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Towards a Morphogenetic Perspective on Cancer

Key words. ageing; Aristotle; catastrophe theory; embryonic regulation; morphogenesis; morphogenetic fields; oncogenes; tumour-suppressor genes.

Abstract. *The purpose of this paper is to present a critique of the current view that reduces cancer to a cellular problem caused by specific gene mutations and to propose, instead, that such a problem might become more intelligible, if it is understood as a phenomenon which results from the breakdown of the morphological plan or* Gestalt *of the organism. Such an organism, in Aristotelian terms, is characterised for presenting a specific* morphe *or* logos *(form) and for having a* telos *(end) to fulfil. A malignant tumour represents an entity separated from both, the organic* logos *and the organic* telos. *According to the basic postulates of Semiophysics – a blend of Aristotelian physics and Catastrophe Theory developed by René Thom – an organism is a source (original) form individuated by a dominant pregnance which corresponds to its morphogenetic field. Here it is suggested that cancer in*

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aged individuals may result from the progressive exhaustion of the developmental constraints that regulate the process of ontogeny, that is expected to go from the fertilised non-differentiated zygote to the mature fully-developed organism, because there is no further point ahead in the developmental pathway past the reproductive age. Cancer in young individuals (before their reproductive maturity) may then be consequence of premature derangement of such fundamental developmental constraints. In all cases the result is the loss of morphological coherence within the organism. Thus representing a conflict between an organised morphology (the organism) and a part of such a morphology that drifts towards an amorphous state (the tumour).

1. INTRODUCTION

The current view on cancer suggests that such a disease is the consequence of random mutations on certain key genes involved in the control of cell growth and proliferation. Therefore, cancer is understood as a genetic or cellular disease which results either from the overexpression or lack of expression of certain genes, but also from the abnormal activity or lack of activity of the proteins coded by such altered genes. Explicit definitions of cancer as a genetic disease can be found in widely read reference sources (Watson *et al.* [1992]; Alberts *et al.* [1994]; Cooper [1997]; Huguley [1997]). In other words, according to the current dominant view, cancer is the result of variations of molecular factors and activities that affect the physiology at the cellular level. Thus, although cancer is a phenomenon that affects the whole organism, it is nevertheless explained within a framework completely in agreement with the reductionist analysis that prevails in experimental science. However, intensive research on cancer, along the lines defined by the current genetic paradigm, has led to several anomalies and paradoxes that cannot be fully explained within such a paradigm.

The dissolution of the organism into genes and the proteins coded by such genes is both, the successful and mindless outcome of the rise of molecular biology in the second half of the twenty century (Aranda-Anzaldo [1997]). Thus, not so long ago, a distinguished molecular biologist did not hesitate to affirm that "everything (of biological significance) is written in the message of the

nucleic acids" (Jacob [1974]). Yet, a few years later, the same scientist also affirmed that "biochemical novelties are not those responsible for the actual diversity of organisms [...] that which distinguishes a butterfly from a lion, a hen from a fly or a worm from a whale, is not their actual differences in biochemical constitution but the different organisation and distribution of such biochemical constituents" (Jacob [1977]). Organisation and distribution; i.e., configuration, or in other words: the relative disposition of the parts or elements of a thing, is but one of the aspects of form. Thus, biology cannot resign to the study of form, a qualitative property that cannot be reduced to mere quantity. Indeed, form and thinking about form has been a central issue for both philosophical and scientific thought since the time of Aristotle. In spite of its partial exclusion from the mainstream after the rise of Darwinism and population genetics, the morphogenetic perspective in biology has kept developing. The central purpose of this work is to suggest how the morphogenetic perspective, as represented by the modern theory of Semiophysics (developed by René Thom), may provide a rather fresh approach towards the understanding of complex biological phenomena such as cancer, that so far do not yield to reductionist analysis.

2. THE GENETIC PARADIGM ON CANCER AND ITS PROBLEMS

Cancer is currently understood to be a disease that begins at the cellular level (Cooper [1997]). It is generally thought that the first step is cancer initiation in a single cell that must be able to pass its acquired abnormality on its progeny. The current mainstream in cancer research favours the idea that tumour initiation results from a genetic mutation at least in one of a set of regulatory genes (the so-called proto-oncogenes), which then becomes an oncogene (Alberts *et al.* [1989]; Franks [1991]; Cooper [1997], Fearon [1999]). Tumour progression is then explained as a sort of micro-evolutionary Darwinian process, whereby an initial genetic alteration leads to abnormal proliferation of a single cell that leads to a population of clonally derived cells. Additional mutations might occur within cells of this clonal population. Some of these muta-

tions may confer a further selective advantage to a particular cell and the descendants of a cell bearing such a mutation will become dominant within the original cell population (Cairns [1975]; Nowell [1976]; Alberts *et al.* [1989]; Weinberg [1993]; Alberts *et al.* [1994]; Fearon [1999]). Moreover, further mutations in some 'tumour suppressor genes', that code for activities that limit cell proliferation and contribute to genome wide stability, are seen as a necessary step for the full-blown development of most spontaneously occurring cancers (Hollstein *et al.* [1991]).

