer as female breast cancer.

Frequency of cancer is strongly correlated with the aforementioned stages of the organism's development, and the highest rate of cancer cases corresponds to old, but not deep age. From 1972 till 1990 4,894 cases of death were diagnosed in the Tokyo Metropolitan Geriatric Hospital. A well defined tendency for the share of deaths from cancer to go down with age was found: among 60 year olds the percent of cancer patients was 50%; among 70 year olds - 47.9%, 80 year olds -43.2; and 39% among ninety years olds and older.[65].

I would say that my general hypothesis on cancer agrees with many empirical observations on the behavior of cancer cells under one very important qualification, that certain somatic changes can transfer to germ cells.

2.2. Cancer and the Sexes

Considerations expounded in the previous chapter concerning the role of the sexes raise interesting questions regarding cancer of male and female reproductive systems.

TABLE 9.2. Cancer frequency in male and female reproductive systems (US,1991).[66]

Organs for	Quantity	Sex	
		Males	Females
Production of germs	26,800	6,100	20,700
Ovary	20,700		20,700
Testis	6,100	6,100	
Delivery of germs and development of fetus			
Uterus	350,100	124,100	226,000
Breast	46,000		46,000
Prostate	175,900	900	175,000
Others	122,000	122,000	
	6,200	1,200	5,000
Total	376,900	130,200	246,700

As expected, changes in the female system lead to more cancers if only because of the greater complexity of the female reproductive system. Statistics shows that in 1991 in the US for 247,000 cases of cancer of female reproductive organs there were about 130,000 cases of cancer of the male reproductive organs.

My hypothesis seems to point to other differences in the cancer of male and female reproductive organs.

Let us examine the subsystem responsible for the production of germ cells.[67] For instance, ovarian cancer is significantly more frequent than cancer of its functional counterpart, the male testis. The chief cause for this discrepancy is that the somatic cells that have undergone change in other organs have a relatively easy time invading the ovaries, while penetrating the testis is practically impossible. Of course there may be many other reasons underlying the frequency gap between cancer of male and female organs and it is rather difficult to isolate and assign weight to the barrier factor, but it might prove to be a viable working hypothesis.

Statistics also shows that in 1991 there were 21,000 new cases of ovarian cancer and 6,000 new cases of cancer of the testis. If we take into

account the potential destructive power of the two types of cancer the difference becomes much more pronounced. For instance, that same year ovarian cancer resulted in 12,000 deaths and cancer of the testis caused about 400 deaths, a 30-fold difference.

Of course, ovarian cancer should not be equated with changes in the ova. By invading the ovaries cancer cells may change rather than destroy them, thus eventually (maybe after one generation) changing the ova. Cancer cells can invade the ova directly, thus destroying them. It would be interesting to explore how cancer cells alter the genetic structure of the ova. A similar investigation of the possible changes in the sperm could be conducted in those rare cases when cancer cells penetrate the testis.[68,69]

Table 9.2 seems to suggest that most types of cancer of the reproductive system strike the subsystem responsible for germ-cell delivery and fetus development. This is true for both men and women. However, male and female organs comprising this subsystem cannot be compared. Although male and female breasts are somewhat similar, they operate on rather different planes. So the observed quantitative gap between male and female breast cancer is not unreasonable.

The male organ most frequently afflicted by cancer (more than 90% of all cancer of the male reproductive system) is the prostate gland. In terms of numbers prostate cancer (120,000 cases) is of the same order of magnitude as female breast cancer (more than 175,000). I would like to show that these two types of cancer are not completely unlike.

