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Paradox of spontaneous cancer regression : Implications for fluctuational radiothermy and radiotherapy

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Abstract Spontaneous Regression of malignant tumours without treatment is a most enigmatic phenomenon with immense therapeutic potentialities We analyse such cases to find that the commonest cause is a preceding episode of high fever-induced thermal fluctuation which produce fluctuation of biochemical and immunological parameters. Using Prigogine-Glansdorff thermodynamic stability formalism and biocybernetic principles, we develop the theoretical foundation of tumour regression induced by thermal, radiational or oxygenational fluctuations. For regression, a preliminary threshold condition of fluctuations is derived, namely $\sigma > 2.83$ We present some striking confirmation of such fluctuation-induced regression of various therapy-resistant masses as Ewing tumour, neurogranuloma and Lewis lung carcinoma by utilising $\sigma > 2.83$ Our biothermodynamic stability model of malignancy appears to illuminate the marked increase of aggressiveness of mammalian malignancy which occurred around 250 million years ago when homeothermic warm-blooded pre-mammals evolved. Using experimental data, we propose a novel approach of multi-modal hyper-fluctuation therapy involving modulation of radiotherapeutic hyper-fractionation, temperature, radiothermy and immune-status

Keywords . Radiotherapy, thermodynamics, cancer, fluctuation, stability

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"The spectacular phenomenon of Spontaneous Cancer Remission persists in the medical annals, totally inexplicable but real . from time to time patients turn up with advanced cancer beyond the possibility of cure The patient is sent home to die, only to turn up again ten years later free of disease. But no one has an idea of how it happens If thousands of patients have succeeded in doing this, the possibility that medicine can learn to accomplish the same is surely within reach" —Lewis Thomas, Sloan Kettering Cancer Center, New York [1]

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1. Introduction

The unexplained paradoxical phenomenon of Spontaneous Cancer Remission, Prolonged Arrest and Tumour Dormancy, appears to be a perplexing case in the tumour stability-instability behaviour. A MEDLINE search (1966-92) yields 11,231 references to the terms "Spontaneous Regression" or "Spontaneous Remission". The phenomenon is not as uncommon as usually assumed, for example 36% of prostate carcinoma, 24% of paediatric neuroblastoma and 30% of basalioma spontaneously regresses or arrests subclinically [2, 3]. For two centuries, it has been wellknown that there is unexplained episodic spontaneous regression or prolonged arrest of cancer [2,4] ; the therapeutic importance of the causes, if properly isolated, seems very great indeed. This anomalous behaviour requires a revision of our understanding of cancer : *cancer is not invariably a progressive or fatal disease*. There are evident cases in which the tumour is in a meta-stable state of prolonged arrest for 10-15 years, or the tumour spontaneously regresses or undergoes de-stabilization, or exhibits tumour dormancy for many years and only later (due to unknown reasons), it flares up and progresses [3]. Evidently these unusual behaviour of tumour appears to be a problem of stability.

Spontaneous remission is understood to have taken place when a tumour undergoes disappearance, either spontaneously or during the course of therapy, when it is known that the therapy is insufficient to produce disappearance of the tumour. Rohdenberg [4] has hinted at the probable factors behind spontaneous regression and concluded that the most probable cause was high prolonged temperature or hyperthermic condition, *eg* 104° F fever for over a week. From an empirical study, he also emphasized the *fluctuation* in energy dissipation and metabolism of the tumour during spontaneous regression. The prolonged temperature was induced by different conditions, such as inflammation, biopsy, cautery, diathermy, curettage, or various types of fevers. The German gynaecologist Kruckenberg [5] observed that the majority of spontaneous regression of uterine cancer were those associated with induction of high temperature during cautery or curettage of the tumor (Kruckenberg's Principle). It is thermodynamically known that higher the temperature, more the statistical fluctuations in a system. The therapeutic promise of spontaneous regression and prolonged arrest is being increasingly emphasized in oncology [3, 6, 7]. There have been a number of institutes, programs and conferences pursuing this problem, such as National Cancer Institute – Bethesda, Helen Dowling Institute – Rotterdam, Sonnenberg Klinic-Allendorf, Institute of Cytology – St. Petersburg and German Cancer Centre – Heidelberg [6-8]. We find that there has been empirical development of various high perturbative therapies as Multi-step therapy, Endostatin therapy and hyperthermia-hyperglycaemia [9-11]. In this paper, we propose that the wellknown phenomenon of fluctuation-induced de-stabilization of a non-equilibrium system transpires to be one of the processes responsible for spontaneous regression of a tumor which can also be utilized as a novel multi-modality approach to cancer treatment.

2. The cybernetic approach : systems theory and synergetics

During recent decades, the disciplines of cybernetics, nonlinear dynamics, stability theory and synergetics, have emphasized the importance of small fluctuations which can drastically alter the behaviour of systems, whether physical, chemical or biological [12-15]. The study of such transitions is one of the most fascinating fields of cybernetics and biophysics, especially neurophysics and immunophysics. Their studies have brought about a more unified vision of the laws which govern self-organisation, stability and instability in biological systems. A major achievement has been the notion of phase transition towards instabilities which occur in

open nonlinear systems. Such instabilities have been known from the turn of the century. Some classical examples from biophysics are Belusov – Zhabotinski reaction in self-oscillations and Lotka – Volterra interaction in ecosystems [14]. The study of stability of biosystems in subsumed under the mathematical theory of stability in cybernetics and synergetics.

Dutta Majumder has shown that there exists various approaches to this cybernetic problem, all having historical roots in analytical mathematics, *eg* Lyapunov – Poincare theory of differential equations, Nyquist control analysis and systems engineering [16]. Using a Systems Theory approach, Roy has attempted an analysis of tumour de-stabilization [17]. Recently the Brussels school of thermodynamics has pursued the stability problem elaborately, enunciating a new theorem of thermodynamics [13, 14], namely :

> *Glansdorff – Prigogine Stability Principle.* This indicates that an open non-linear system may become unstable at an appreciable distance away from stationary state, by means of sufficient non-equilibrium fluctuations.

This theorem is the basis of our approach. Roy, Dutta Majumder and co-workers have explored the principle's applicability in several other biological problems [18, 19] including the problem of spontaneous regression and its therapeutic applicability [20, 21]. Apropos these authors [16, 17], Cybernetics, along with General Systems Theory, form an universal theory of action, and are applicable to the full range of disciplines of the life sciences, *e.g.* neurology, immunology, ecology *etc*. Extrinsic and intrinsic environmental fluctuations of different modalities–such as temperature, pH, oxygenation (pO_2) and radiation inputs–seem to have considerable effect on (i) the macroscopic properties of nonlinear biosystems, as population dynamics, (ii) microscopic properties of the organism, such as extinction of cancer cell population and instability of tumours. There has been substantial work in the last several decades in biology, regarding the importance of *explicit* and *implicit* fluctuations of environmental or tissual parameters [13–15].