Many experimental protocols and the known epidemiology of cancer clearly show that a single mutation in a single gene is not enough to cause cancer (Land *et al.* [1983]). For example, the incidence of colon cancer increases more than tenfold between the ages of 30 and 50, and another tenfold between 50 and 70. This increase of cancer incidence with age suggests that most cancers develop as a consequence of multiple abnormalities that accumulate over periods of many years (Doll and Peto [1987]). Studies carried out with natural occurring colon cancers suggest that several stepwise genetic alterations are necessary for cancer development, and at least four independent mutations in four different genes are necessary for full tumour development (Fearon and Vogelstein [1990]; Vogelstein and Kinzler [1996]; Ilyas *et al.* [1999]). At a difference of rodent cells, primary human cells are very difficult to transform in vitro. Recently, it was reported the transformation of primary human cells by deliberate introduction of three synthetic mutant genes that affect four independent genetic functions (Hahn *et al.* [1999]). However, another group realised similar manipulations, targeting the same four genetic functions, without achieving any success in transforming primary human cells (Morales *et al.* [1999]). Indeed, a recent work seriously questions the interpretation of the data of Hahn *et al.*, and suggests that the human cells transformed in vitro were the result of genome-wide instability, leading to aneuploidy, and not the consequence of specific mutations that alter specific gene functions (Li *et al.* [2000]).

It is known that the mutation rates of somatic cells are very low, and the mutation rates of most types of cancer cells in culture are usually not greater than those of non-malignant cells (Loeb

[1997]). Therefore, it is highly unlikely that such four experimentally induced genetic events (mutations) might occur spontaneously within a single cell in the appropriate order and fashion (since some are inactivating mutations while others must be activating mutations). A simple estimate, based on the known mutation rate of somatic human cells of around 10^{-12} per nucleotide per generation (Drake [1969]; Friedberg [1985]), suggests the actual impossibility of such a stepwise accumulation of four independent mutations within a single cell and within the average life span of a human being.

For rather obvious reasons, cancer research favours the study of model systems where brief exposure to a strong carcinogen or outright genetic manipulation produces a high incidence of cancer within weeks or months. But naturally occurring cancers arise at a slow rate after incubation periods of many years. Currently, there are more than 70 oncogenes and at least seventeen tumour suppressor genes have been described, though so far, only four qualify as bona fide tumour suppressors (Bishop [1991]; Marshall [1991]; Kinzler and Vogelstein [1997]; Pennisi [1997]). Indeed, the criteria for considering a gene as a tumour suppressor are far from being universally established (Clurman and Groudine [1997]). It is likely that many more oncogenes and tumour suppressor genes shall be discovered; all these genes are involved either in cell-signalling, control of the cell cycle, control of gene expression or modulation of adaptive responses to cellular stress. Basically, all kinds of genes which are not coding for essential metabolic enzymes or essential structural proteins are likely to be found in a mutated state in one or another form of cancer, or in one or another type of cell transformed in vitro. Because such mutations do not put at risk the survival of the individual cell (at least in the short term). Most mutations that are really incompatible with cellular life are those in genes that code for key metabolic enzymes or structural proteins (Aranda-Anzaldo [2001]). Actually, there is no evidence that any of the so-called oncogenes is expressed at a higher rate in a primary cancer cell than in its normal counterpart (Duesberg [1987]; Jen *et al.* [1994]; Duesberg [1995]; Hua *et al.* [1997]; Li *et al.* [2000]). Recent technological advances that make the comparison of the gene-expression profiles of thousands of

genes feasible, suggest that many of the so-called oncogenes are actually non-expressed or lowly expressed in tumour tissues (Bialy [1998]; Alizadeh *et al.* [2000]; Li *et al.* [2000], Perou *et al.* [2000]).

Usually the model tumours are lymphomas, leukaemias or sarcomas which altogether represent less than 10% of naturally occurring tumours, while more than 90% of human tumours are epithelial in origin and the overwhelming incidence is in aged persons beyond their prime (American Cancer Society: Cancer Facts & Figures [2000]). Indeed, this fact has led to doubt that tumour suppressor genes might be selected for by evolution, given that the tumours supposedly curtailed or restricted by these genes are diseases of late, post-reproductive life (Hall and Lane [1997]). Thus, based on the significant developmental abnormalities observed in null-p53 mice (Armstrong *et al.* [1995]), it has been suggested that p53 is more likely to have evolved as a teratological suppressor, while its role as a bulwark for neoplasia is secondary (Hall and Lane [1997]). The emergence of p53 as a stress adaptive-response regulator that promotes cell growth arrest and apoptosis, helps to preserve genome-wide stability in the bodily cells (Lane [1992]; Aranda-Anzaldo et al. [1999]). However, preservation of genome stability is a rather superfluous function once the organism is past its reproductive age (Aranda-Anzaldo [2001]).

Oncogenes and tumour suppressor genes are wrongly defined: it is unlikely that alteration of a single key cellular factor may transform a normal cell into a cancer cell under non-artificial circumstances. Ninety percent of cancers occur in persons fifty years old or more. In an aged individual the developmental potential is exhausted and as such, there is no further need of such an individual as a vehicle for survival, since usually both the individual and the species survival have been satisfied by the production of offspring. Therefore, selective pressures are very likely to cease having any impact on the aged individual. Under such conditions the cells and tissues of the aged organism are fully available for undergoing a process of random genetic drift at the level of both nucleotide sequence and genome organisation. Genes that control intercellular and intracellular regulatory activities (such as the oncogenes and tumour suppressor genes), shall give the impression

of being preferentially affected, but this results from the fact that mutations in such genes are still compatible, in the short term, with cell, tissue and whole organism survival. Therefore the individual organisms harbouring such mutant cells and tissues are available for sampling, while any mutation in a key metabolic or structural gene would lead to the immediate demise of the affected cell. Then it is obvious that cancer can only develop from cells displaying non-lethal mutations, this will produce the false impression that such non-lethal mutations are the cause of cancer (Aranda-Anzaldo [2001]).

