Chapter 9
The Philosophical Quest of a Cancer Cell: Redefining Existentialism

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Abstract Poised in a seemingly prepared calm stasis with trust in the intangible, cancer cell makes decisions from a point where philosophy seems to be its major compass. As pure biological presuppositions cannot access or fathom this invisible philosophical realm of a cancer cell; syllogism rooted in scientific ratiocination alone without philosophical analysis will elude understanding of the objectivity of a cancer cell. Appreciation of this undiscovered unseen dimension (which is but a counterpart of the comprehensible visible), will unravel the deep interconnectedness between these two and provide insight far greater than empiric epistemology.

Introduction

In the same light employed by philosophical doctrine of existentialism to interpret the meaning of human existence; the existence and essence of "being a cancer cell" can also be analyzed. Immanuel Kant distinguishes the "*noumenon*" vs. the "*phenomenon*" or "the being-in-itself" vs. the "being-as-it-appears", to understand the realities behind appearances. While for Kant the phenomenon hides the "being-in-itself"; for Sartre, the phenomena do not mask being-in-itself they reveal it. As appearance involves a duality structure of showing, which connects it to the phenomenon; could a similar analogy be drawn to correlate the ontics and ontology of a cancer cell? Does the ontics of a cancer cell 'announce' or "mask" the ontological structures that underlie it? Does a cancer cell show itself in such a way (through replicative immortality, genetic instability, altered bioenergetics, immune evasion...) as to announce something else that does not show itself? Or is it 'something' else (such as deleterious tumor microenvironment) which does not show itself but appears through something which does show itself? Is cancer an "epiphenomena" or an "emergent effect" hidden beneath the mask of a phenomena?

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Sympathetic Understanding of a Cancer Cell's Philosophy

While being-in-itself (l'etre-en-soi) refers to essence or objectivity, being-for-itself (l'etre-pour-soi) refers to its existence or subjectivity. Since the "for-itself" lacks a predetermined essence, it strives to absorb "in-itself" in order to escape its own nothingness. What Jean-Paul Sartre brings out strongly by stating that 'Existence precedes essence' is that- first of all man exists, and only afterwards defines himself and *he will have made what he will be* [1]. Is it the strong desire of the 'for-itself' normal cell to become synonymous within the 'in-itself' that triggers the imposition of its subjectivity on the other's objectivity? What if it believes that there is no pre-established nature or essence that can set limits on what it can be or can do? Is the transformation into a cancer cell a mere reflection of the Promethean struggle against the conditions of its existence or an opposition against nihilism? Is it its urge to live for and through itself that makes it very existence an act of rebellion? In The Rebel Camus explains "In any event, the reasons for rebellion cannot be explained except in terms of an inquiry into its attitudes, pretensions, and conquests". Besides "rebellion though apparently negative since it creates nothing, is profoundly positive in that it reveals the part of man which must always be defended". Also " ... the individual is defined only by his relationship to the world and to other individuals; he exists only by transcending himself" Simone de Beauvoir. Therefore, to dissect the "raison d'etre" of a cancer cell not only requires sympathetic understanding of its philosophy but even deeper understanding of the tumor's normative social structures. As "philosophy can be used for anything, even for transforming murderers into judges" [2], this essay uses philosophy as the alibi of cancer cell to examine the arguments that it uses to sustain its identity and function despite the onslaught of oppression.

Acquisition of a New Language

Stressors are well recognized opportunistic windows that can compel a normal cell to become cancerous. Besides, "the spirit of revolt can only exist in a society where a theoretic equality conceals great factual inequalities" [2]. Does the rebel cancer cell confront these factual inequalities with its own principle of justice to establish theoretic equality? Are cancer cells victim of larger ideological, social, and existential forces? Can inequalities of conditions make a cell receptive to new influences that metamorphose it? Is the act of rebellion a demand for clarity and reassessment of condition which it refuses to accept? Does it stem from the innate desire to free itself from the totalitarian tutelage and to set up an open society free from the bondage of merely established laws? Does it stand for something of its own by denying passive submission to traditional authoritarian societal rules?