3. A cybernetic and biothermodynamic foundation of tumour regression

Classical experimental data of Warburg and of Acs and Straub indicate that during carcinogenesis, energy dissipation, as measured by metabolic activation, increases considerably [22]. In other words, we can say that carcinogenesis is a non-equilibrium state as it dissipates higher energy. The normal non-malignant state is a physiological homeostatic state. As per definition of homeostasis [23], this normal state is a stationary state with less energy dissipation. Our conclusion is also corroborated by other investigators [24, 29]. Hence we can enumerate the reciprocal transformations :

Tumour Progression .	*Stationary state (non-malignancy) → Non-equilibrium state (malignancy)*
Tumour Regression	*Non-equilibrium state (malignancy) → Stationary state (non-malignancy)*

These two complementary processes go on simultaneously, and forms a closed cybernetic loop, as detailed later.

In vast majority, Tumour Progression dominates over Regression ; whereas in prolonged arrest of cancer, we adduce that Regression is in dynamic balance with Progression. It has been established that cancer onset is a stochastic random but rare mutational process arising usually

from a single cell clone (monoclonal origin) [25] ; the cancer progression can be treated as amplification of fluctuation [26]. Correspondingly, we contend that spontaneous cancer regression can be taken as fluctuation regression. In other words, tumour progression and regression are reciprocal processes, mediated respectively by amplification and regression of fluctuation.

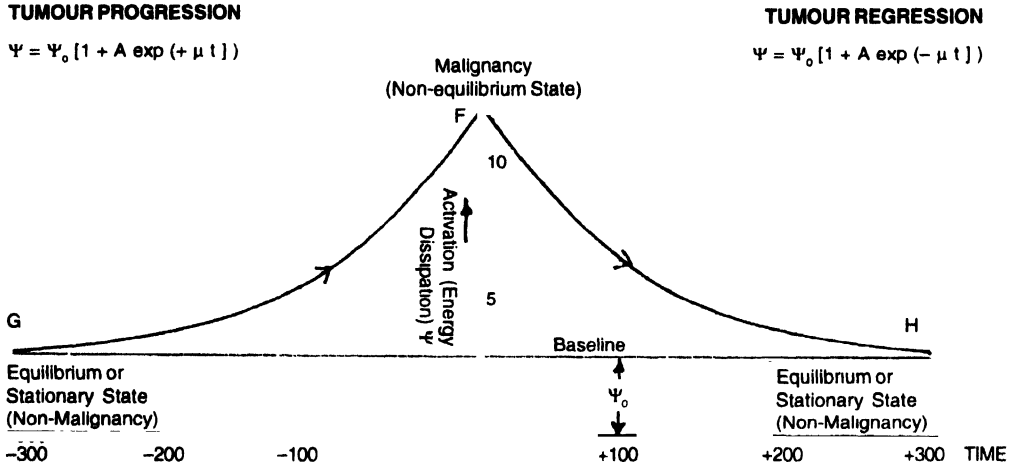

Figure 1(a). Cancer Progression and Regression . Schematic representation of exponential hypo-activation and hyper-activation eqs (2) and (3) Arbitrary units in axes used Note changes of sign before μ.

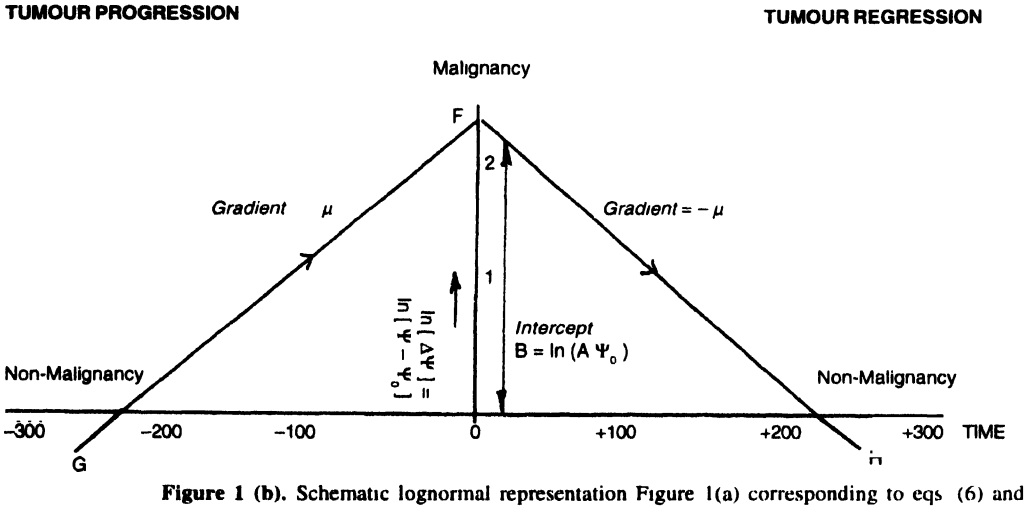

Figure 1 (b). Schematic lognormal representation Figure 1(a) corresponding to eqs (6) and (7) The parameters μ and B can be measured as gradient and intercept. Parameter A can be calculated as B = $ln[A\ \Psi_0]$, *i.e.* A = (exp B)/Ψ_0.

As a system approaches equilibrium or stationary state from the non-equilibrium state, the thermodynamic fluctuations of the system gradually relaxes and reduces ; conversely amplification in fluctuations occur during the reverse approach from equilibrium or stationary state to non-equilibrium state. The fluctuations are described by Einstein's fluctuation formula [27]:

$$p = C \exp(\Delta S / k), \tag{1}$$

where p is probability density of fluctuation of parameters $U_1....U_n$ from the equilibrium or stationary values U^o_1, ...U^o_n ; the k is Boltzmann constant and ΔS is entropy change, *i.e.* $\Delta S = S - S_0$. Here S_0 is the value of entropy at stationary state. Note that Einstein equation is inversion of Boltzmann entropy equation

$$S = k \log_e p.$$

An equation analogous to Einstein's, can also be derived independently using Markov analysis [24] based on Medawar's formulation that biological development is stochastic. Prigogine has extended Einstein's eq. (1) to non-equilibrium domain. It leads to the entropy curvature ($\delta^2 S$) equation :

$$p = \exp(\delta^2 S / 2k'),$$

i.e. $$\delta^2 S = 2k' \log p,$$

where k' is a constant. From eq. (1), one can show that for the non-equilibrium state → stationary state transition [18, 23] :

$$\psi = \psi_0 + \left[(B.T / p).(dp / dt)\right]$$

and $$p = p_0 \left[1 - C \exp(-\mu t)\right].$$

Here ψ is specific energy dissipation function, ψ_0 is ψ 's value at stationary state, p_0 is value of probability at stationary state, T is temperature and C and B are constants. Thence, one can derive that [18, 23] :

$$\psi = \psi_0\left[1 + A \exp(-\mu t)\right] \tag{2}$$

which is the Evolution Equation for the Non-equilibrium state → Stationary state transformation. Note that A and μ are positive numbers. Eq. (2) can also be derived through irreversible thermodynamic [19, 28].