If cancer development were truly an event due to the accumulation of mutations in a few key genes, then once the threshold has been crossed, there should be no way back towards normality. Yet, this conclusion is not consistent with the thousands of spontaneous cancer regressions quoted in the specialised literature (Challis and Stam [1990]). Such regressions cannot be attributed to the action of a hypothetical 'immune surveillance' as it has been shown elsewhere (Beverly [1991]). Moreover, if malignancy is not a strictly genetic phenomenon, there should be some evidence for its reversibility. In leopard frogs, isolated nuclei from Lucke carcinoma cells (a kidney tumour induced by a herpesvirus) have been introduced into activated, enucleated frog eggs. Following nuclear transplantation, a small proportion of the nuclei allowed the development of tadpoles with normal, differentiated tissues (Weiss [1991]). Mouse teratocarcinomas contain pluripotential embryonal carcinoma cells. The introduction of such cells into the embryonic blastocyst allows incorporation into the inner cell mass, and hence to the embryo. Using genetic markers it has been shown that the embryonal carcinoma cells contribute to most of the normal tissues of the mouse, although such mice have a higher incidence of teratocarcinomas. It has also been found that the descendants of embryonal cell lines can form a normal germ line (Papaioannou *et al.* [1978]; Illmensee and Stevens [1979]). Thus, heritable normal behaviour can be restored to certain cancer cells by transplantation, or cultivation, in a suitable environment. It is highly unlikely that the restored normal cellular behaviour results from the specific reversion of multiple specific gene mutations that are claimed to be the cause of cancer.

3. CANCER AS A PROBLEM OF UNCHECKED CELL PROLIFERATION AND DISSEMINATION

Our main concerns in relation to cancer are unchecked cell growth, proliferation and dissemination of cancerous cells to other parts of the body. A dysfunctional cell, like a T lymphocyte displaying a defective T-cell antigen receptor, is not a cancer cell, even though it may have a mutated gene that explains why the cell is unable to bind a specific antigen. Molecular biology has established that most genes which code for proteins directly involved in the control of cell growth and proliferation in multicellular organisms, have their homologous counterparts in simple unicellular eukaryotes (Murray and Hunt [1993]; Nasmyth [1996]). Therefore, mutations in such genes are not enough to explain the loss of coherence between a tumour and its host. An organism must be able to regulate differences in specific cell activities. The control of cell growth and proliferation cannot be an exclusively internal cellular issue when the cell belongs to an organism. Thus, it should be the breakdown of the organic control or organisation that results in the pathology of cancer.

Benign tumours usually resemble their tissue of origin, arise in most tissues, increase in size but do not invade. Usually, they are separated from the surrounding normal tissue by a capsule of connective tissue. The specific tumour cells do not differ substantially from the structure of the normal organ cells (Willis [1967]). Malignant tumours display two main characteristics: cellular abnormalities and invasion of the surrounding tissues. The standard cellular criteria include a local increase in cell number, loss of the normal regular arrangement of cells, variation in cell shape and size, increase in nuclear size and density of staining (both of which reflect an increase in total DNA), an increase in mitotic activity (increased cell division), and the presence of abnormal mitoses and chromosomes. However, the only definitive evidence of malignancy is invasion of underlying tissues. The tumour cells destroy and replace normal tissues, also they invade the blood and lymphatic vessels and then, they may be carried to other parts of the body and develop into secondary tumours (metastases) in distant sites. Malignant tumours have no well-defined capsule and the

tumour cells grow in a much more disorganised form than is found in benign tumours (Willis [1967]).

Malignant tumours represent dynamic entities where there is a gradual acquisition of new characters as the tumour develops. This process is called tumour progression and the general trend is for tumours to go from bad to worse, showing a movement towards a more aggressive behaviour and an increase in their ability to invade. All cells in a single malignant tumour are not identical but there is a range of populations of cells expressing many different characters (phenotypes). Cells in a tumour may show differences in structure: morphology, growth rate, karyotype or behaviour. This diversity is a consequence of tumour progression (Ruddon [1981], pp. 283-322; Aranda-Anzaldo [2001]).

A cancer cell is potentially immortal, but there is no natural way for a cancer cell to survive outside its host (the immortality of malignant cells is an artefact, since there is no chance that the cells will survive outside from the strictly controlled laboratory conditions). Thus, a cancer cell is an entity undergoing the process of leaving the organic plan. The malignant cell has a different quality than the normal cell. Cancer is not simply a matter of the higher or lower degree of expression of certain abnormal regulatory genes. The more malignant the cells of a tumour are, the farthest the tumour is from showing any degree of morphological organisation. Paradoxically, a cancer cell displaying multiple mutations is more autonomous than the rest of the cells of the organism, but such a collection of mutations is not incompatible with cellular life in the short term. However, cancer cells do not respect morphology, they grow beyond their expected boundaries, they occupy the wrong places, that is the main problem with them.