We observe that the great majority of all cancers of the reproductive system (about 93%) afflicts the subsystem comprised of organs that accommodate germ cell movement as well as fetus development in females (including feeding the infant). I noted above that breast cancer prevails in women and prostate cancer in men. I would venture to say that these particular organs are most sensitive to the organism's response to changes in the environment and must implement changes in the respective organs that produce such ingredients as milk or fluid that protects sperm from its antagonist, the urine during the sperm's movement through the urethra. Moreover, considering the importance of these changes for the offspring, it is essential that these changes be transmitted quickly, perhaps even to the germ cells (directly or through other organs). This could explain why metastasizing starts early in breast cancer even when the tumor is relatively small. It would be interesting to compare breast cancer and ovarian cancer from this point of view.

2.3. Why are Not All Organs or All Organisms Susceptible to Cancer?

Statistics reveals that cancer does not strike all organs with the same frequency and, in fact, it varies by country and over time in the same country.

Naturally, external conditions, especially such factors as pollution, smoking habits, foods, etc. can trigger cancer.

All these geographic and dynamic differences not withstanding cancer exhibits certain universal frequency patterns. I would like to take an extreme case of certain cancer-free organs although adjacent organs that may be similar in tissue structure are stricken. For instance, cancer of the trachea is non-existent while cancer of the adjacent bronchii, i.e., lung cancer, is widespread. Another example is the duodenum. It is resistant to cancer that does invade the adjacent stomach and esophagus. If cancer starts in the stomach it moves upwards and if it goes downward it terminates at the duodenum. Cancer is also possible at the junction of the liver excretions with the duodenum.

These examples suggest the following very speculative conjecture: the less change experienced by a given organ over the course of evolution, the less prone it is to cancer. The notion that different organs have evolved differently is more or less an established fact.[70] In any case, this correlation between the changeability of an organ and cancer distribution by organs merits an investigation.

At the phenomenological level, if we consider an organism as a whole, biologists observed a certain correlation between organisms' changeability and the respective frequency of cancer. As Meckler points out, the tempo of evolutionary change in a given taxonomic class is correlated with the frequency of tumors it experiences.[71] For instance, marmoset monkeys evolved much faster than baboons and the former experience spontaneous tumors 4-6 times as often as the latter. Tumor frequency among rodents has the following distribution, in decreasing order: most frequent among mice, then rats, rabbits, and finally guinea-pigs. This distribution is correlated with the pace of evolution of these animals. Cartilagenous fishes are the slowest among vertebrates to undergo evolutionary change.

Correlation between the pace of evolution of the given species and tumor frequency is no proof that cancer is a manifestation of an impaired mechanism of change, but at least the two phenomena show positive correlation. It would be fascinating to study this link at the structural level to test whether this correlation underlies a true cause and effect relationship.

Especially interesting in this connection are certain species of much studied fish that have changed relatively little over time and experience very little cancer. I mean the sharks.[72]

We know that sharks have not changed much over the last 400 million years and cancer among sharks is practically unknown. Since shark harvest is rather large - about 5-7 million a year, scholars had an opportunity to verify these claims empirically. In fact, for many years researchers placed sharks in pools containing carcinogenic substances but tumors failed to materialize.

The reason for the sharks' resistance to cancer are unclear. But three factors do enter into the explanation.

The first is the cartilage rather than the bone skeleton of the shark. Its cartilage contains six or seven proteins that can prevent the formation of blood vessels (angiogenesis) to the organ (the cartilage itself needs no blood supply). In moving through the blood stream cancer cells prefer to move through new vessels, as they do not fare as well through the old vessels, and their growth requires an additional blood supply. Therefore, tumors frequently surround themselves with their own blood supply system.

The capacity of cartilage, shark cartilage in particular, to block the development of blood vessels, and in fact destroy blood vessels thus depriving the tumor of the blood supply and waste disposal, stirred some interest in using cartilage to make drugs. Its primary use is for cancer treatment, but it could also prove effective in helping treat arthritis, psoriasis, as well as some other ailments.

Quite possibly compounds found in cartilage affect the immune system: in any case cartilage-based drugs have proved effective in treating all kinds of inflammatory processes.

