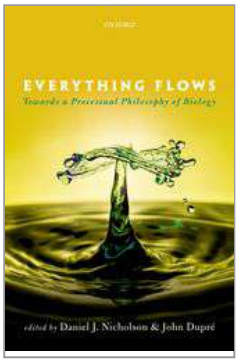

Everything Flows: Towards a Processual Philosophy of Biology
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A Processual Perspective on Cancer

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Abstract and Keywords

This chapter attempts to illuminate the dynamic stability of the organism and the robustness of its developmental pathway by considering the biology of cancer. Healthy development and stable functioning of a multicellular organism require an exquisitely regulated balance between processes of cell division, differentiation, and death (apoptosis). Cancer involves a disruption of this balance, which results in unregulated cell proliferation. The thesis defended in this chapter is that the coupling between proliferation and differentiation, whether normal or pathological (as in cancer), is best understood within a process-ontological framework. This framework emphasizes the interactions and mutual stabilizations between processes at different levels and this, in turn, explains the difficulty in allocating the neoplastic process to any particular level (genetic, epigenetic, cellular, or histological). Understanding these interactions is likely to be a precondition of a proper understanding of how these mutual regulations are disrupted in the processes we call cancerous.

Keywords: apoptosis, biological rhythm, cancer, cell differentiation, dynamic stability, morphogenetic field, multilevel coupling, process ontology, relational ontology, somatic mutation theory

1. Introduction

Life can be characterized as a hierarchy of processes. It is dynamic at all levels (molecules, cells, tissues, organisms, lineages). This chapter thus starts from the premise that living systems should be understood not within a mereological framework (as things) but within a processual one (as processes).[1] For present purposes the most crucial corollary of this ontological observation is the

following: whereas for a thing the default is persistence, for a process it is persistence that requires explanation. A table may sit in the attic for decades, undergoing little change that could not immediately be reversed with a duster. If you accidentally shut your cat in the attic, it will soon be a dead cat and, before too long, the skeleton of a cat. Without food and water, it is no longer able to perform the activities that sustain it. To put the point rather crudely, for things, what needs explanation is, typically, changes that they undergo; for processes, it is rather, or at least equally, their continued existence that calls for an explanation. For living systems in particular, this point is well captured by the familiar observation that these are systems far from thermodynamic equilibrium. To keep them there requires work, and this work comprises the processes that sustain the system.

The topic of this chapter is cancer, and the relevance of the above remarks to this topic should be obvious. It is generally supposed that the key to understanding cancer is to find out what causes it. What is it that interacts with a healthy individual organism to initiate the eventually fatal neoplastic process? From a processual perspective, on the other hand, one might rather ask, why do organisms generally *not* develop neoplasms? In slightly more detail, the persistence of an organism requires an exquisite balance between cell division, cell differentiation, and cell death. Many departures from this balance constitute cancers. Given how much activity and appropriate higher-level context are required to maintain the dynamic **(p.322)** stabilization of a multicellular organism, it is remarkable that these conditions can be sustained at all over long periods of time. Cancer, which in this chapter we regard as the progressive destabilization of the coupling of cell division and differentiation required to sustain the organism’s life cycle, is a phenomenon very much to be expected.

As Denis Noble has stressed, the core issue in accounting for the dynamic stability of living systems is *modelling across scales*. ‘[I]n order to unravel the complexity of biological processes we need to model in an integrative way at all levels: gene, protein, pathways, subcellular, cellular, tissue, organ, system’ (Noble 2002: 1). Given that the stable persistence of an organism requires such interactions between multiple systems at multiple organizational levels, it is no surprise that cancer has proved to have many causes at many levels. If there is anything general to be said about the phenomenon of cancer, then, it is more likely to be about what *prevents* it—that is, about what enables the healthy stabilization of cell populations—than about what causes it. Seeing health as depending on the highly regulated intertwining of different organismic processes implies, in turn, the necessity of adopting a processual view in defining and explaining carcinogenesis.

This dynamic, process-centred perspective has various other important implications for our general approach to biological systems. Focusing on the causes of stability draws attention to the relations of a system to the

environment to which it must respond appropriately if it is to persist. More generally, we suggest that the stabilization of a biological system will always, or almost always, depend not merely on the properties of its parts, but also on its position within a larger system. Attention to this point resonates with various very active areas of contemporary research: epigenetics tells us how the effects of the environment on the organism can reach right into the nucleus, affecting gene expression in ways that are presumably often adaptive (Goldberg et al. 2007). Niche construction theory explores the ways in which much of the behaviour of an organism is directed towards creating and maintaining features of the environment that are favourable to the survival and reproduction of the organism (Odling-Smee et al. 2003). And so on.