4. THE ARISTOTELIAN POSTULATES OF THOMIAN SEMIOPHYSICS

For Aristotle, form is the truly active principle in the real world. When a thing is known it is known as a form, and anything further known about such a thing it is known as dependent on its form. In nature there are many individual forms and many

of them possess internal complexity. But nature is not only form, it is also matter. It consists of forms which can only exist as materialised or embodied. Therefore, the science of nature deals with formed matter, or bodies. But it is a commonplace that they are in constant change. However, for Aristotle, such a change is simply the effort of bodies to achieve perfection in their kind, to become in fact what in principle they always are, to reach their form. Hence, all change which is not degeneration or failure is the process by which the relatively unformed becomes formed. From the Aristotelian point of view, change leads us to regard form as an end to be attained, the content of a purpose implicit in the being of particular things. Each thing is striving to grow into the form which its matter is fitted to receive.

Simple living beings such as bacteria and amoebas are rather monotonous in their morphologies, being no more than three-dimensional balls from the mathematical point of view. Complex multicellular organisms can be defined as three-dimensional balls displaying internal stratification. Thus being a mixture of homogeneous and heterogeneous parts. Following Thom's definition: an entity H is said to be homogeneous if every part c of H is considered to be semantically (phenomenologically) equivalent to H. Although c is less than H the qualities of both are equivalent. Thus H has a homogeneous substrate, such is the case for water and oil, which are examples of homogeneous entities (Thom [1990], p. 148). All non-homogeneous entities are heterogeneous and the substrates of such entities present qualitative discontinuities, which means that they have a form whereas homogeneous parts are intrinsically 'formless'.

Aristotle distinguishes between totality and whole; homogeneous parts make up a totality, but a whole like a living body has 'canonical parts' separated by well-defined surfaces which give its form. Thus, the parts of an entity in *actuality* are limited by heterogeneous parts. The totipotential egg, in higher organisms, is divisible and in theory it could be treated as a homogeneous part. For Aristotle, the local quality of a homogeneous part is a quiddity. According to Thom, in modern terms the egg's quiddity would be the 'genetic heritage' which makes it possible to form a perfect animal: the adult (Thom [1990], p. 185). Ontogeny is the

individual development of an organism from the fertilised egg to the adult. Such a development implies the process of morphogenesis, consisting in the formation of biological structure by changing the spatial relationships of cells or tissues, or in other words: the process of bringing about changes in form in the developing embryo, so as to eventually achieve the full organic form which is proper to an individual organism of a given species. Therefore, the mystery of ontogeny lies in the passage from the invisible form of the germinal homogeneous substance to the visible form (*morphe*) of the finished organism.

According to Thom, all entities suppose the existence of a substrate which is a material spatial-temporal set (R^3 x T). Two entities with the same substrate are identical. The states of an entity A form a set $S(A)$. The entity A may be subject to various kinds of change (such as movement or deformation), *but its substrate must be permanent if the permanence of its individuality is to be ensured.* The potential set of changes in A define a class of entities associated with A. Thus, (A,a) means entity A in state a. If there exists a temporal evolution which can conceivably be realised, transforming (A,a) into (A,b), then it will be said that (A,b) proceeds from (A,a) or that (A,b) is within the potential of (A,a). However, the transformations may be reversible or irreversible, an extreme example of this is illustrated by the following fact: every man alive is a potential corpse, but the converse is not true.

The phenomenon of ontogeny unfolds itself upon the so-called 'epigenetic landscape' of the organism, which goes from fertilisation to embryonic development, functional maturity, senescence

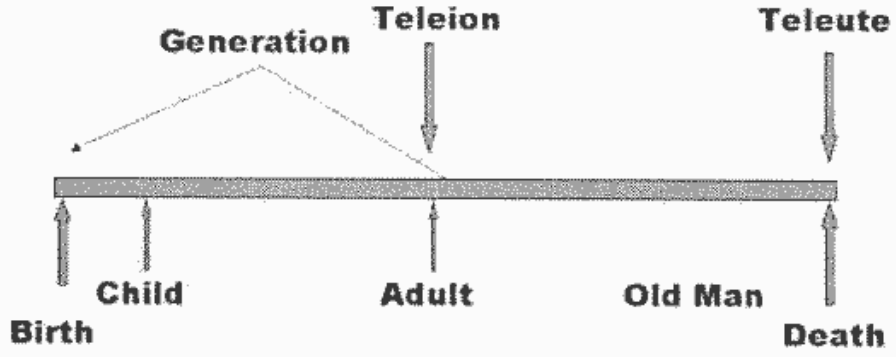

Fig. 1 – Birth, telos and end of an entity (after Thom [1990]).

and death (Waddington [1940]). According to Aristotle, the natural transformations of an entity culminate in the *teleion*, the perfect state of adulthood, which must be distinguished from the terminal point (*teleutè*). The Aristotelian *telos* is sometimes identified with the *teleion* and represents the central point of the existence of an entity: it determines both what precedes and what follows[1]. René Thom interprets the *telos* as the organising centre of a morphogenetic field of beings and events evolving in time (figure 1).