Awakened to the knowledge that obstacle can be transformed into opportunities, and aware of its latent inner power which only it can unleash; the cell swallows its past to reinforce its new existence. The newly acquired essence is one of sheer emptiness, a field of infinite possibility, of pure potential—a "tabula rasa"—an erased slate for

writing poetry in a novel language—the language of tumor. Writing on the uses of language, Russell states that "Language has two primary purposes, expression and communication .... Communication does not consist only of giving information; commands and question must be included ... It enables transactions with the outer world". The newly acquired language provides expression for its thoughts which would have otherwise remained private.

Cancer Cell's Ascendency—A Rebel's Fait Accompli

In "The Rebel" Albert Camus asks "What is a rebel?" To which he answers "A man who says no ... his no affirms the existence of a borderline ... Rebellion is founded on the categorical rejection of an intrusion that is considered intolerable ..... " Does the feeling of revulsion at the intolerable societal laws of bias and intrusion coupled with the innate desire to preserve the integrity of its being, trigger the act of rebellion? Initially, the rebel cell tries to adjust into the society by accepting conditions however unjust, in despair. Till this stage a delicate balancing-act of adjustment prevents it from disintegrating in the face of all odds, the cell remains benign and the society does not fear the rebel being detrimental to its equilibrium. However, the adjustment is constantly *in flux,* changing. Actually, it *is* a flux, since the *being* of the "for-itself" cell is not inert, but is an *event,* a *process.*

The society ignores these distress calls as random and meaningless. The cell confronts oppression in silence while trying to preserve the integrity of its being till it extends beyond the borderline of its tolerance. At this point it "demonstrates with obstinacy, that there is something in him which is worth while ... and which must be taken into consideration .... But from the moment the movement of rebellion begins, suffering is seen as a collective experience" ... "Rebellion's claim is unity ... is dedicated to creation so as to exist more and more completely" [2].

Social Engineering

But when was society tolerant to non-conformists? Society in itself is "a conspiracy against the manhood of each of its members, where self reliance is its aversion" Emerson. The society promotes synergy and symbiosis but abhors antagonism. Therefore, when the cell finally achieves that milieu where its ***"self reliance"*** is fully manifested, society becomes desperate to put a check fearing that the rebel will break normative law to become a criminal. The consequences being that the altruistic self destruction mechanisms of the cell are permanently lost, it turns from benign to malignant. This raises the question as to why the society had not attempted to iron out the indifferences at the first signs of appearance or even engaged in a balanced debate. Why was the societal law not executed and punishments inflicted at the first sign of upraise? But one could favorably argue for this rebel cell "a criminal cannot break

a law and that it is only broken only if the criminal does not receive the punishment prescribed by the law" [3].

This metamorphosis is thus a reflection of potentiality being actualized While struggling with itself it becomes committed to itself. At this stage it decides to no longer refer, defer, prefer, or suffer ..... *The rebel denounces the family name of "conformists*". In the process of transformation the cell develops an identity that emanates an aura of confidence which subsequently seduces others to join the cause. It convinces the others to analyze the principles of democratic social reconstruction—the principles of "piecemeal social engineering". Popper wrote "the piecemeal engineer will adopt the method of searching for, and fighting against, the greatest and most urgent evil of society, rather than searching for, and fighting for, its greatest ultimate good" [3]. The social engineer cancer cell does not question historical tendencies but believes that it is the master of its own destiny and can influence a change. If "genius is what a man invents when he is looking for a way out" (Sartre), then the cancer cell is undoubtedly a genius!!!

Evolution of Heterogeneity: Brilliant Orchestration and Mammoth Choreography

The capacity of developing tumors to escape immune control involves the process of cancer immunoediting which incorporates three phases: elimination, equilibrium and escape designated as the 'three E's'. In the first phase of immuno-surveillance, recognition of transformed cells by the immune system, leads to its elimination. However, cells that escape elimination enter the equilibrium phase where they may be either maintained chronically or immunologically sculpted by immune "editors" to produce new populations of tumor variants [4]. In Open state and its enemy Popper reasons "that the widely held prejudice that destruction or control of an aggressive state implies misery of subjugation of its individual citizen" is dangerous. Popper opines that harsh treatment by victorious state "is likely to give the aggressor state a chance for new aggression; it will also provide it with the weapon of the moral indignation of one who has been wronged" [3]. Thus, a rebel cell that escapes the arsenal of immuno-surveillance acquires weapon of increased resistance with which it evades subsequent immunological defense.

