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Aneuploidy theory explains tumor formation, the absence of immune surveillance, and the failure of chemotherapy

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Abstract The autocatalyzed progression of aneuploidy accounts for all cancer-specific phenotypes, the Hayflick limit of cultured cells, carcinogen-induced tumors in mice, the age distribution of human cancer, and multidrug-resistance. Here aneuploidy theory addresses tumor formation. The logistic equation, $\phi_{n+1} = r\phi_n(1 - \phi_n)$, models the autocatalyzed progression of aneuploidy in vivo and in vitro. The variable ϕ_{n+1} is the average aneuploid fraction of a population of cells at the $n+1$ cell division and is determined by the value at the nth cell division. The value r is the growth control parameter. The logistic equation was used to compute the probability distribution for values of ϕ after numerous divisions of aneuploid cells. The autocatalyzed progression of aneuploidy follows the laws of deterministic chaos, which means that certain values of ϕ are more probable than others. The probability map of the logistic equation shows that: 1) an aneuploid fraction of at least 0.30 is necessary to sustain a population of cancer cells; and 2) the most likely aneuploid fraction after many population doublings is 0.70, which is equivalent to a $DNA_{index} = 1.7$, the point of maximum disorder of the genome that still sustains life. Aneuploidy theory also explains the lack of immune surveillance and the failure of chemotherapy.

1. Introduction

The origin and nature of cancer has been one of the great enigmas since the time of the Egyptians and Greeks. The central paradox is that tumors are us and yet not us. The hundreds of different types of cancer are distinguishable in their details, yet they all display the global or macroscopic characteristics that readily identify them as cancer: anaplasia, autonomous growth, metastasis, abnormal cell morphology, DNA indices ranging from 0.5 to over 2, genetic instability, the high levels of membrane-bound and secreted proteins responsible for invasiveness and loss of contact inhibition, multidrug-resistance, and the exceedingly long times of up to decades from carcinogen exposure to the appearance of cancer.

Since Hansemann [1] first observed chromosomal abnormalities over a hundred years ago in all of the epithelial cancers he investigated, an overwhelming body of evidence has established an inseparable connection between cancer and aneuploidy [2–5]. By 1969, Albert Levan was confident enough to say that, "there is safe evidence that carcinogenesis, as well as all stages of malignancy, is accompanied by chromosomal irregularities . . ." [6]. But he went on to add that, "nothing is known, however, as to the significance of these chromosome irregularities in relation to the carcinogenic transformation." In other words, he raised the perennial question: Is chromosomal imbalance (aneuploidy) a cause or consequence of cancer?

While leaving the question open, Levan acknowledged that aneuploidy satisfies at least one requirement of a cause: "Chromosome variation is an integrated part of tumor development from the earliest beginning of carcinogenesis to the latest progressive stages. Even before any malignancy has started chromosome variation in a normal tissue is generally associated with an increased tendency to cancer" [6].

Recently, we revived Theodor Boveri's somatic mutation theory [7] and have directly addressed the question of whether aneuploidy is the cause or a consequence of cancer. We [8–11] and others [12] have provided evidence that an imbalance in the number and composition of chromosomes (aneuploidy) is the underlying cause of cancer and is sufficient to explain all of the characteristic phenotypes and properties of cancer.

Here is shown: 1) how carcinogenesis is the process of aneuploid cells self-organizing themselves into a tumor; 2)

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that cancer and immunity cannot be connected; 3) that cancer therapies directed at specific genes and gene products are doomed to fail; and 4) the aneuploidy theory implies reinvigorating old strategies of cancer prevention and therapy.

2. Results and discussion

2.1. Carcinogenesis is a self-organizing process, from the microscopic to the macroscopic

Most cancers appear to begin with undifferentiated epithelial cells at the boundary between two cell types [13]. Differentiation is a bifurcation process where the normal diploid cell "chooses," for example, to become either a squamous cell or a glandular cell [14]. Aneuploidy introduces an additional bifurcation of the developmental course of a cell. Once a cell becomes aneuploid, its offspring irreversibly head toward either almost certain oblivion or very rarely cancer. It is the progression to cancer that is of interest.

A population of aneuploid cells tends to experience a net gain in genetic material because a loss of gene dose is more deleterious than a gain [10,12,15–17]. The survival advantage of the hyperploid cells, coupled with the inherent genetic instability of aneuploid cells, leads to the autocatalyzed progression of aneuploidy with each cell division [10,11]. But the gain in DNA content of the aneuploid cells is constrained by the negative feedback growth kinetics.