The second reason for the shark's "untouchability" is their extremely powerful immune system. Their wounds heal quickly and sharks are basically free of infections. Antibodies found in the sharks' blood combat bacterial and virus infections as well as protect sharks from all kinds of harmful chemicals that are lethal to many other kinds of mammals. Unlike the human immune system which is normally passive the sharks' immune system is constantly circulating ready to attack.

The third reason is the sharks' unusual capacity to prevent the activation of aflatoxin B_1 that stimulates cancer. Aflatoxin itself is a kind of forerunner to carcinogenic substances. When aflatoxin is excited it links DNA with these substances and the resulting compound may attack genes that would otherwise prevent the expression of cancer by cells.

It seems to me that all these safeguards that protect sharks from cancer have to do mainly with a very dormant internal mechanism of change combined with a highly stable and powerful immune system that can prevent or eliminate any change in the shark's organism.

Encouraged by the infrequency of cancer among sharks a number of scholars have expressed optimism regarding the use of shark cartilage in treating cancer. Their enthusiasm was not welcomed by biologists at large.

In October 1993 Tim Beardsley published a brief article "Sharks Do Get Cancer. Cartilage cure relies on wishful thinking."[73] The title itself implies that sharks' immunity to cancer is a pseudoscientific myth and cancer treatment with shark cartilage relies on wishful rather than factual data. The article dethrones the aforementioned book by W. Lane and L. Comac whose title Sharks Don't Get Cancer suggests just that and advocates cancer treatment methods using shark cartilage.

Beardsley referred to data provided by reputable scientific organizations that shows 20 registered cases of cancer in sharks, including shark cartilage. The authors of the targeted book do not deny that sharks get cancer, but it is very rare. The fact that 20 cases have been documented does not refute Lane's and Comac's basic contention. A more serious argument presented by Beardsley quotes John Harshbarger, director of the registry of tumors in lower animals at the Smithsonian Institution in Washington, D.C.: "data do not exist to determine whether sharks get cancer more or less often than do other creatures." However, evidence for the lower frequency of cancer among aquatic animals as well as the statistics gathered by Land and Camac does indeed support the claim that sharks are less predisposed toward cancer than other creatures.

Perhaps, the authors' enthusiasm in advocating cancer treatment with shark cartilage is indeed excessive. But Beardsley himself acknowledges that under certain conditions shark cartilage can be beneficial in treating cancer.

Beardsley also notes that The National Cancer Institute tested a number of venues of treating cancer using shark cartilage, but the results were less than promising. At about the same time that Beardsley's article appeared in Scientific American, Wall Street Journal published a report by Chrisn Frampton, "Alternative Medicine to Treat Cancer Undergoes Mainstream Study by NIH" (National Cancer Institute is part of National Institutes of Health). According to the report NIH will conduct research into the use of shark cartilage in cancer treatment. Evidently the data cited by Beardsley has not deterred NIH from conducting further research.

My critical attitude toward Beardsley's article is not meant to defend the proponents of shark cartilage treatment. Generally speaking, I

am not a big fan of alternative medicine if only because the scope of its application is not well defined. But what are we to do in the face of this devastating disease? We lack methods of treatment based on profound understanding of the malignant process as well as cures effective as far as practical treatment is concerned. Under the circumstance, alternative solutions that seem promising, or at least not harmful, should not be ignored!

3. QUASI HYPOTHESES STEMMING FROM THE MATERIAL PRESENTED IN THIS CHAPTER

I have formulated a number of quasi hypotheses amenable to experimental verification based on my definition of cancer as a radical pathological attempt to restructure an organism by means of the somatic mechanism of change.

These hypotheses that I have tried to corroborate throughout the present work are presented below:

1. Cancer is a disorder at the second level of a hierarchically organized internal mechanism of change (the zero level genetic program controls development, the first level program changes the zero-level one, and so on).

2. The frequency of cancer is directly proportional to the species' predisposition toward change and, inversely, to the defense afforded by the immune system.