We can now modify eq. (2) to describe the reverse transformation : Stationary state → Non-equilibrium state, which is associated with gradual amplification of fluctuation instead of relaxation. In other words, there is a time reversal, which is based on Onsager's stochastic "detailed balance" concept, namely the time reversal invariance of the elementary steps associated with various irreversible phenomena [13]. Hence, for this reverse transformation of Stationary state → Non-Equilibrium state, we construct our evolution equation as

$$\psi = \psi_0\left[1 + A \exp(+\mu t)\right]. \tag{3}$$

Note the change of the sign before μ, where μ is a positive number. Graphs of eqs. (2) and (3) are shown in Figure 1(a). Transposing eqs. (2) and (3), we obtain respectively :

$$\Delta\psi = A\psi_0 \exp(-\mu t) \tag{4}$$

$$\Delta\psi = A\psi_0 \exp(+\mu t) \tag{5}$$

where $\Delta\psi = \psi - \psi_0$, that is $\Delta\psi$ denotes the increase of ψ over the baseline stationary state value ψ_0. Taking natural logarithms, we respectively have :

$$ln\,[\Delta\psi] = B - \mu t\,, \tag{6}$$

$$ln\,[\Delta\psi] = B + \mu t\,, \tag{7}$$

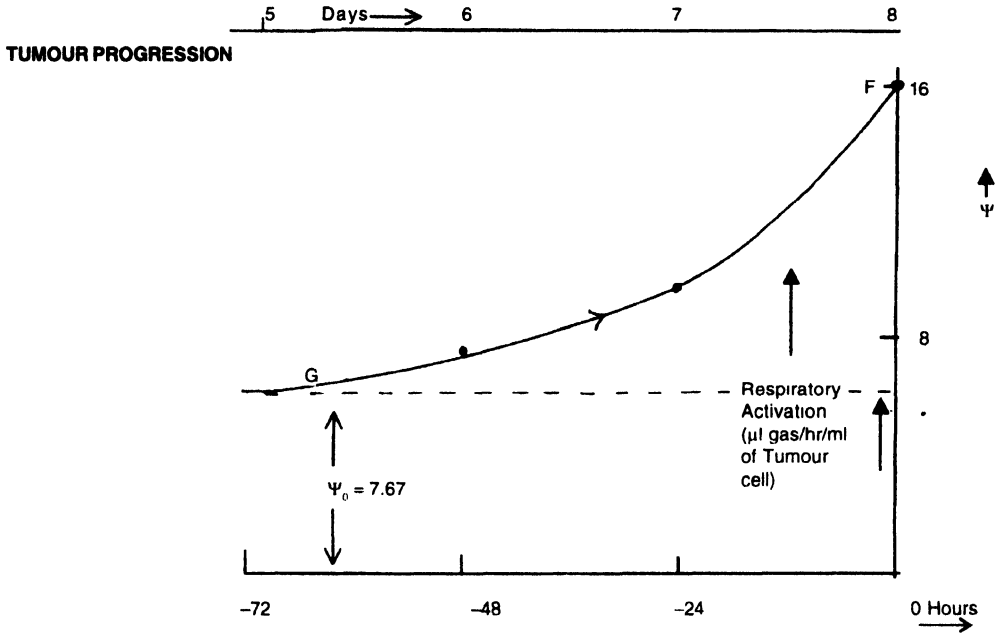

Figure 2(a). Tumour Progression Rise in Activation or Energy dissipation as Ehrlich ascites carcinoma develops

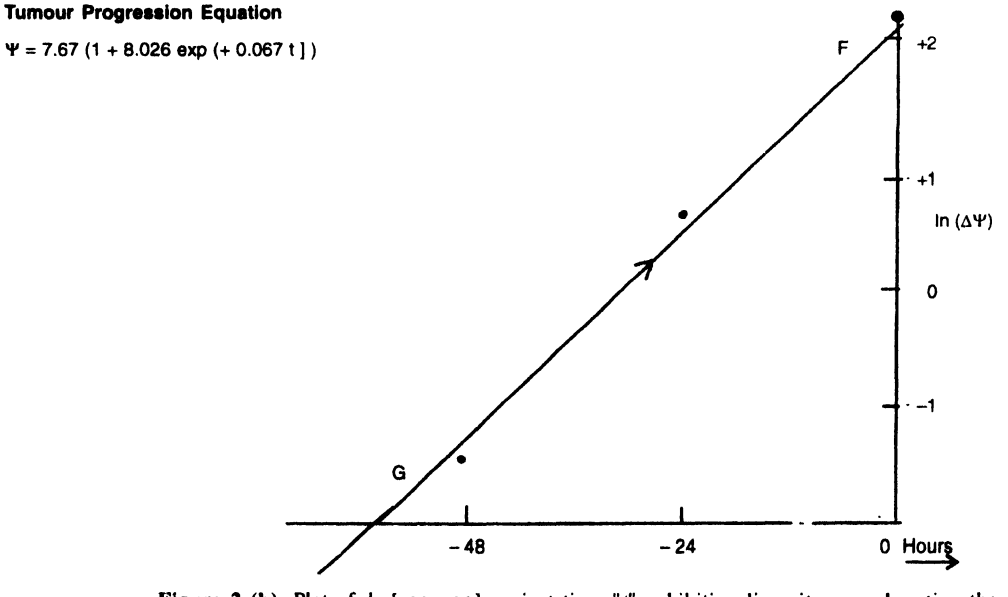

Figure 2 (b). Plot of $ln\,[\,\psi - \psi_0]$ against time "t" exhibiting linearity, corroborating the applicability of fluctuation formalism and non-equilibrium thermodynamics to carcinogenesis

where $B = ln\ (A\psi_0)$. In other words, the lognormal plot of $ln\ [\ \Delta\psi\ ]$ against time t would yield straight lines [Fig. 1(b)] with negative and positive slopes respectively. Note that in the two equations, time is measured positively into the future, and negatively into the past, respectively. Observe that for a biological system, energy dissipation ψ corresponds to metabolic activation, *i.e.* heat production [24].

In Figure 2(a) we present experimental data of metabolic activation as described by glycolysis intensity in Ehrich ascites carcinoma [22]. The valueof Day 5 has been extrapolated from Acs and Straub's data [22]. In later days (*e.g.* Days 9 to 11, not shown in graph), glycolysis falls due to exhaution of glycose supply. In Figure 2(b), we construct the lognormal plot of Figure 2(a). Observe the linearity which confirms eq. (7). By measuring the intercept and gradient, we can formulate the evolution equation of this Ehrlich carcinoma event :

Tumour Progression : $\psi = 7.67\,[1 + 8.026 \exp(+0.067t)]$.