Because aneuploid cells are damaged cells they generally do not survive in competition with dividing diploid cells [15,18], especially if the genetic imbalance is far from normal. The viability of aneuploid cells falls off sharply as the aneuploid fraction, ϕ, of the genome increases [12,16]. Therefore, aneuploid cells become less viable with each cell division. How, then, do aneuploid cells avoid oblivion as they progress toward the even greater genetic imbalance of mature cancer cells?

Fortunately, most aneuploid cells do not survive and reach the macroscopic level of a tumor. But there is certainly a route from the low level aneuploidies, commonly referred to as near diploid aneuploidy, to the hypertriploid to hypotetraploid cells of invasive cancer [19].

Oksala and Therman [20] have described numerous routes to the production of polyploid cells. Because pure tetraploid cells (i.e., exactly four copies of each chromosome) have a balanced genome they are phenotypically normal and thus quite viable. Tetraploidization doubles the genome content of near-diploid aneuploid cells, which allows them to make the leap to DNA indices above 1.5 and yet retain the viability of the near diploid state [10,21].

While the near-tetraploid aneuploid cells initially have the same small degree of chromosomal imbalance of their near-diploid former lives, after many cell divisions the level of chromosomal imbalance will have grown to a significant fraction of the genome due to the autocatalyzed progression of aneuploidy [10,11]. But because the DNA content of an aneuploid cell is constrained by the negative feedback of the growth kinetics as the aneuploid fraction increases [11], the near-tetraploid cells readily lose chromosomes as the cells continue to divide [19,21–24]. Tetraploid cells more readily survive the loss of genetic material than their diploid precursors because of the redundant chromosomes.

Because cancer only becomes a problem at the macroscopic level, the production of a few near-diploid or near-tetraploid cells does not make cancer. In order for these cells to progress toward invasive cancer requires the production and maintenance of significant populations of aneuploid cells. For example, a 1-gram tumor contains 10^8–10^9 cells, which requires more than the expected 30 cell divisions because of the high death rate of tumor cells in vivo [18,25]. Once a substantial population of viable aneuploid cells has been established, the process of polyploidization can produce "overtone" populations (2, 4, 8 . . . 2^n times the genome) of viable aneuploid cells with DNA content up to the octaploid level and above [26]. With each doubling of the aneuploid genome, the spread in the DNA content of the aneuploid cells gets broader and broader [26]. The presence of aneuploid cells with very high DNA content is a clear sign of advanced cancer [26–28] because they could only have come from well-established aneuploid precursors in the DNA index range of 1.5–2 (See Section 2.2.).

2.2. Self-organization of aneuploid cells leads to tumors

> "The chromosome variation in malignancy is of a specific kind: it generally oscillates around average karyotypes, and each cancer cell population is characterized by one predominant karyotype, the stemline karyotype, and in addition often one or more sideline karyotypes. After long periods of progression, tumors of many different kinds tend to converge towards a vaguely uniform karytopic pattern." *Albert Levan* [6]

Normal tissues are made up of countless diploid cells with characteristic and reproducible properties that form an organized structure that spans the tissue. Cancers, however, are made up of a mass of autonomous aneuploid cells, no two of which are genetically alike [10,29,30]. Aneuploid tumor cells behave like a coherent beehive of single-cell organisms [6,8,11]. The coherence makes them pathogenic. What is the source of the coherence? How do autonomous aneuploid cells organize themselves into a tumor beehive?

Complexity theory addresses, among other things, the process of self-organization. A self-organizing system spontaneously creates a globally coherent pattern out of the local interactions of initially independent components. A self-organizing system has properties that are emergent if they are not intrinsically found within any of the parts (e.g., an individual gene or an individual aneuploid cell) and exist only at a higher level of description (e.g., an aneuploid phenotype or a tumor mass).

Typical features of self-organization include: 1) absence of centralized control; 2) evolution over time; 3) fluctua-

tions; 4) symmetry breaking or loss of freedom; 5) instability; 6) self-reinforcing choices; 7) multiple equilibria; 8) thresholds; 9) global order; 10) energy usage and export; 11) insensitive to damage; 12) self-maintenance; 13) adaptation; 14) complexity; and 15) structural hierarchies [31]. These general features of self-organization are characteristic of carcinogenesis and tumor formation.