An equally important context is what we might think of as the wider temporal environment, the reproductive lineage of which a particular organism is part. To exist at all, an organism must of course be part of such a lineage. And a stable lineage must be one that produces individuals that contribute to the maintenance of the lineage, namely by reproducing. Reproduction must result in the production of new organisms that have the capacities to maintain the (lineage) process of which they are part; and it is now appreciated that there are a variety of processes by which this transmission of adaptive features is effected, for example the niche construction just mentioned.[2]

Scientists are increasingly aware that the methodologies required to model across scales contrast with the traditional, reductive approach, which is grounded on a simplistic mereological view of the natural world. The peculiar complexity of biological systems readily accounts for the difficulties we experience in scientific practice in separating the dynamics at any given level of organization from the coupled dynamics of all other levels, including that of the environment within which the **(p.323)** system is embedded. These issues have been explicitly addressed by one of us in various places (Dupré 1993, 2010; O’Malley and Dupré 2005; Powell and Dupré 2009) in terms of the ineliminability of context dependency and top-down causation from biological explanation, and by the other more explicitly in studies on the evolution of explanatory models of cancer (Bertolaso 2009; 2016). From an ontological point of view, the inadequacy of a simple, hierarchical view of living systems in which explanatory relations are exclusively from parts to wholes, culminating in the absurdity of considering every feature of biological form as somehow encoded in a single molecule, is argued to be a central problem, which can be disposed of by adopting a more adequate process ontology for living beings (Dupré 2012). Growing insights into the importance of epigenetic changes and the evolutionary and developmental co-dependencies between different organisms further reinforce this processual view of the biological world.

This chapter will discuss the biology of cancer from the processual perspective just sketched, which will be further elaborated upon in the next section. It is acknowledged that cancer is a process that disrupts the functional coupling of organismic lifetime processes, notably cell proliferation and differentiation. We shall argue that the proliferation–differentiation coupling (in a normal individual) or uncoupling (in a pathological one) as well as the time-context dependence of the neoplastic process are best understood within a relational process-ontological framework that emphasizes the interdependence of these and other key processes (section 3). This perspective stresses the mutual determination of, and regulation between, different processes involved in the development and physiological maintenance of the organism. Such relations also hold between the various organizational levels of a multicellular organism, so we shall need to consider from this processual perspective the balance between autonomy (intrinsically determined behaviour) and connectedness (contextually determined behaviour) of cells or tissues belonging to a multicellular organism. We shall finally suggest that these various dimensions, both spatial and temporal, might be integrated through the concept of *morphogenetic fields*, a notion commonly used by scientists but still almost unexplored by philosophers (section 4). This concept refers to ‘large-scale systems of physical properties that have been proposed to store patterning information during embryogenesis, regenerative repair, and cancer suppression that ultimately controls anatomy’ (Levin 2012: 243).

2. Cancer as a Process

A process view of cancer in the scientific literature is generally motivated by the causal complexity of the disease, the explanatory problems of a reductionist genetic view of carcinogenesis, and the limits of molecular treatments and target therapies that derive from tumour latency and its dependency on time and context (Harris 2005; Sonnenschein and Soto 1999; Sporn 1991, 2006). Cancer is a paradigmatically complex disease. It appears to involve causes of many different kinds—for example environmental, tissue-level, genetic, and epigenetic causes—and it is well known that there are many different varieties of cancer. There is, however, one general characterization that applies to all forms of cancer: it is a failure of the processes that regulate the production and destruction of cells. A functional metazoan requires an **(p.324)** exquisite balance between the various different cell types that make up its organs and systems. This balance is maintained by processes of cell division, cell differentiation, and cell death. We noted earlier that, in a sense, what most fundamentally requires explanation is not so much the presence as the absence of cancer, because the regulation and alignment of these processes is a remarkable achievement, and it is no surprise that it should be liable to fail in many different ways and for many different reasons. The proper balance of cell types is not something that is achieved once and then maintained by inertia; its maintenance requires a continuous and dynamic set of activities. Moreover, this

functional balance is itself something that changes over the life cycle of an organism, and cancer can be seen as a failure to follow the ‘correct’ developmental trajectory. It has been described as development gone awry (Soto el al. 2007), as blocked ontogenesis (Potter 1978), and as a disease of the developmental or morphogenetic process (Biava 2002; Bizzarri and Cucina 2014).