Here, ψ is glycolytic intensity in micro-litre of gas/hr/ml of cancer cells, and time t in (negative) minutes before the peak value F. Figure 3(a) presents a typical pattern of experimental data representing approach to a stationary state as in regression of a lesion (*e.g.* tumour or wound) or in differentiation during regeneration [29]. The vertical axis here is drawn to pass through the peak activation point F_1. We construct the corresponding lognormal plot in Figure 3(b), the linearity confirms eq. (6). By measuring gradient and intercept, we obtain the complementary evolution equation

Regression : $\psi = 9.46\,[1 + 0.41 \exp(-0.0083t)]$.

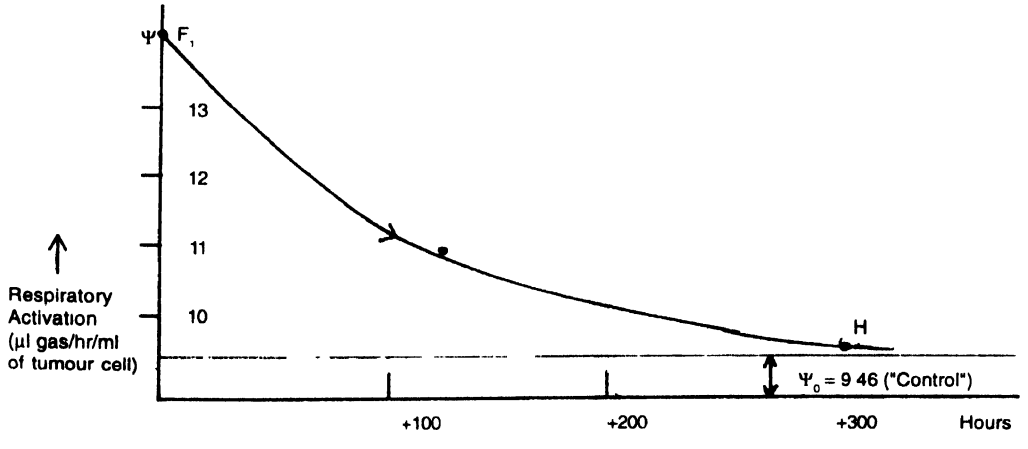

Figure 3(a). Regression of lesion, *eg* tumour, wound or regeneration Decrease in activation or energy dissipation as estimated by glycolysis intensity

Here, ψ is metabolic activation (micro-litre of gaseous exchange/hr/mg of cells), and time t is in (positive) seconds after peak state F_1. Hence our non-equilibrium thermodynamic formalism, based on fluctuation theory, appears to describe the bi-directional transformations :

Non-malignant state ‹ › Malignant state.

Our concept of the backward transformation, *i.e. "normalization of malignancy"* has considerable experimental and theoretical corroboration [7, 8].

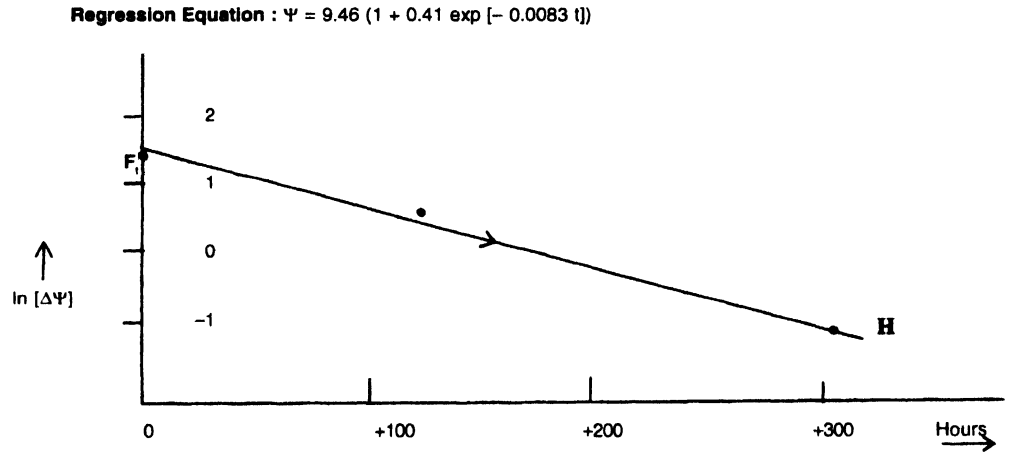

Figure 3(b). Plot of $ln\ [\psi - \psi_0]$ against time "t", exhibits linearity

4. Non-equilibrium tumour de-stabilization using fluctuations

Rohdenberg's findings [4] indicate that higher temperature is related to tumour de-stabilization. Increased temperature increases the thermodynamic fluctuations. Furthermore, increased fluctuations can de-stabilize a system as per Glansdorff – Prigogine Theorem [13]. We construct a model of spontaneous tumour regression and progression as a Predator-Prey system. Here Predator (T-lymphocytes and cytotoxic macrophages/natural killer cells of immune system)

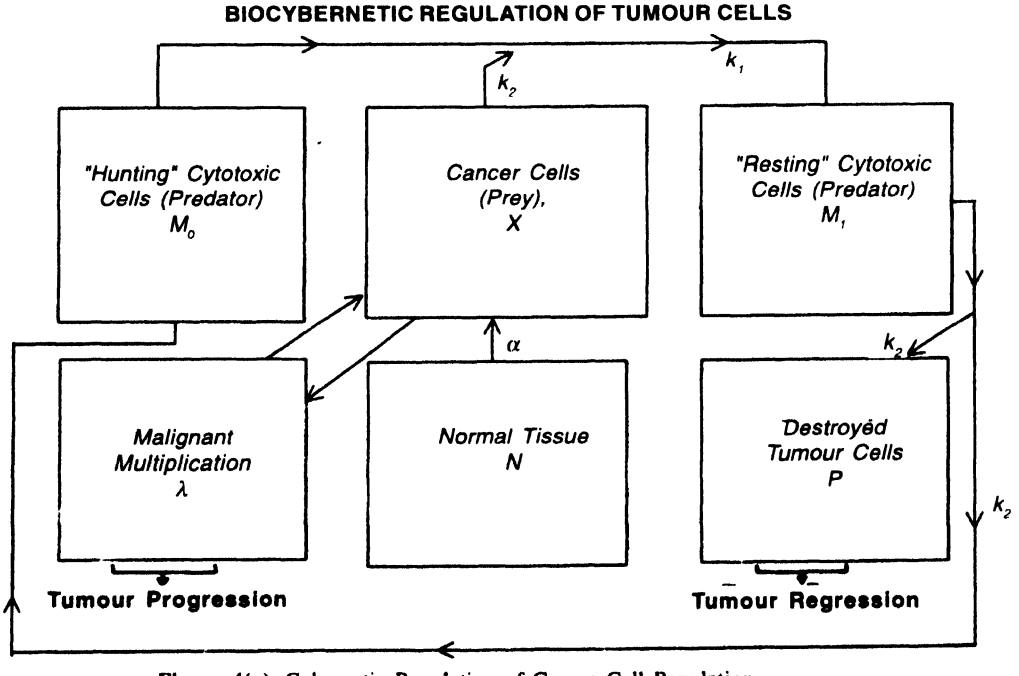

Figure 4(a). Cybernetic Regulation of Cancer Cell Population

has two states "hunting" and 'resting" and destroys the Prey (cancerous cells). The rate constants are in lower-case alphabets and various cellular densities are in upper-case letters Figure 4[a]).