Self-organizing systems by definition organize in the absence of external direction. A dynamical system of dividing aneuploid cells can spontaneously move from a disorganized state toward the more organized state called an attractor of the system, which in this case is a tumor. An attractor is a preferred position for a system, such that if the system is started from another state it will evolve until it arrives at the attractor and will stay there in the absence of other influences. A DNA index around 1.7 is an attractor for many cancers [23,32].

Previously, we have shown that equation 1 models the autocatalyzed progression of aneuploidy [11]. The variable ϕ (range 0–1) is the fraction of the genome, as described previously, which is out of balance (aneuploid) relative to the euploid state. The term $1-\phi$ represents the fraction of the genome that is not aneuploid. The control parameter, r, is unitless and is a measure of the strength of the nonlinear growth of ϕ. Equation 1 shows that the average aneuploid fraction, ϕ, of a population of cells at the $n+1$ cell division is determined by the average level of aneuploidy at the nth cell division [11]. The growth control parameter, r, is shown below to play a key role in carcinogenesis and the self-organization of aneuploid cells into a tumor.

$$\phi_{n+1} = r\phi_n(1-\phi_n) = r\phi_n - r\phi_n^2 \quad (1)$$

Equation 1 is the well-studied logistic equation [11,33] used here to describe the progression of aneuploid states as the growth control parameter, r, increases (Fig. 1). The dynamics of a self-organizing system are typically nonlinear because of positive and negative feedback. Since an analytical description of the nonlinear dynamics of equation 1 is impossible, the best we can hope for is a statistical theory that predicts the likelihood of the variable ϕ taking on any particular value [33].

Following an induction period of slow growth, the positive feedback term $r\phi_n$ of equation 1 eventually leads to an explosive growth in aneuploidy [11], which ends when all the aneuploid cells have been absorbed into the attractor states of DNA indices between 1.5 and 2 that are characteristic of cancer [23,32]. The same process governs the progression of aneuploidy and determines the DNA index attractor values of cells at the higher multiples of genome doubling. Once in the attractor, the aneuploid cells are controlled by the negative feedback term, which allows for the relatively smooth evolution toward the equilibrium state at $\phi=0.7$ (Fig. 1). We have shown previously that after a large number of cell divisions $DNA_{index}=1+\phi$ [10,11]. Therefore, the attractor centered at $\phi=0.7$ of Fig. 1 corresponds to the attractor at $DNA_{index}=1.7$.

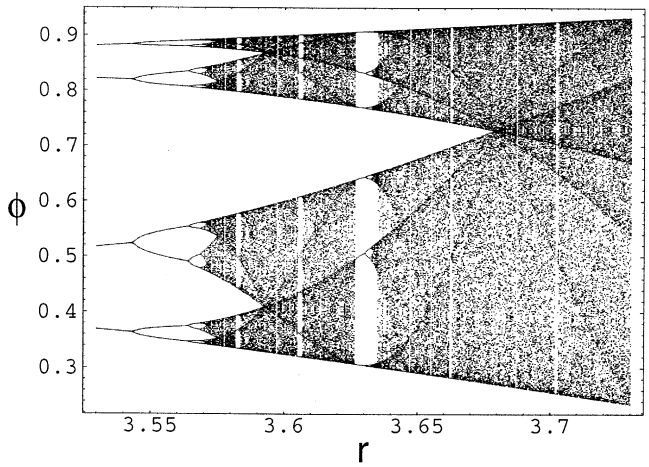

Fig. 1. The auto-catalyzed progression of aneuploidy leads to cancer. Equation 1 was iterated to generate a map of the probability that after numerous divisions cells will have particular values of the aneuploid fraction, ϕ, for various values of the growth control parameter, r. At relatively low values of r, the aneuploid states bifurcate until r reaches the critical value of 3.57, beyond which the progression of aneuploidy becomes chaotic. The denser regions of the probability map represent the more likely values of ϕ. Aneuploid cells evolve toward the attractor readily visible at $r=3.68$ and $\phi=0.7$ ($DNA_{index}=1.7$). At values of $r > 3.68$, the aneuploid cells become less coherent as their genomes become too disorganized and chaotic to sustain viability. That's why mature cancers tend to have DNA indices near 1.7 and its overtone multiples—they have evolved to the point of maximum disorder of the genome that still sustains life. Equation 1 was iterated 300 times using the Mathematica program by Wolfram Research, Cambridge, MA. Only the last 200 points for each value of r (450 values of r) were plotted.