Historically, cancer was deemed to be a disease that was due as much to the environment as to endogenous factors. However, this pathology was not subject to careful scientific investigation until the end of the nineteenth and the beginning of the twentieth century, when Rudolf Virchow (1821–1902) explored its relationship to both genetic and cellular factors. Subsequent development of new biochemical tools, advances in microscopy, and more sophisticated analyses of environmental data led to more thorough studies of cancer at various levels. Several hypotheses on the origin of cancer began to emerge, ranging from the ‘biological theory’ (Rous 1910) to the ‘chemical theory’ (Potter 1964; Doll and Hill 1956; Colditz et al. 2006; Parkin 2004), which envisaged an alteration of the cells’ physiological balance caused by toxic substances in the environment, and to the popular ‘viral theory’ (Duesberg 1980; Klein 2002; Burmeister 2001). In the 1950s and 1960s, the ‘genetic theory’ (Knudson 1971) began to dominate oncological thinking and, as a result, decreasing attention was paid to the relevance of the organismic environment and of the immune system. This theory was originally supported by the evidence, first described by Boveri (2007 [1914], 1929), of the highly disorganized character of chromatin in cancer cells. Following the identification of DNA as the molecular basis of genetic inheritance, this disorganization was reinterpreted in genetic terms, resulting in what is today commonly referred to as the ‘somatic mutation theory’ (see section 3).[3]

Throughout the twentieth century, the aetiology of cancer remained at the forefront of epidemiological research, and the relevance of environmental, epigenetic, immune system, and microenvironmental (e.g. tissue architecture) factors in carcinogenesis was never completely overlooked. Indeed, a number of historical studies showed conclusively that both environmental and organismic factors play a causal role in carcinogenesis, and their effects can be surprisingly precise. A telling example is the wave of cases of cancer diagnosed in female survivors of the atomic bombs of the Second World War (Tokunaga et al. 1979): tumours arose only after a period of time and in an almost synchronous manner for many of those who had been exposed to atomic bomb radiation.

(p.325) It has long been recognized that cancer is an inherently complex phenomenon. This complexity manifests itself in the diversity of causal factors and in the timescales on which these factors operate. This should not be all that surprising, given the multiplicity of processes at different timescales that are involved in stabilizing cell division and differentiation. As we have already

mentioned, long-range signals provide positional information to regulate organism-wide systemic properties like anatomical polarity, size control, and the multilevel functional integration of cell behaviour. When these various modes of stabilization fail in sufficient number, cancer ensues. This is why cancer cannot be considered a discrete event; still less can a tumour be regarded as a static thing. Rather, it is a process, or a set of processes, which extends over considerable periods of time and generally involves various levels of organization in the body.

The causal complexity of cancer is not simply due to a multiplicity of causes, among which researchers can pragmatically select in their investigations. Multiple alterations at different levels (e.g. genes, proteins, membrane structures, tissues) are all required for a cancer to develop. The eventual outcome is an aberrant proliferation of cells, with the progressive disruption of functional integration, and thus of biological order, at different scales, from genes to cells and tissues. The morphological order that usually characterizes tissues and organs is lost. Although cancer is usually diagnosed on the basis of a morphological disruption of tissue organization, it typically requires the loss of dynamic stability at other levels of organization as well (Bertolaso 2013, 2016). The diversity of the phenomenon of cancer becomes evident when we consider the *temporal dynamics* of the neoplastic process. The course of the disease varies between different patients and generalizations seem hard to find, not for lack of experimental data but because the variables relevant to the timing of the neoplastic process vary widely from case to case.

The appearance of clinical symptoms of a tumour is preceded by a variable period of time called the *latency period*, which in many human tumours can last for years. Throughout this period of latency, cancer already exists as an aggregation of cells whose normal process of proliferation–differentiation has been somehow compromised, but is not yet clinically identifiable. A number of experimental studies have suggested that the onset of cancer may be more directly dependent on the alteration of morphogenetic dynamics over time than on specific genetic mutations. Compelling evidence for the requirement of a properly ordered timing of inputs for the development of neoplastic phenomena dates back to studies conducted in the 1970s on the carcinogenic effects of chemicals applied to the skin of mice (Boutwell 1978). It was found that these animals develop skin cancer if repeatedly exposed to potentially mutagenic chemical carcinogens (such as benzopyrene or dimethylbenzoanthracene). More importantly, this research provided evidence that both the *sequence* and the *frequency* of these exposures are relevant to the onset of cancer.