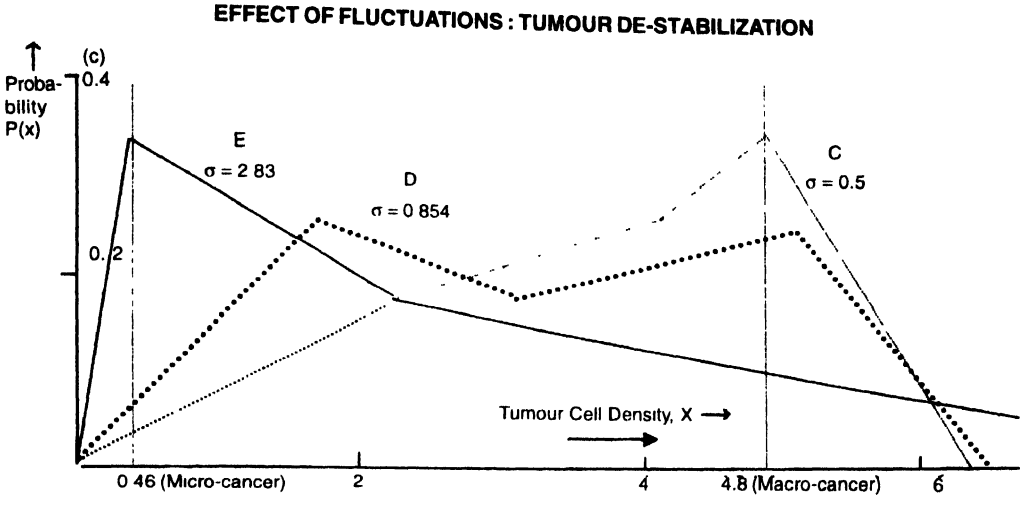

Figure 4(b). Tumour Regression and System Instability by increasing fluctuations in tumour cells destruction rate β Its standard deviation σ increases from 0 5 to 0.854 to 2 83 ; *i e.* from C to D to E, whereby the mode value of tumour cell density X decreases from 4 8 (Macro-cancer) to 0 46 (Micro-cancer) enabling regression (Data adapted from Ref [30])

One can see from Figure 4[a] that the tumour progression equation is :

$$dX / dt = (N - X).(\alpha + \lambda X) - k_1 M_0 X \tag{8}$$

and that tumour regression equation is :

$$dM_1 / dt = k_1 M_0 X - k_2 M_1 . \tag{9}$$

In an adimensional form, eq. (8) can be re-formulated as [30] :

$$dx / dt = \varepsilon + (1 - \theta x)x - \beta x / (1 + x) . \tag{10}$$

Of special clinical interest to us is β, the cancer cell reduction rate, where $\beta = k_1/\lambda$. The eq. (10) displays a cusp catastrophe, with bi-stability and critical points ε_c, β_c and x_c. Now consider β's fluctuation, *i.e.*

$$\beta_{fluc} = \beta + \sigma \xi_t ,$$

where ξ_t is statistical perturbation. Eq. (10) becomes a stochastic differential equation (SDE) [30]:

$$dx_t = [\varepsilon + (1 - \theta x)x - \beta x / (1 + x)] dt + [\sigma x / (1 + x)] \xi_t \, dt .$$

Analysing this equation by the wellknown Ito approach of SDE, we can obtain the probability density function P of tumour cells in terms of σ, the standard deviation of the fluctuations :

$$P = x^{\{[(2/\sigma^2)(1-\beta)]-2\}} .$$

The cancer cell reduction rate β can be fluctuated by perturbing the various parameters on which it depends e.g. pO_2 oxygenation level, radiothermia, chemotherapeutic agent concentration, temperature, blood glucose level, radiation flux *etc*. Variations in these parameters are reflected as random variations of indices like β which give them a stochastic character [30]. In fig. 4[b] we show the effect of increasing σ's value during the fluctuations. As σ increases from 0.5 to 0.854 to 2.83, from C to D to E, the probability density function exhibits a non-equilibrium phase transition, apropos Glansdorff – Prigogine Theorem. Sometimes chaotic immunodynamic behaviour may also occur [15]. In fig 4[b], the peak probability shifts to very low values of tumour cell density X, namely X shifts from 4.3 ("macro-cancer focus"), to 0.46 ("micro-cancer focus"), *i.e.* there occurs the phase transition :

$$\text{Macro-cancer focus} \xrightarrow{\text{Perturbation}} \text{Micro-cancer focus.}$$

This corresponds to regression and elimination of malignancy. Hence we infer that if one or more parameters as oxygenation, radiation or temperature, is varied with $\sigma > 2.83$, then the tumour may regress. Observe that a variation of $\sigma = 2.83$ *per se* is statistically relatively rare [31] ; this explains the relative uncommonness of spontaneous cancer regression in clinical practice. We can enunciate the corresponding Stability Principle for Malignancy, with $\sigma = 2.83$ as a threshold value :

> *Stability Principle for Tumour Regression : A tumour may have predisposition to de-stabilize and regress if there is a high fluctuation of the malignant cell reduction rate, so that σ exceeds 2.83, which may be achieved by correspondingly high fluctuation of temperature, oxygenation, radiation etc.*

5. Experimental confirmation and clinical utilization

We now present several experimental confirmation of our model and its therapeutic applicability.