Fig. 1 is a map of the probability that after numerous divisions cells will have particular values of the aneuploid fraction, ϕ, for various values of r. At relatively low values of r, the aneuploid states of Fig. 1 bifurcate until r reaches the critical value of 3.57, beyond which the progression of aneuploidy becomes chaotic [11,33]. Nevertheless, even in the midst of chaos there are regions of order represented by the dark streaks in Fig. 1, which mark the upper and lower boundaries and crisscross the chaotic domains. The intersections of the dark streaks correspond to crises in the chaotic dynamics, where disjoint intervals of chaotic regions collide to form larger regions [33]. The most spectacular crisis is readily visible at r=3.68 and $\phi=0.7$ ($DNA_{index}=1.7$).

The "order in chaos" that is apparent in Fig. 1 plays an important role in delineating the range of the long-term viable values of the aneuploid fraction, ϕ, and the structure of the statistical descriptions [33]. The denser regions of the probability map represent the more likely values of ϕ. The probability density is greater for values of ϕ above 0.7 than below. Therefore, one would expect near-tetraploid aneuploid cells to be the more common precursors of invasive cancer. The dark streaks represent values of ϕ that are most probable and visited more often as the cells evolve toward the attractor at $DNA_{index}=1.7$. The attractor of the next higher overtone is

centered at $DNA_{index}=3.4$ (i.e., $2 \times 1.7=3.4$) [26]. At values of r greater than 3.68 the dark streaks diverge and the probability density thins out. Therefore, beyond $r=3.68$, the aneuploid cells become less coherent as their genomes become too disorganized and chaotic to sustain viability. That's why mature cancers tend to have DNA indices near 1.7 and its overtone multiples—they have evolved to the point of maximum disorder of the genome that still sustains life.

Paradoxically, the basic mechanism underlying the self-organization of a population of aneuploid cells into a coherent tumor mass is the random, or entropy-driven, variation inherent in each cell division. Every time an aneuploid cell divides, the genome is scrambled and becomes more disorganized than before. In other words, the entropy of the genome increases with each cell division, causing r to increase in an iterative process ending at the attractor at $\phi=0.7$. Therefore, as aneuploid cells divide, r is not really a parameter but actually a time-dependent variable that is driven by the increase in the entropy of the aneuploid cells. In the chaotic domain, the variable r governs not only the growth in the aneuploid fraction, ϕ, but also increases as the entropy of the aneuploid cells increases. As the value of r increases toward greater entropy, the dark streaks converge to the attractor at $\phi=0.7$ ($DNA_{index}=1.7$), where the values are most dense, i.e., the probability greatest [11]. One of the important consequences of the continued presence of a carcinogen is the acceleration in the growth of r [11,34].

Albert Levan has pointed out, "The fact that the chromosome variation in tumors is never haphazard but gathers around stemlines and sidelines is compatible with the idea that the development in each tumor takes place according to an evolutionary pattern: the most viable karyotype prevails at all times" [6]. In keeping with Levan's idea, there are values of the aneuploid fraction, ϕ, that are compatible with the long-term viability of aneuploid cells and values that are not. Specifically, for values of r up to the viable limit of disorder at $r=3.68$, no significant long-term populations of cells having an aneuploid fraction below $\phi\approx0.3$ ($DNA_{index}=1.3$) or above $\phi\tilde{}0.9$ ($DNA_{index}=1.9$ and corresponding overtones) are expected. These limiting values of ϕ represent the threshold values of aneuploidy leading to cancer. This result is consistent with the range of 60 to 90 ($\phi=0.30$ to $\phi=0.96$) chromosomes observed in mature human cancer [19]. While the limiting values of ϕ remain the same for all of the genome doubling overtones, the limiting DNA indices increase and the distributions of cells on both sides of the peaks broaden [26].

Once a population of aneuploid cells has entered the attractor centered at $DNA_{index}=1.7$, the freedom of the individual aneuploid cells to act independently and evolve to a different attractor is restricted to the overtone multiples. The restriction to limited values of DNA content is equivalent to an increase of coherence, which defines self-organization (tumor beehive) and causal closure [35]. Closure sets the tumor apart from the host, defining it as an autonomous new species of obligate parasite [8].

2.3. Immunity and cancer are not connected

> "A surprising argument used in some of the reviews dealing with immune surveillance is based on the assumption that in any information transfer system, such as somatic cell replication, there are inevitable errors, and neoplastic transformation therefore must be frequent. The argument is made that immunological surveillance must be efficacious or overt clinical neoplasia would necessarily be more frequent than it actually is. This circular argument also includes the assumption that frequent accidents of somatic cell replication produce neoplastic variants that are invariably antigenic and thus can be rapidly eliminated by the immune system." *Osias Stutman* [36]

The idea that the clinical course of cancer depends on whether or not a tumor's potential for unrestricted growth wins out over inherent host defenses is 200-years old [37]. A modern formulation of this view known as the immune surveillance hypothesis of cancer was advanced by Burnet [38] and Thomas [39]. The main assertions of the immune surveillance hypothesis are 1) most tumors are antigenic; and 2) such antigenic differences can "under appropriate conditions" provoke an immune response [40].