5. INDIVIDUATION AND MORPHOGENETIC FIELDS

Individuation is a system's ability to attain pattern and form from an initial condition in which these properties are absent. It is, therefore, an aspect of epigenesis that characterises ontogeny (Waddington [1956]). Individuation is possible because the elements of the embryonic system can organise responses according to the requirements of the specific developmental conditions that exist, rather than according to a rigidly determined plan. Yet, final individuation implies that all constituents of the organism (cells, tissues, organs) are structurally and functionally integrated into a single complex whole. Such an integration and organisation must be respected and maintained during the organism's life if the organism is to survive. Thus replacement or regeneration of tissues must be guided by a general and constant normating principle, which harmoniously integrates the parts into a whole. The enormous amount of experimental evidence demonstrating this phenomenon of individuation, posed the need of finding and explaining the source and nature of the integrative ability that is manifested during individuation. This led to the concept of biological field, first applied to biological systems after 1914 by Gurwitsch ([1914], [1922]). Yet, the concept, more restricted in scope, of embryonic or morphogenetic field, became widely known after its adoption by Paul Weiss in 1923. Used first to describe the regen-

[1] 'Further, where a series has a completion, all the preceding steps are for the sake of that. Now surely as in intelligent action, so in nature; and as in nature, so it is in each action, if nothing interferes'. *Physica* II 8, 199a, 8-11. Translat. Hardie and Gaye, ed. Ross, Clarendon Press, Oxford, 1930.

eration of organs, it was later applied to embryonic regulation in a more general sense (Weiss [1969]).

Gurwitsch introduced the notion of a 'normating principle' in biology, which should work on certain specific parameters common to different biological phenomena. Gurwitsch suggests that these are vectorial parameters of cell behaviour. Any factor acting within the limits of steric parameters and, hence, making the elements behaviour to depend on their co-ordinates within the whole, is a field factor. Gurwitsch brought his theory as a working instrument, that may help to explain the phenomena observed at all level of biological organisation (Lipkind [1998]). Thus, the biological field is first and foremost a working tool, as it was clearly appreciated and further developed by René Thom in the context of Catastrophe Theory.

The unit of organisation that embodies the attributes of positional information in individuating systems is the embryonic field. It constitutes an embryonic system or part of such a system, that contains elements that acquire their potential properties in relation to a common source of positional information but can also re-establish the informational system, its constituent elements, and their responses following the disturbance of spatial relationships within the system. The egg of a regulative embryo is a single field: the primary field. The processes of cleavage and primary determination subdivide the primary field into smaller internal secondary fields, whose regulatory powers are restricted to a certain type of determination. These fields are equated with organ-forming areas and display their regulatory powers through the control of regional individuation. Thus, fields exist at both the cellular and supra cellular level.

A striking property of fields is that they can anticipate the need for potential formal properties independently of its apparent properties. Thus the half-egg can direct the development of a whole embryo by reprogramming its constituents with regard to a future state of organisation and not the present state. Thus fields provide an operational definition of organic wholeness as the state of organisation towards which the regulatory powers of the field are directed. Fields can interact with one another in different ways. Normal morphogenesis requires the interaction of fields, since as

the embryo proceeds past primary determination it becomes subdivided into smaller organ-forming areas, each of which is a morphogenetic field. It is likely that proportion in the normal embryo is achieved through competition between fields for the available mass of the embryo. *Thus, abnormal development might result when for some reason, one field loses strength and is dominated by another.* The competition between fields is particularly obvious in the marginal zones between organ-forming areas. Fields can recognise different spatial relationships and they regulate growth as well as differentiation. Therefore, generation of a particular structure in an organism depends not only on the properties of the elements making up the structure (cells in this case) but upon additional influences affecting the spatial order that emerges from cell-cell interactions (Webster and Goodwin [1996]). Embryonic or morphogenetic fields provide the constraints on cellular function that are necessary for differentiation and individuation. Embryological systems cannot be reduced beyond their constituent fields without the disappearance of the very properties that characterise ontogeny. The egg is a field that can be subdivided only to the extent that it preserves its field properties. Later in development, the original single field of the egg becomes subdivided into smaller, more restricted fields, which have essentially the same basic properties operating on a smaller scale (for a thorough discussion of morphogenetic fields see: Willier *et al.* [1971]; Hamburger [1988]; Webster and Goodwin [1996]).

6. CANCER AS A FORMLESS PHENOMENON

There is no specific morphogenetic field associated with cancer. Cancer morphogenesis is aberrant. Malignant tumours show no defined tissue architecture. In fact, solid tumour growth leads to the production of aberrant masses known as spheroids, so poorly irrigated that the cells occupying the central regions of such spheroids become necrotic for lack of oxygen and nutrients. Also, the blood vessels in solid tumours show aberrant configurations that lead them to bleed rather easily (Ruddon [1981], pp. 284-286).

Currently, it is known that the cell nucleus and cytoplasm are

'hardwired', so the cellular structure is amenable to a vector field treatment, and the cellular tissues constitute rather complex three-dimensional vector fields. There is experimental evidence that physical force, inducing specific deformations of cellular structures, can modify the pattern of gene expression, since the DNA itself is subjected to a complex topological arrangement as supercoiled loops anchored to the nuclear substructure and the specific anchoring pattern is critical for differential gene expression. Such interactions are very important for nuclear physiology but also represent topological parameters which define a complex nuclear morphology (Aranda-Anzaldo [1989]; Pienta *et al.* [1991]; Aranda-Anzaldo and Dent [1997]; Ingber [1997]; Maniotis *et al.* [1997]). Thus, altering the distribution of forces acting upon a solid tissue, might lead to morphological changes within the cell nucleus and modifications of gene expression and cell activity. A perturbed or weak morphogenetic field can lead to such an altered distribution of forces. The chromosome instability and aneuploidy commonly observed in cancer cells represent major alterations of the internal nuclear morphology. These alterations may be the evidence, at the cellular level, of perturbed interactions between the tumour cells and the local morphogenetic field.