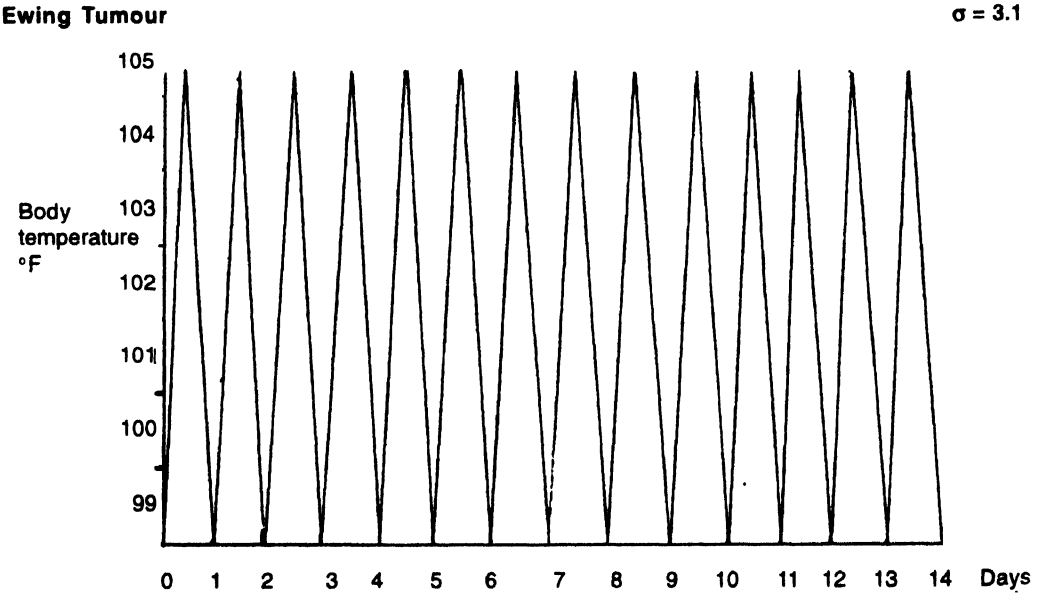

Figure 5(a). Complete permanent regression and disappearance of end-stage Ewing tumour of hip after fluctuating temperature.

5.1 Radio-resistant Ewing's bone tumour :

Our case concerns a 17 year old patient with terminal Ewing sarcoma of left hip. He rapidly went downhill with no response to surgery and 42,200 rads of cobalt-60 radiotherapy with T-11 chemotherapy. As shown by X-rays, CAT and Technitium-99 scans, he had massive metastasis or spread in chest, mediastinum, spine, skull, ribs and limbs. Later he underwent a prolonged high temperature fluctuation for a fortnight, with the temperature fluctuating between 99°F and 105°F daily (Figure 5[a]). This was due to a secondary microbial colonisation of surgical site. The temperature fluctuations terminated after antimicrobial therapy. Nevertheless the tumour and metastasis underwent a rapid regression [32, 33] and within two months there was no trace of tumour on CAT and bonescans ; the patient lives cancer free today. Note that we calculate the σ of temperature fluctuation of Figure 5(a) to be 3.2 thus satisfying the tumour regression principle stated above.

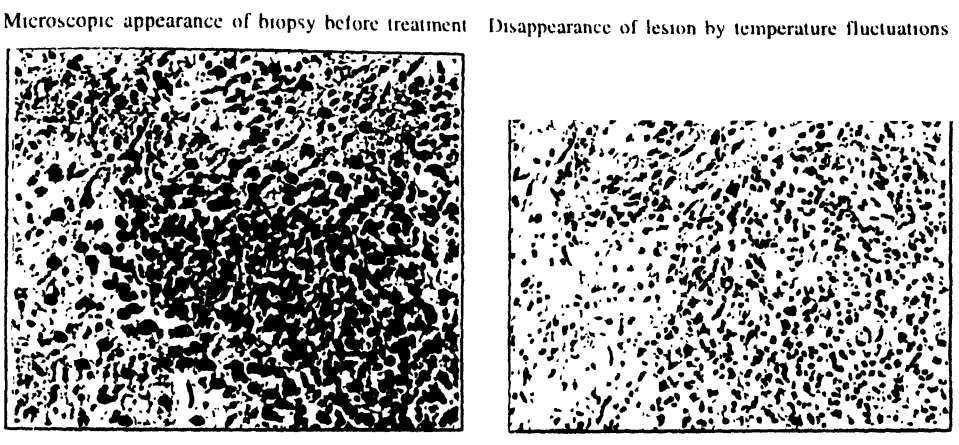

Figure 5(b). Regression of otherwise fatal neurogranuloma by fluctuating thermotherapy or radiothermia

5.2 Fluctuational Thermotherapy and Radio-thermia :

We can regress a lethal trepanomic neurogranuloma mass in the brain [21, 34], using fluctuating temperature induced by pharmacological, microbial or physical measures, such as nitro-phenols, mucopolysaccharides, trophozoite micro-organism or radio-frequency diathermy (Figure 5[b]). However, uniform high temperature, instead of a fluctuating one, is considerably less efficient [35]. The latter empirical observation had no methodological explanation, however our non-equilibrial model seems to furnish one. The radio-thermia can be induced by a "Selectotherm" equipment using radiofrequencies and robot-controlled spatial scanning apparatus [9]. We observe that the dynamics of neurogranuloma progression and regression can be analyzed by similar nonlinear dynamic principles sketched earlier (Figure 4[a]). The Prey is the causative trepanoma organism, and Predator the lymphocites and giant cells ; α vanishes as there is no malignant cellular transformation.

By long trial-and-error, the Viennese school of Wagner-Jauregg made a therapeutic breakthrough by observing the anti-neurogranuloma effect of artificially induced thermal fluctuations from 98.4°F to 104°F [35], which appears to be quantitatively accounted for by our analysis. One can use trophozoites for producing 10 spikes of body temperature fluctuations,

one spike occurring every 2 days (called "tertian" periodicity). Indeed we calculate $\sigma = 2.87$. These values clearly satisfy the Stability Principle. Subsequently the temperature spikes are stopped by anti-trophozoite drugs. Note the close correspondence with our Ewing example. Actually, the Jauregg approach is one of the notable techniques of physical therapies. Even when anti-trepanomic chemotherapy fails, fluctuational thermotherapy or radiothermia can succeed [34].

5.3 Fluctuating oxygenation by endostatin therapy :

This experiment concerns repeated administration of endostatin (a collagen fragment) to young tumours of Lewis lung carcinoma, a very aggressive tumour (Figure 6[a]). Endostatin attacks endothelial cells of new blood vessels serving the tumour and markedly reduces the tumour oxygenation. Six perturbations of endostatin are given at intervals of several weeks causing fluctuation of blood-supply and pO_2 level [10]. We find that pO_2 of a young tumour is 11 mmHg; and during acute oxygen-shortage in a tumour, as with endostatin, pO_2 is 2.5 mmHg (average) [36]. Thereby, the tumour, obstinately resistant to chemotherapy, undergoes permanent regression. We compute $\sigma = 4.26$ for Figure 6[a], further corroborating the regression principle. This therapy appears to be a promising approach, as many tumours become chemotherapy resistant.