Sculpting of variants does not involve a rigid evolutionary pressure but rather dynamic and 'inter individually variable' factor [5]. The co-existence of genetically divergent tumor cell clones within tumors [6, 7] indicates that tumors are an extremely heterogeneous population consisting of the original rebel cell and its followers. Besides, intratumor heterogeneity also arises from convergent phenotypic evolution with multiple mutations in the same tumor-suppressor gene across different regions of the tumor [8]. Thus the sculpting force of the microenvironment delicately hews these variants from the parental rebel cell. 'I think therefore I am" (*cogito, ergo sum*)

metamorphoses into "I rebel- therefore we exist"- Camus [2]. The rebellion gain momentum.

Realizing its unique power as an archetypal renegade, each variant acquires its own modus operandi for strengthening and expanding the campaign against the exactions of an unjust system. The sense of solidarity, harmony and unshakeable commitment towards achievement of the core goal promotes an *espirit de corps* amongst rebels despite their individual variation and myriad personalities. Belief in the common philosophy, coupled with perspective of the present moment and foresight for the future propels the 'team' to victory. The rebellion is consummated and perpetuated in the act of real creation. This realization of vision manifested in mass proportion at multi-levels is the culmination of brilliant orchestration and mammoth choreography.

Organizing for Constant Change

Rudolf Virchow in 1863 had postulated that "chronic irritation which is manifested by chronic inflammation is a key promoter of cancer" [9]. Increasing epidemiological, pharmacological and genetic evidences clearly indicate that the mediators and effectors of inflammation are indispensable participants in tumor [10]. Malignant tumors often develop at the sites of chronic injury, and inflammation at these sites influences the processes of wound repair. However, unlike wound healing where inflammation is self-limiting, persistent unresolved inflammation in the local tumor microenvironment amplifies the response to support "wound overhealing" [11]. Tumors are rightly the "wounds that do not heal" [12]. As inflammatory tumor microenvironment plays a crucial role in the evolution of tumor, anti-inflammatory therapy targeting the local inflammatory milieu will be efficacious towards neoplastic progression [13, 14]. However, this will require better understanding of how the local "tumor promoting" inflammatory milieu regulates the fate of the "wounded cell" and nurtures its evolution towards a malignant one. Thus, what starts off as a single rebel cell ultimately culminates in rebels varying in mutations in "driver" genes. Since variants are not necessary identical in terms of its driver gene mutation, heterogeneity fosters tumor adaptation and therapeutic failure through Darwinian selection [8]. Importantly, many of these driver mutations can turn out to red herrings, distracting attention from the actual issue that instigated the cell to become rebellious in the first instance.

Tumor heterogeneity poses a great challenge for therapy [15]. This process is influenced by alteration in the microenvironment which dictates the selection pressure [16].

It is obvious that heterogeneity within a single tumor with respect to gene expression will affect several signal transduction pathways. Given that a number of driver mutations can co-exist with passenger mutation in these variants, heterogeneity coupled with complex signal interactions fans the flame of revolt. As with electrical grids that are interconnected through wide networks to provide multiple "redundant alternative routes" for power to flow should failures occur; the intricate network of

signaling pathways possibly act in a similar fashion to ensure spare that capacity is available in case of failure in another part of the network. Therefore, targeting one or a few pathways in this intricate web of signaling cascades runs the risk of switching on "alternative routes" at emergencies.

Ecological Niches: Template for Diversification

The physical tumor microenvironment composed of low oxygen and high acidity can expose a putative cancer cell to selective pressure by regulating changes in gene expression [17]. The regional selection pressure exerted by hypoxia and acidosis promotes rapid adaptation by triggering genetic alterations [18, 19]. Therefore understanding the microenvironmental factors and corresponding adaptive strategies the cell adopts to survive and flourish in its immediate ecological niche is crucial. Most importantly, selection pressure could promote or impede expression of different sets of genes among the rebel variants residing in different ecological niches, if those genes are linked to different fitness effects in different micro-environments. This further contributes to the intra-tumoral heterogeneity as rebel communities from different habitats are influenced by niche diversity and are shaped by the prevalent ecological factors. The coexistence of different ecotypes indicates that expansion into alternative niches and extinction from others can occur over evolutionary time.