There is no specific *logos* and no *telos* associated with tumour development, a malignant tumour is going nowhere from the morphogenetic point of view. Phenomenologically speaking, a malignant tumour is meaningless because it cannot survive as a separate entity with defined morphology, in that sense it is completely different from a true parasite which may survive the demise of its current host and it has developed strategies for its introduction into new hosts. There is no natural way for introducing a tumour into a new host. The malignant tumour has no further potential than to return to its former 'normal' state if it is to remain as a part from an organised whole. There is no future for a tumour as an autonomous entity in nature.

The set of transformations that may occur within a tumour tend to enhance the individuality of the tumour cells: the cell showing the highest degree of dedifferentiation (anaplasia, which includes chromosomal instability and aneuploidy) and the fastest growth rate, will prevail upon the rest of the tumour cells, thus

giving origin to a new clone with new properties. Such a clone will apparently compete with the previous cells for nutrients and space, but its temporary success will eventually lead to its own dismissal and death of the host organism. In Aristotelian terms, a tumour has no essence (*ousia*[2]), it lacks a morphogenetic potential, there is no specific *telos* for it, all its potential transformations are not natural but 'accidental'. The substrate of a tumour is always changing, therefore it is not possible to establish the individuality of the tumour, but only of one or another of its cells. Within a tumour the cellular individuality is enhanced at the expense of tissue organisation.

As it was mentioned before, tumour progression is characterised by chaotic cycles of mass growth and destruction and the tumour itself can be visualised as a set of poorly differentiated homogeneous parts. Metastasis is quite an inefficient process, most tumour outgrowths are bound for spontaneous destruction or involution due to the lack of internal organisation, a situation that impairs the flow of oxygen and nutrients into the tumour. Actually, the toxic substances liberated into the bloodstream as a consequence of tumour self-destruction are often responsible for the demise of the affected organism (Ruddon [1981], pp. 284-286).

7. A SEMIOPHYSICAL PERSPECTIVE ON CANCER

According to Thom, an intelligible ontology is characterised by a space where all the beings considered reside: the substrate space *B*. Within such a space the beings of this ontology are divided in two classes: salient forms and pregnances. A salient form is a closed set *F* on space *B*. If the form is individuated it will have an interior *a*, where the closure $\underline{c}$ of *a* is a ball. The individuated form is said to be organised if it has a canonical model of closed sets

[2] For Aristotle *ousia* means 'the thing that really exists' or 'the existence' of a thing that truly is. He also employs the terms *eidos* and *logos* as synonyms for *ousia*. For Aristotle, as well as for Plato, *eidos* refers to the form or figure of a thing. However, when Aristotle wants to stress the form of a thing, he uses the term *morphe*. Phrases like *logos kai ousia* and *logos tes ousias*, mean that the form explains what a thing really or truly is. See: I. Düring, *Aristóteles*, p. 416. Trans. B. Navarro, UNAM, México, 1990.

contained in *a* which are themselves organised, the total organisation being described by the tree *Tp* of an individuating pregnance (Thom [1990], p. 16). Two distinct salient forms are topologically disjoint. Pregnances are non-localised entities emitted and received by salient forms[3]. The nature of a pregnance can be more subtle and complex than a material substance. The specific morphogenetic field of a thing is likely to be a pregnantial entity. When a salient form seizes a pregnance, it is invaded by this pregnance and consequently undergoes transformations in its inner state which can in turn produce outward manifestations in its form. These effects are called figurative effects.

The fact that malignant tumours are more frequent in early childhood and old age fits with the idea that such are the regions in a graph of the natural transformations of the species (figure 1), which are farther away or beyond the morphogenetic-organising power of the *teleion*. Therefore, such periods of a potential lifetime could be understood as the more labile and susceptible to suffer morphogenetic disturbances. A common finding in necropsies from old people is the presence of tumours in different stages of progress (even though such tumours may have nothing to do with the direct cause of death). Domestic animals, indirectly subjected to the benefits of human public health, tend to live longer than those living in the wild, but they also show an overwhelming incidence of tumours in their old age. These facts suggest that a dominant pregnance, represented by the morphogenetic field of the organism, is more likely to be weakened, disturbed or displaced from a certain part of the organism, when such an organism is beyond its prime. It may be stressed that the current dominant hypothesis, which explains cancer as the result of multiple random mutations that affect the functions of certain genes, it is also con-

[3] The term *pregnance* comes from the German *Prägnanz* used by the Gestalt theory school. According to this school, where a physical form of homogeneous material properties can yield sufficiently to the systematic forces acting upon it, it seems to be a general rule that very simple and regular spatial arrangements are reached in the stationary state. This tendency towards simple *Gestalten* is called the law of *Prägnanz*. Thus for the Gestalt theorists, *Prägnanz* is a dynamical term which refers to the factors that trigger and regulate progression towards the stationary state. However, Thom modifies the use of that term, because for him *pregnance* means the morphology of the stationary state itself.

sistent with the evidence for a higher incidence of cancer in old age. However, the postulated need for the stepwise accumulation of four or more mutational events in the same cell in order to develop cancer (Vogelstein and Kinzler [1993]), coupled to the very low mutation rate typical of somatic cells, requires the existence of a mutator phenotype as a precondition for cancer development (Loeb [1991]). Then, if such is the case, the logical outcome is that the true 'oncogenes' would be those genes whose mutation leads to genome-wide instability. But genome-wide instability alters the topological parameters within the cell nucleus, and as it was mentioned before, this constitutes an important morphic disturbance at the cellular level.