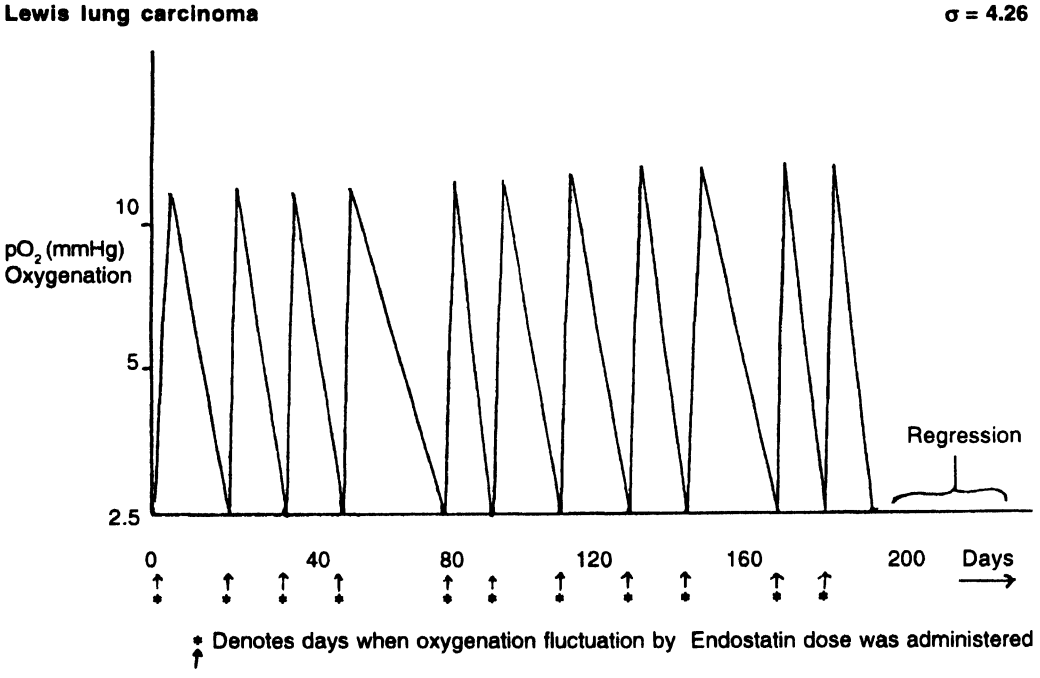

Figure 6(a). Regression of chemotherapy-resistant Lewis lung carcinoma by fluctuation of oxygenation, *i.e.* pO_2 level, using angiogenesis-inhibitor Endostatin.

5.4 Radiotherapy : Hyper-fluctuation and Hyper-fractionation :

Radiotherapy induces external perturbations and fluctuation of tumour cell reduction parameter β. Hence our analysis predicts that more efficient tumour regression would be induced by increasing radiotherapetic perturbations. This efficacy of hyper-fluctuation is confirmed by the technique of radiotherapetic hyper-fractionation [37], where increased tumour regression

is achieved by radiation administered ten times weekly (with reduced dose) instead of the conventional five weekly (Figure 6[b]). Decreasing the number of perturbations in a week, namely hypo-fractionation, decreases efficiency (Figure 7[a]).

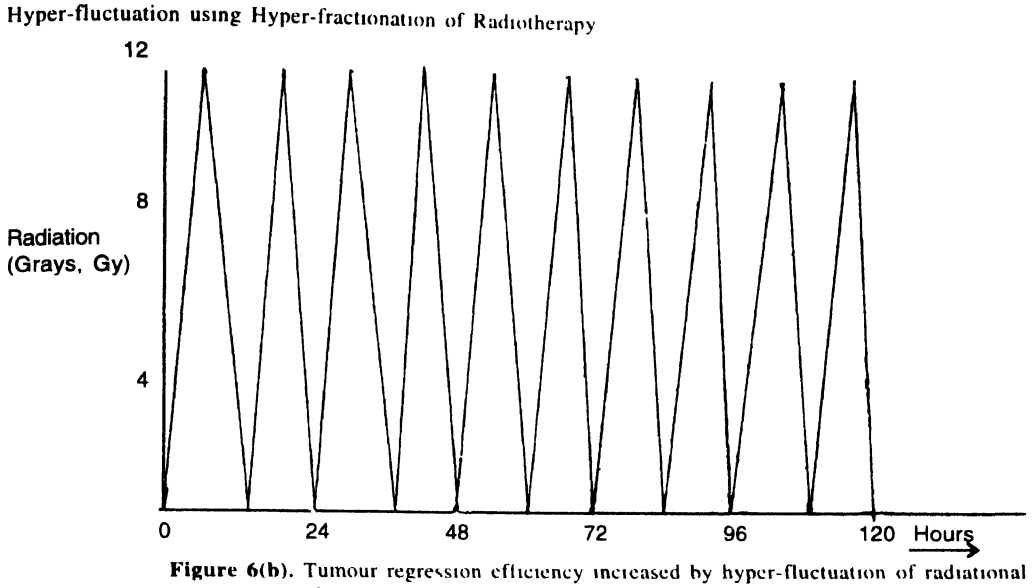

Figure 6(b). Tumour regression efficiency increased by hyper-fluctuation of radiational cytotoxicity, administered by hyper-fractionation of radiotherapy

6. Multiplicative fluctuations as a new Multimodality therapy

Another important type of fluctuation which can produce system de-stabilization is multiplicative fluctuations, combining different fluctuations [14]. We elucidate that tumour de-stabilization

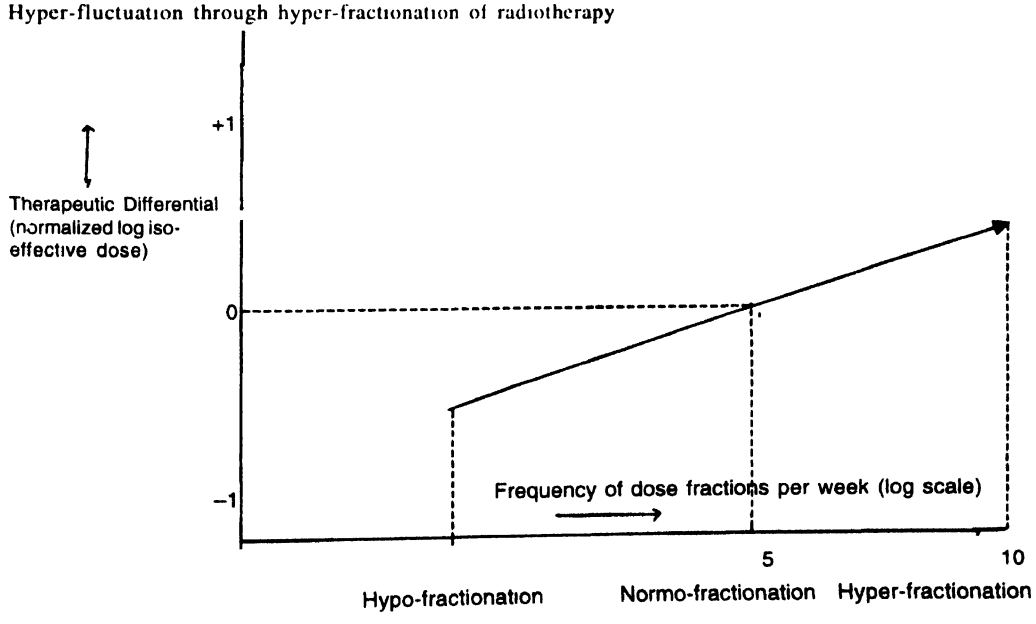

Figure 7(a). Increased efficiency of hyper-fluctuation over hypo-fluctuation in radiotherapy : More the fluctuation, more the tumour regression