As niche-specific selection pressure affects the responsiveness of different ecotypes to chemotherapy, the choice of therapy would be difficult to predict. To maintain a dynamic equilibrium between change in its ecological niche and continuity, tumor cells not only adapt to but also survive the deleterious microenvironments. By envisaging a future that already exists, the rebels hone their intelligence information system in a way that variations in its niche pose little surprise. Like social engineers the rebel variants analyze and understand the immediate social system, so as to arrive at appropriate decisions based on careful evaluations and objectivity.

Toll Booth Strategy: Acquistion of Impenetrable Position

Writing on the economics of innovative strategies Peter Drucker state that the entrepreneurial "toll-booth strategy" allows an innovator to establish a virtual monopoly in its small niche thereby creating a product that is indispensable for a larger process. Similarly, by exploiting the incongruity of its immediate ecological niche the innovative rebel cell utilizes the "toll-booth strategy", not only to succeed but also acquires an invincible position. Since evolutionary specialization for one particular micro-environment is concurrent with ecological dependency, these ecological dependencies can serve as important anti-tumor targets. However, this may be complicated by the fact that coevolution can occur where the specialized phenotype and its ecological niche influence each other's evolution. As evolution in each niche can

proceed in unpredictable pathways it invokes heterogeneity by regulating balance between extinction, survival and dispersal. The importance of tumor microenvironment in evolution of cancer can be compared to ways inherent characteristics of different soil types dictate edaphic-driven diversification. Since ecological diversity is important driver of tumor heterogeneity, and as rebel cell exists only in contemplation of the whole system; understanding selection forces in its ecological niche that contribute towards its adaptation, growth and adjustment will elucidate strategies for constraining its survival and evolution.

Delineation of Novel Therapeutic Principles on The 'Communicative Resolution' of Existentialist Considerations

A malignant cell is the obvious sign that something is off balance in the system. It's the tip of an iceberg whose base lies deeply buried underneath its apparent expression. The manifestation of malignancy is the mere reflection of the inner state of the cell ... an expression of its hurt and deepest feelings. It would therefore be a mistake to treat any rebellion as a generic situation comprised of a series of familiar events. Therefore, rather than forcefully eradicating or suppressing the end-stage symptoms, understanding what triggered the off-balance and offering a blueprint by which the rebel cell can heal its hurt from within would establish *status quo –ante*. While the former generalizes, the later is an effort to understand the meaning of contingent and unique *phenomena*. Tumor progression is a process of Darwinian evolution involving natural selection in its natural ecosystem. The classic Darwinian evolution process is commonly studied by nomothetic, mostly reductionist methods. These methods are sufficient to describe an evolution history, but do not contribute to an evolution theory, which should explain the 'metabolism' of evolution. As nomothetic explanations are probabilistic, the problem remains unsolved. However, as idiographic approach specifies and focuses on casual relationships it might stimulate empathy to secure greater understanding of the cause of rebellion.

The Idiographic Therapeutic Method

The prerequisite of the idiographic method will therefore involve the analysis of the timely and spatially unique phenomenon of a tumor in a patient. This approach will raise the following questions (i) how are normative structures, functions and decision maxims (tumor-immanent normative notions) physically and situatively organized (rationalized)? (ii) what is the novel situative validity and denotation of tumor systems participators in a respective communicative context, which evolved during 'social engineering'? By answering these questions, we may achieve systematic and reproducible parameters which will provide the basis for stratifying therapy and for guiding therapeutic approaches (adaptive trial designs).

While switching research methods to systematic idiographic considerations, we must acknowledge that communication adheres to rules and is not arbitrary. By uncovering the communication-derived rules, we may reconstruct the rebel's intentions (normative notions) and how these are physically organized (rationalized). This way, we learn more about the rules of communication and communicative expression among systems participators in a tumor system (serum proteome and miRNA analytics, molecular imaging of 'hallmarks' of cancer). Further, we anticipate that systems participators gain novel validities and denotations within evolutionary processes (social engineering), and that 'corrupt' rationalizations of normative notions are permissible.

Expressive, Objective and Appellative Communications

Habermas points in Pragmatics of communication that to engage in a successful communicative act, both the speaker and the hearer must share the goal of reaching mutual communicative understanding. To improve communication, exchange of information should not only convey the intentions and/or subjective experiences of the speaker to indicate the states of affairs but also establish relations with the hearer. The rebellion can be resolved on a communicative level, even though it may result in 'corrupt' rationalizations (organizations) of tumor-immanent normative notions and in 'bellum'. Since the neglected aspect of the rebel self is seeking recognition, it is not "instruction;" but rather the "negotiation" that might change its attitude of aggression and enable it to adopt a state of co-operation. In the absence of resistance the tenor of antagonism will diminish.