Morphogenetic or morphic disturbances might be the consequence of the weakening of the normating principle represented by the individual's morphogenetic field, once such an individual is beyond its prime and therefore it has exhausted its developmental potential. The morphic disturbances may also result from the seizing of a set of cellular elements by a pregnance different from the morphogenetic field of the organism, or from a random clash of pregnances (i.e., two different, non-related morphogenetic fields) upon the domain (substrate) occupied by the set of would-be transformed cells. Thom's first axiom of actuality states that: all non-natural transformations of A, require the presence of at least one different entity M (the mover), which comes into contact with A. M transmits a secondary entity to A (a 'species') which modifies its state. For Thom the entity M is able to transmit a pregnance to A (Thom [1990], p. 149).

The dominant pregnance, represented by the morphogenetic field of the organism, might either gradually disappear or be displaced or substituted by another kind of pregnance, when such an organism is beyond or far away (in ontogenetic terms) from the *teleion*, which corresponds to the organising centre of the morphogenetic field. This might be the first real step in tumorigenesis. The fact that nuclei from tumour cells can be reprogrammed to follow a normal behaviour after transplantation into enucleate normal eggs (Weiss [1991]), suggests that the normal morphogenetic field is the dominant pregnance in early development and thus it can be restored under certain circumstances. Moreover, the

observed spontaneous cancer regressions quoted in the specialised literature are numbered in thousands, suggesting that the normal pregnance (morphogenetic field) might sometimes regain control over the tumour (Challis and Stam [1990]).

A very interesting finding is that malignant neoplasms arise when normal rat ovarian tissue is transplanted into normal rat spleen (Biskind and Biskind [1944]). Thus, normal tissue situated in the wrong location within the context of the organism, degenerates into a tumour. On the other hand, tumour cells introduced into a blastocyst become normal and contribute to the formation of organised bodily structures (Papaioannou *et al.* [1978]; Illmensee and Stevens [1979]). These facts are quite paradoxical, considering that within the early embryo there is an elevated amount of growth factors that should speed up the growth of the tumour cells, because such cells already require less growth factors than normal cells in order to stimulate their growth. Moreover, there is no obvious way that the simple change in the location of the ovarian cells might be inducing the somatic mutations which, according to the standard paradigm, are claimed to be the causal origin of cancer. Yet, these results can be understood on the one hand, as a normalisation of the tumour cells by the action of a strong, normal morphogenetic field associated with a developing system. On the other hand, as evidence that the loss of coherence (artificially induced in this case) between a set of bodily cells and the weakened morphogenetic field of an adult organism (about to exhaust its developmental potential), induces tumour formation.

Irregular objects that are statistically similar when observed at different scales, have the property known as 'self-similarity'. Fractal objects display self-similarity and their fractal dimension (connected to their irregularity) has a non-integer value, at a difference of regular or homogeneous objects that have integer dimensions (the topological dimension such as 1 for lines, 2 for planes and 3 for volumes). Analysis of bone marrow biopsies shows that normal or anaemic bone marrow display a fractal dimension while leukaemic bone marrow lacks the fractal structure and displays a topological dimension of two (Naeim *et al.* [1996]; Bianciardi *et al.* [2000]). There is evidence that the space to be conquered by emerging populations of cancer cells possesses a

fractal structure, while the distribution of expanding tumour cells possesses an integer dimension (Waliszewski [2000]). Therefore, the loss of the fractal structure and a drift towards geometrical homogenisation appears to be a characteristic of malignant tumours.

The trend in contemporary science is towards reducing every phenomenon to a direct interaction between salient forms and thus, to eliminate any reference to pregnantial entities. However, many phenomena can be understood as the interaction between a salient form and a pregnance. The result of such an investment of the salient entity by the pregnance could be the re-emission of the pregnance by the invested form, such a re-emission can be more intense or weaker than the original pregnance (e.g., light diffused by an opaque object). But also the invested form may undergo a morphological transformation even to the point of destruction, such as in the case of a pane of glass shattered by a sound wave. It is also possible to envisage interactions between different pregnances when they happen to share the same substrate space. It could be argued that the presence of one pregnance can influence the propagation of another. Thom has already suggested that a conflict between individuating pregnances satisfies a catastrophic model which has collision as its limit (Thom [1990], p. 43).

8. CONCLUSION

Modern science is dominated by the analytical, quantitative approach, and thus it favours explanations based on quantitative measurements, but pays little attention to differential qualities. However, complex systems such as living organisms are more than the sum of their elements or parts. They possess qualities that cannot be reduced to the simple addition of quantities. Among such qualities are a specific form and a specific organisation. Semiophysics is a blend of Aristotelian physics and Catastrophe Theory, previously developed by Thom. Catastrophe Theory gives an account of the forms proper to living things but not on the basis of physical-chemical principles. Instead, this mathematical theory explains living forms on the basis of a *logos*, a geometric entity that

governs and regulates the development of the different parts of an organism. In the context of Catastrophe Theory, the local morphologies developed within a living organism (the tissues and organs of the anatomists) are modelled by a local potential, a local *logos*. But these local potentials are engulfed by a global potential that governs the organisation of the organism as a whole. This global potential is equated with the global morphogenetic field which is a mathematical entity representing both a principle of spatial connection and a principle of functional correlation among the parts of the organism (Thom [1980], p. 159).