3. Quite possibly, under the assumption that certain changes in somatic cells do transport to germ cells, cancer occurs most frequently during the period when the organism begins to age, but prior to deep old age. The reproductive system through which changes are passed on and which supports the mechanism of change begins to grow weak, but does not fade away completely as does the mechanism of change. The immune system which prevents the formation of pathological changes suffers a similar decline.

4. The frequency of cancer of specific organs is directly proportional to the organ's predisposition to change and inversely proportional to its defense by the immune system.

5. In one particular case of male and female reproductive organs that produce germ cells, the difference in the respective frequency of cancer stems from the functional role of the two sexes (male characteristics are geared toward assimilation of changing environmental conditions while

the female system is structured to accommodate major changes in the organism).

6. Metastasis take root in organs that are "suppliers/consumers" of the organ where the malignancy originates. The extent of infiltration depends not so much on the capacity of the vascular/lymph system to carry the cells but the scope of change demanded of the "consumer/supplier" organ. Another possibility is that organs susceptible to metastasis are morphologically linked. Finally, cancer may strike organs that are formed according to the sequential logic of the genetic program as it unfolds.

7. The process of change via the somatic cells incorporates a return of the messenger cell to its host organ; this holds for cancer cells as well. Therefore, even if cancer has disappeared from a particular organ, it can relapse because the emigrant cancer cell has come back rather than because new cancer has flared up, especially after the organ has undergone radiation, chemotherapy, or surgical treatment.

8. Assuming cancer cells are of a dissident type, rather than destroy these cells treatment should aim to limit the scope of their activity, possibly by isolating them temporarily. Under extreme circumstances when the danger posed by cancer cells is lethal and their profusion cannot be curbed, they must be removed from the organism.

NOTES TO CHAPTER 9

[1]. "We have studied HOX gene expression in several human tissues and organs as well as in their neoplastic counterparts. We have observed (a) characteristic patterns of HOX gene expression for each normal solid organ analyzed, (b) altered HOX gene expression in kidney and colon cancer, (c) a correlation between HOX gene expression and different histological types of primary small cell lung cancer (SCLC) and (d) marked alterations of HOX gene expression among primary and metastatic SCLC variant types. Furthermore, we have shown that differential patterns of HOX gene expression correlate with the adhesion profile (VLA-2, VLA-5, VLA-6 and ICAM-1) and N-RAS mutation in clonal melanoma populations isolated from a single human melanoma metastasis. This suggests that HOX genes act as a network of transcriptional regulators involved in the processes of cell to cell communication during normal morphogenesis, the alteration of which may contribute to the evolution of cancer."[74] pp. 38-49.

[2]. N.Vorontsov gives the following description of cancer at the chromosome level:
"In case of pathology, the rodents die as a result of papillomatosis disease before one year of age having bred several litters. Fixation of the macromutation of papillary structure of stomach as a specific character seems to be related to a shift of macrovilli formation to the early stages of ontogenesis, while the lethal effect of the neoplasm is shifted to the postreproductional period. Evidently, in this case the

macromutation fixation can be accompanied by a selection of variants submitted by heterochrony."[75] pp.53-54.

See also O. Oliveros, *et.al*. [76]

[3]. In children cancer is not strongly correlated with external factors. In adults many carcinogenic substances enter the system through breathing. At the same time cancer of nasopharynx is rare and cancer of the trachea is altogether unknown while cancer of the lungs is widespread.

[4]. If decreased differentiation merely involved cell *degeneration* to an earlier stage and was not accompanied by cell *rebirth* the natural approach to treating cancer at that particular stage would be to reinstitute the normal level of differentiation. The problem is how. Techniques used to treat trophic ulcer which involves disintegration of the tissue with no rebirth provide some clues. One method helps the tissue itself to recuperate. It was assumed that tissue "management" on the part of the nervous system appeared at a later stage of evolution and was thus limited to the more developed groups of tissues. These considerations suggested to the following methods of treatment. Roughly speaking, the links between the disintegrated part of the tissue and the nervous system were severed by novocain blockage and tissue feeding was done by a compress. When the process of tissue recovery warranted reconnection with the nervous system the Novocain blockage was suspended.