Based on this thinking, in the late 1950s Jonas Salk attempted to stimulate the immune systems of terminally ill cancer patients by injecting them with what he thought were monkey heart cells. He had hoped that the patients' activated immune systems would attack the cancer cells. However, in 1978 Salk revealed that he had not injected the cancer patients with monkey heart cells but mistakenly with HeLa cancer cells [41]. The cancer patients' immune systems did indeed become activated and functioned well enough to eliminate the small tumors formed at the sites of injection of the HeLa cells within 3 weeks, never to return. Yet the activated immune systems of these same cancer patients were not effective against their natural tumors.

It is not the purpose here to rehash the exhaustive analysis of, and compelling arguments against, the immune surveillance hypothesis [36,42,43], but simply to add that the aneuploidy theory provides additional support for the view that there is no significant connection between cancer and immunity.

Cancer is us because it is derived from our own genome. What makes cancer cells not us is that they have rearranged our genome to differ from their diploid predecessors in both the number of chromosomes and the dosage of thousands of genes. Since there are no new genes, and no cancer-specific mutant genes, and no new chromosomes (except hybrid or marker chromosomes) in cancer cells [8], there is little or nothing for immune surveillance to monitor. This is especially true for the earliest stages of carcinogenesis where the immune surveillance mechanism is supposed to be most effective but the aneuploid cells are least abnormal. Even if an aberrant antigenic cell happened to result from the chaotic scrambling of the genome, the immune system could be expected to eliminate it, while the vast majority of aneuploid

cells remained invisible to the immune system. Therefore, even in principle, there is no possibility of an immune surveillance system guarding against the appearance of cancer cells.

2.4. Drug resistance is an inevitable consequence of aneuploidy

> "It is true that during certain periods, the stemline may become less predominant, for instance after drastic environmental changes . . . but if the population survives long enough, a definitive stemline will again form." *Albert Levan* [6].

> "There is disbelief when I try to convey gently the sad truth that in 1998 the impact of gene-based therapy is zero and of biological treatment is minimal." *Ian Tannock* [44].

> "After decades of intensive clinical research and development of cytotoxic drugs, there is no evidence for the vast majority of cancers that chemotherapy exerts any positive influence on survival or quality of life in patients with advanced disease." *Samuel Epstein* [45].

The simple strategy of chemotherapy is to kill as many cancer cells as possible without killing the patient. But a 1-gram tumor is composed of 10^8–10^9 cells. If a drug kills 99.9% of the cancer cells, that still leaves 10^5–10^6 cancer cells, which "will escape clinical and radiological detection but will be a few hundred micrometers in diameter" [44]. Since the fractional cell survival after an entire course of adjuvant chemotherapy is about 0.01 [44], chemotherapy doesn't even come close to eliminating cancer cells.

A fundamental misconception is that there are anti-cancer drugs. The drugs used to treat cancer are actually antiproliferative drugs that target the same DNA and RNA synthesis, microtubule assembly and function, and topoisomerases required by normal cells, especially rapidly proliferating normal cells [44]. It is not surprising that these drugs are quite toxic.

To get around the high toxicity of the current crop of chemotherapeutic agents, efforts are now being directed toward developing drugs that possess greater specificity for cancer cells. Nevertheless, the problem remains of identifying cancer-specific targets. But as Hansemann said, "[cancer] displays no characters absolutely and completely lacking in the mother cell" [46]. The only hope, then, of finding a cancer specific target for drug development would be to determine if there are essential genes expressed in cancers that are not as critical in normal tissues. None has been identified to date. Even if a new drug target is discovered, it will likely be rendered ineffective by the rapid appearance of drug resistant cancer cells.

The gene mutation hypothesis is hard pressed to explain drug resistance, especially the appearance of multidrug resistance after exposure to a chemotherapeutic drug targeting a specific gene product. The aneuploidy theory, however, explains and even predicts the rapid appearance of drug resistance [8,47]. Indeed, recently chromosomal reassortment due to aneuploidy has been demonstrated experimentally to produce rapid drug- and multidrug-resistance in Chinese hamster cells [47].