Hence, tumour development may have to be understood in terms of a conflict with the field processes that establish and maintain the whole body plan and organisation. It might be the case that cancer is not a disease but a problem resulting from exhaustion or alteration of the normal dynamics of development in vertebrates. Indeed, whatever the developmental constraints that regulate the process of ontogeny (Raff [1996]), we know that such a process is expected to go from the fertilised non-differentiated zygote to the mature fully-developed organism. However, once such a fully developed state has been achieved, thus giving opportunity for the mature organism to leave offspring, there is no further need that such developmental constraints remain in action, since there is no further point ahead in the developmental pathway. It is obvious that ageing represents the gradual loss of metabolic efficiency as well as the involution of bodily structures (tissue growth and repair are gradually impaired in the process of ageing). Cancer then may represent one of the most radical and deepest consequences of ageing, because it represents the loss of morphological coherence within the organism. A malignant tumour is a formless entity, it has no specific organic structure to achieve, nor it has any specific place to occupy within the body's economy. There are no high-fitness tumour cells that survive the demise of the host. Moreover, metastasis is the evidence that the tumour itself is never a coherent cellular mass that might achieve survival. Metastasis is the evidence of the formless and chaotic atomisation of abnormal biological tissue. It is rather absurd the notion that the ability to produce metastasis is a sort of adaptive property of tumour cells (Fearon [1999]). One may ask, adaptation to what? Indeed, most

metastatic growths are bound for spontaneous destruction and never achieve a significant size. When widespread metastases occur the result is the death of both the host and the tumour. Thus, metastasis is essentially acting against any possible survival of the tumour and the cells that constitute such a tumour. On the other hand, cancer in children and young people might be understood as a developmental aberration resulting from a failure of developmental constraints before the system reaches maturity. This means that the system drifts to an amorphous state before having reached its fully mature form. The rarity of childhood cancers supports the notion that developmental constraints are very effective at curtailing cellular growth that is out of pace with the rest of the growing organism.

The morphogenetic field, as a working principle, theoretical construct or abstract descriptive tool, is closer to any criteria of scientific rationality than any empirical gathering of gene-product interactions (such as those described in the genetic paradigm for cancer). The concept of morphogenetic field applied to the problem of cancer gives us clues to a possible intelligible ontology for such a phenomenon, which is lacking altogether in the current genetic paradigm. Since wholesale affectation of an organism's organisation, by local molecular disturbances affecting a limited number of cells, is assumed but it is never explained by such a paradigm.

The alternative view presented in this work, suggests that cancer is first of all an organic problem that cannot be exclusively reduced to the cellular, genetic or molecular level. Secondly, such a view suggests that the normal organism is organised by a *logos* or pregnantial entity represented by the morphogenetic field. Thus, the spontaneous appearance of a tumour might be the evidence that the properties of the field are gradually lost when the organism is beyond its prime (the *teleion*). The weakening of the original morphogenetic field also makes room for the influence of aberrant or spurious pregnantial entities that may seize a part of such a previously organised morphology. Therefore, cancer might be the result of a conflict between an organised morphology (the organism) and a part of such a morphology that drifts towards an amorphous state (the tumour).

It must be acknowledged that the current genetic and molecular model for cancer causality has a great heuristic content, because it immediately suggests multiple experimental approaches to further cancer research and for developing potential new therapies, such as the so-called gene therapy. Only time will tell us about the eventual success or failure of such endeavours. On the other hand, the alternative view suggested above, it is so incipient that it has little to offer from the practical point of view. We still need to know much more about the nature of the morphogenetic field and about the nature of pregnantial entities in general, before we could glimpse the rules that govern the interactions between pregnances (such as the morphogenetic field) and salient entities like the bodily structure of an organism. Yet, it is worth to consider what Sir David Smithers, an influential physician, wrote many years ago: "Cancer is no more a disease of cells than a traffic jam is a disease of cars. A lifetime study of the internal combustion engine would not help anyone to understand our traffic problems" (Smithers [1962]).

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Armando Aranda-Anzaldo

VERSO UNA VISIONE MORFOGENETICA DEL CANCRO

Riassunto

Nel presente lavoro vengono avanzate critiche all'opinione corrente secondo la quale il cancro sarebbe un mero problema cellulare causato da specifiche mutazioni genetiche. Viene suggerito invece che esso vada considerato come un fenomeno che deriva dalla rottura del piano morfologico, o *Gestalt*, dell'organismo. In termini aristotelici, un organismo è informato da uno specifico *logos* e persegue un determinato *telos*. Un tumore maligno costituisce un'entità priva sia dell'uno che dell'altro. Facendo ricorso ai concetti della Semiofisica, una fusione di fisica aristotelica e teoria delle catastrofi sviluppata da René Thom, l'autore propone che il cancro in individui anziani sia il risultato del progressivo venir meno dei vincoli che regolano il processo ontogenetico che dallo zigote indifferenziato conduce all'organismo maturo, mentre in individui giovani (prima dell'età riproduttiva) sarebbe la conseguenza di un prematuro allentamento di tali fondamentali vincoli morfogenetici. In ogni caso, il risultato sarebbe la perdita di coerenza morfologica all'interno dell'organismo. Il cancro rappresenterebbe dunque un conflitto tra una morfologia organizzata (l'organismo) e una parte di tale morfologia che tende verso uno stato amorfo (il tumore).