by multiplicative fluctuations is illustrated by the empirically-observed "Multi-step therapy" developed by von Ardenne and Barke in Dresden and by Fradkin and Alexandrov in Minsk [9, 11]. The investigators combine radiothermy, hyperoxygenation, radiotherapy and hyperglycaemia (glucose shocks). Figure 7(b) shows complete regression of a huge 2 Kg clear-cell tumour above knee with this multi-perturbative therapy [9] ; the patient is healthy for over 5 years. We are presently exploring the various multiplicative fluctuation modalities to pursue more efficient tumour regression. We are devising pH perturbation and "*Bi-thermia*" which combines hyperthermia and hypothermia. Much higher fluctuation ($\sigma = 5$) can be obtained safely by temperature variation from 96°F to 102°F.

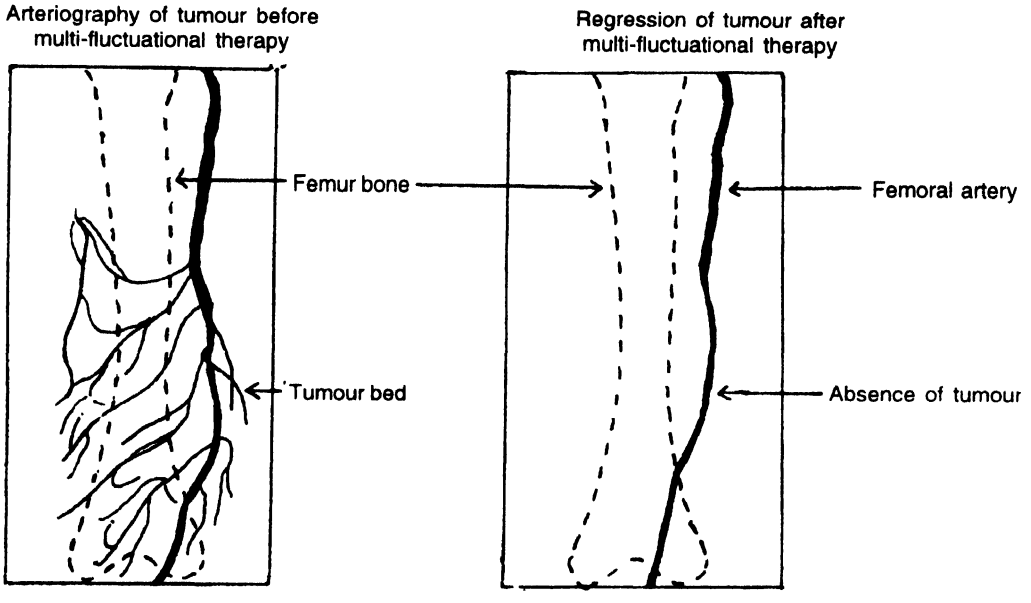

Figure 7(b). Effect of Multiplicative fluctuations ["Multi-step therapy"] combining fluctuation of Selectron radiothermy, hyper-oxygenation, radiotherapy and hyper-glycaemia using high glucose variation, thereby producing complete regression in severe clear-cell sarcoma near knee

7. Advantage of multimodal multiplicative fluctuational therapy

The main handicap of contemporary cancer treatment is drug-resistance, because genetically-unstable cancer cells mutate into drug-resistant ones. However, all the earlier examples of our fluctuational therapies do not target the genetic mechanism of neoplastic cells *per se*, but works through temperature, pO_2 or glucose perturbations which are non-genetic. Recently, the great promise of non-genetically targetted treatment (like ours) has naturally evinced keen interest [38]. Of course, ours is a nonlinear dynamical model and we have made some assumptions, otherwise mathematical analysis could not be readily done. Some of the assumptions are that : (a) microscopic time-scale of cancer cell reduction is shorter than that of macroscopic tumoral growth, (b) there is no drug-induced massive immuno-suppression, and (c) there is no surgical intervention which may suddenly alter the prey-predator ratio producing chaoticity [15]. However these assumptions are generally valid in a large number of patients in an oncology ward. Ours is basically a heuristic approach ; we shall modify the assumptions and techniques to better suit the gathered data and patients as our investigations evolve.

8. Bio-thermodynamics of evolutionary history of cancer

Cancer has a long evolutionary history from cold-blooded molluscs as snails which appeared about 500 million years ago. However, 74% of molluscan cancers spontaneously regresses, only 26% becomes fatal [39]. As organisms evolved, cancer became more irreversible and obstinate and less regressable. We observe that tumour progression and aggressiveness increased much more from the origin of warm-blooded vertebrates onwards, *e.g.* dinosaurs and pre-mammals which appeared around 230-250 million years ago, as evidenced by aggressive malignancy in their fossil bones [40]. However, cold blooded reptiles, as snakes, can have much less tumour progression, even for serious tumours as melanoma, which is usually fatal to warm-blooded mammals [41].

Our thermal de-stabilization analysis appears to illuminate this evolutionary oncological paradox. There is high temperature fluctuation of cold blooded invertebrates, reflecting the daily environmental variation which of 15°–30° F, whereas for advanced warm-blooded mammals, body temperature is constant, producing negligible fluctuation. So cold-blooded animals might usually regress tumours, whereas warm-blooded ones generally cannot. Hence we may elucidate that irreversible malignancy was the price animals had to pay during evolutionary and bio-energetic advancement from cold-blooded heterothermicity to warm-blooded homeothermicity, *i.e.*

$$\text{Heterothermicity} \xrightarrow[\text{Aggressive Malignization}]{\text{250 million years ago}} \text{Homeothermicity}$$

Elsewhere we have used cybernetics and non-equilibrium thermodynamics to develop a foundation of the homeothermic evolution and bioenergetics [19].

9. Conclusion

We elucidate how the recent developments of non-linear dynamics, based on physics, synergetics and cybernetics, seem to open a novel approach to medicine and oncology, through newer physical therapies as multi-modality fluctuational therapies. This appears to be a challenge to physicists and mathematicians, as it is to physicians and biologists ; naturally a collective collaborative effort is imperative if success is to be attained. The paradox of spontaneous cancer regression and its radiothermic and radiotherapetic implications, provides a really substantial promise for tumour patients at large. Indeed, the remarkable phenomenon of Nature's spontaneous self-repair of cancer gives a solid hope that, with further research, there is full possibility of complete recovery from malignancy.

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