Complex Equations: Mantra for Modern Therapy

"Lasting peace can come only if we consider fully the 'underlying dynamic force' that may produce war or peace" [3]. Importantly, war is not a phenomenon and neither all wars have the same contributing conditions. The rebel cell is just a seed groping in the dark soil, establishing and spreading its roots while surmounting obstacles to reach the surface. Its manifestation is the *triumph of its principles* and establishment of its identity. The conventional "Pruning the leaves and branches therapy" will therefore not only results in thicker foliage but facilitate deeper penetration of the roots into the soil. This is manifested by the so-called "dandelion phenomenon" of recurrent malignancy following a complete response to chemotherapy [20]. The conventional cancer therapies is analogous to cutting dandelion like weed off at ground level to eradicate the visible signs of the disease. Though apparently gone, the root remains and the cancer re-grows often with renewed vigor. We cannot attribute the root to the tumor microenvironment or the tumor cell. The '**root**' is the situative communicative process which adheres to communication-derived rules and is therefore accessible for therapeutically implemented non-normative boundary conditions.

Therefore, finding that "root value" which when substituted for the unknown element in the complex equation of evolutionary cancer dynamics will satisfy the equation. Since this equation is not simple linear but simultaneous equations ranging from functional to transcendental to parametric, multiple equations exists with multiple unknowns. As assignment of one value to all the unknowns will not solve the equations, understanding the philosophy of cancer cell will require explicit consideration of the edaphic conditions of its geographical landscape that serves as the ultimate template of its fruitification.

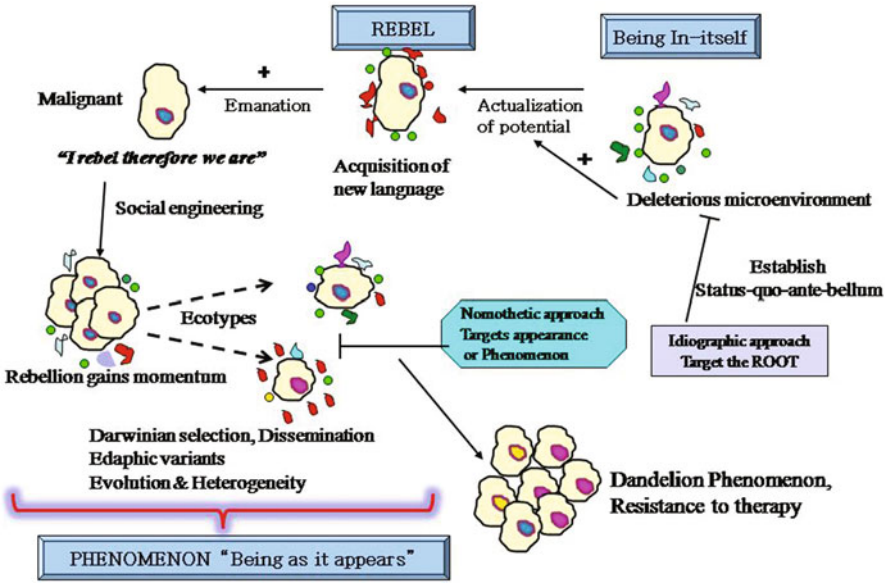

Figure Legend

The normal cell constantly adjusts to stressors in its ecological niche. To express its repugnance towards a society where theoretic equality conceals great factual inequalities, it acquires a new language- the language of a rebel. Denouncing the family name of conformists, the social engineer emanates and the rebellion gains momentum. Darwinian selection increases the rate of evolution. Dissemination of rebels into different ecological niches gives rise to eco-types that adapt to the edaphic condition of its immediate landscape. This contributes to intra- tumor heterogeneity. The conventional nomothetic "pruning therapy" targets this "being-as-it-appears" or "the phenomenon"; subsequently resulting in resurgence with renewed vitality and resistance. Idiographic approach aimed towards sympathetic understanding of the root cause will establish status-quo-ante. Different shapes outside the cell indicate different components of the micro-environment.

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