I realize the simplicity of this analogy for devising methods for treating cancer.

[5]. "A frequent characteristic of many malignant tumours is an increase in anaerobicglycolysis, that is the conversion of glucose to lactate, when compared to normal tissues."[77]

[6]. The quoted article reads: "In some ways many malignant tumours behave much like parasites, drawing upon the host for nutrients such as glucose and returning waste productssuch as lactate to the host for recycling or disposal." [78]

I prefer to call these cells criminals rather than parasites. Parasites do not generally ruin the host or force the host to process their waste (oftentimes parasites engage in beneficial activity). Criminals, on the other hand, not only seize things from the master and ruin him but may also force him to work for them or even murder him.

[7]. "The speculation that telomerase may play a role in human cancer is not new and has been discussed in a variety of contexts. However, a study by Counter, *et all* demonstrates that telomerase is activated in ovarian carcinoma. Their data indicate that expression telomerase and the resulting stabilization of telomeres may be important for the expansion of a human tumor."[79]

[8]. Higher correlation between AIDS and cancer was discovered in patients needing organ transplant. "AIDS patients and children with inherited immune deficiencies also have higher than expected rates of certain tumors, including some of the same cancers found in transplant patients."[80]

A particularly striking correlation between AIDS and Karposi's Sarcoma was discovered. "Approximately 15% of AIDS patients have the sarcoma, which makes it 20,000 times more common in the AIDS population than in the population at large."[81]

[9]. Assuming the cell with its "desire" to fulfill its biological potential forms the "epicenter" of a multi-cell organism there are a number of options for cells to

achieve this end. The option selected (manifest primarily in the "urgency" of cell action) depends on the type of cell. An analogy with society should clarify the point. Different social systems may eventually arrive at the same result aspired toward by many humanists: to ensure that each individual is able to fulfill his/her potential. Of course it is difficult to determine the minimum amount of money (subsistence level) needed to implement this goal. It varies in different countries and at different periods. But whatever this minimum level is history has presented us with many alternatives. One quality that distinguishes different options is the rate at which some minimum is to be achieved. This feature reflects the difference between communists, social democrats, and the bourgeoisie.

Communists content that the production capacities are sufficient for this goal to be attained *immediately* provided the chaos of the marketplace is conquered in the revolutionary manner, public property, plan, and income redistribution instituted.

Social democrats claim the goal must be achieved step by step. It should be actively pursued by the government through steep progressive taxes, nationalization, etc. Communists want to attain the goal quickly and by any means whatsoever, while for the social democrats the process itself becomes the crucial issue.

Competition based structure of a bourgeois society with the various political forces provides every human being an opportunity to realize his/her potential no less successful than in countries with social democrats in power (not to speak of the communists).

[10]. West German President, Richard von Weitzaker, in a speech on May 24, 1989, commemorating the fortieth anniversary of the establishment of the Federal Republic, said that in his country "The present generation of policy makers is made up of people who learned from history. This generation understands that the tragedy of Weimar was not that it produced too many extremists too fast, but that for far too long it had too few democrats."[82] p.153.

[11]. "Some of the cellular changes underlying the presentation of cancer in a patient can already be understood in terms of mutations affecting specific gene functions. So far, only a few of the mutated genes responsible for carcinogenesis have been identified and these are chiefly involved in deregulation of cell growth rather than with the processes of invasion and metastasis."[83]

[12]. An analogous situation arises with social security received upon reaching a certain age. All the practical complications aside, pension should be awarded based on one's condition, meaning the individual's ability to continue to work. However the problems involved in implementing this individualistic approach preclude its enactment.

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