The collective order described of a tumor's aneuploid cells protects it from perturbations. This robustness is achieved by the distributed or redundant control provided by the myriad of unique metabolic solutions produced by each individual aneuploid cell. Thus, drug- or radiation-induced death to the susceptible part of a tumor can be replaced by the remaining, undamaged aneuploid cells.

The aneuploidy theory of cancer shows that it is unlikely that essential cancer-specific genes exist [10]. As with normal cells, there are essential gene products for each individual cancer cell. However, there is a profound difference between normal and cancer cells. Normal cells of a particular type and from a particular tissue express a consistent ensemble of essential genes. Cancer cells, however, comprise a heterogeneous mix of heteroploid cells expressing perhaps an uncountable assortment of essential genes [10,29,30]. Many cancer cells express the same essential genes, but due to the scrambling of the genome as a result of aneuploidy, other cancer cells from the same tumor will either not express or not rely on one or more of those genes. Therefore, these privileged cancer cells will not be sensitive to drugs targeted at gene products they do not express or no longer rely upon. This at least in part explains the phenomenon of intrinsic resistance to chemotherapeutic drugs in the absence of prior exposure. Thus, the appearance of estrogen receptor-negative breast tumors in women treated with tamoxifen [48] and relapse in 80% of blast crisis leukemia patients on STI-571 [49] is not surprising.

2.5. Aneuploidy theory suggests old strategies of cancer therapy and prevention

> "That cancer cells are often sick cells and die young is known to every pathologist." *Peyton Rous* [25].

It is clear that the long-standing strategy of trying to kill cancer cells before killing the patient with radiation and cytotoxic drugs has just not worked for the vast majority of lethal cancers [44]. The aneuploidy theory explains the inevitable failure of this approach. So what are the prospects for prevention and therapeutic intervention in cancer? Does the aneuploidy theory suggest new strategies? The answer is yes.

One of the most stubborn misconceptions is that cancer cells are rapidly dividing super cells, "the enemy within" that is bent on our destruction [50]. Hence the military metaphors of the "War On Cancer." However, observationally [1–3], experimentally [34,51], and theoretically [7,8,10,11,51], cancer cells are aneuploid cells. Aneuploidy damages cells—the more severe the chromosomal imbalance, the greater the damage [12,16]. Being damaged, aneuploid cells typically divide at slower rates than normal diploid cells [52] and "progression does not necessarily lead to dominance of the tumor over its host" [53]. Being damaged, aneuploid cells tend to

die at high rates [18], one of the "liabilities of the neoplastic state" [25]. It is only the "successful" tumors that attract attention; the "unsuccessful" ones escape notice [53]. Herein lies the key to prevention and much more effective and less toxic therapeutic approaches to cancer.

Cancer cells are not super cells but damaged aneuploid cells, which for the most part spontaneously die. Because aneuploid cells typically lose in competition with normal diploid cells [15,25], the new strategy is to stop devising poisons to kill cancer cells and to focus more on the interactions between tumor and host. The fact that propagation of primary human cancer cells in vitro requires finely-tuned, stable environments [15,30,52] implies that nontoxic perturbations of the host may be sufficient to nudge the tumor out of its stable, comfortable environment into a different attractor that leads to the death of the cancer cells.

Aneuploidy theory demonstrates that in order to alter a phenotype it is necessary to change the activities of hundreds or even thousands of genes and their products [10,11]. Therefore, global, nontoxic perturbations are called for. While alterations in the activities of large numbers of genes merely exercise normal cells, massive changes in metabolic activity should destabilize the cancer cells, reducing their viability within the host [25,54]. Such perturbations may be responsible for the 741 documented examples of spontaneous remission from more than 45 different types of cancer [55].

Consistent with this reasoning, the global perturbations associated with onset of pregnancy, severe dietary changes, infections following surgery, other operative trauma, and common viral infections may explain the spontaneous remission of many different cancers [55]. There are also the cases of spontaneous remission that seem to happen for no apparent reason [56]. But as Rous and Kidd have demonstrated, many neoplasms "require continual aid for their survival" [25]. Perhaps, as Rous and Kidd have suggested, the fortuitous removal of the chronic presence of carcinogen is what led to tumor regression in these cases.

In summary, spontaneous remission probably has more to do with changes in the person than changes in the tumor. The former emphasis on controlling and preventing cancer through diet, exercise, avoidance of carcinogens and similar nontoxic strategies needs to be revived and vigorously investigated.

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