By the 1980s it became apparent that carcinogenesis could be characterized as a disruption of the organism’s regulatory processes (Lotem and Sachs 1974; Potter 1978; Soto and Sonnenschein 1985). The loss of certain cellular functions began to be seen in correlation not so much with various molecular causes of

tumour formation as with the decoupling of regulatory mechanisms. This led to a shift in focus from the causal relevance of molecular mechanisms and the effects of their alteration to the **(p.326)** coordination of crucial regulatory processes, specifically those pertaining to cell proliferation, differentiation, and apoptosis. This change of emphasis has had important theoretical ramifications. The development of cancer had long been seen as processual in the narrow sense of constituting a linear sequence of events, such as a cumulative series of genetic 'knockouts'. However, recent models of carcinogenesis construe it in a more thoroughly processual vein, as a progressive change in the *rhythm* that orchestrates development and synchronizes the coupled regulatory processes that are part and parcel of healthy physiological function. The distinguishing characteristic of tumours remains the heterogeneity of cell behaviour, which results in an accumulation of cells with aberrant phenotypes within the tumour (Hanahan and Weinberg 2011; Dalerba et al. 2007; Ailles and Weissman 2007), but this is no longer viewed as constituting the final stage of a linear process. Instead, it is increasingly regarded as merely one of the various levels at which the breakdown of order occurs during carcinogenesis.

The disruption of the organism's normal physiological rhythm is manifested in the disturbance of the balance between cell proliferation and differentiation on the one hand, and apoptosis on the other. In addition, there are disruptions in the regulation of gene expression and in epigenetic modifications at a lower level of organization, as well as a breakdown of tissue organization at a higher level of organization. It is misleading to attribute a determinate causal order to the relations between these failures. Rather, as the orchestrating rhythm of the overall system degenerates, order begins to break down concurrently at multiple levels. Because the regulation of each level is achieved by means of cyclical processes acting at both higher and lower levels, multiple causal relations can be identified in this multilevel breakdown of organization. It is a mistake to privilege any particular level over others. It is the hierarchy of cyclical processes and their mutual regulation that generates the remarkable dynamic stability of the multicellular organism. When this stability deteriorates, it does so simultaneously at these interlinked levels.

Accumulating evidence is converging in support of the characterization of cancer as a progressive disorganization of a variety of organizational levels. As an organism's self-maintaining organization is fuelled by the continuous input of energy and information, compromise of the channels through which these are supplied constitutes the most systemic root of cancer. Recent research suggests that synchronized physiological rhythms play a key role in mediating the flow of energy and information at different levels (Plankar et al. 2012). Cancer, rather than being a genetic disease, is more fundamentally 'characterised by a global impairment of energy and information flow through the system, as manifested in genomic, transcriptomic and proteomic dysregulation' (ibid., 21). Moreover, as biological organization does not only pertain to topological order, but also has

dynamic manifestations, such as synchronization, cancer is also rooted in the breakdown of the rhythmic coordination of different levels that facilitates these flows.[4]

(p.327) 3. The Relational Ontology of Levels

A historical–epistemological view of the evolution of the interpretive models of carcinogenesis (see Bertolaso 2013, 2016) highlights how models at different levels of organization (from genes to tissues) converged towards analogous morphogenetic and morphostatic principles in their effort to account for the distinctive phenomenology of the neoplastic process we have described in section 2. Such principles do not have their basis in the intrinsic features of molecules, but rather refer to the systemic properties and functions of cells, tissues, and organs, which are processual in nature. In explaining the stability of a multicellular organism and its destabilization following the onset of cancer, it is the dynamic relationships among parts at different levels of the organizational hierarchy that are causally more relevant than the intrinsic properties of those parts. Describing tumours as a progressive disruption of the hierarchical organization, with predictable consequences at the organ level as well as at the level of cells and genes, requires a specific, non-reductionist explanatory approach. The *relational ontology* of levels (Bertolaso 2016, 2017) clarifies the epistemological status and ontological foundations of the explanatory categories needed to account for the interactions of different levels of organismic organization, as well as clarify how their reciprocal dependency works within a processual philosophy. It submits that there is a hierarchy of levels in the functional organization of a metazoan; and, rather than assume a privileged causal level in the explanatory account of diseases such as cancer, it calls for a pluralistic account, able to fully accommodate the temporal coordination between distinct levels of organization.

Let us illustrate the fruitfulness of this perspective with an example. Despite the popularity of genetic accounts of cancer, the majority of mutations actually seem to be the result, rather than the cause, of carcinogenesis (Baker 2014). This does not fit a standard, bottom-up, mechanistic account of carcinogenesis. It is, on the other hand, consistent with an account in which morphogenetic and morphostatic constraints play the most important role in the maintenance of the developmental process—a process actively stabilized at many levels by various robust sub-processes. It can be hypothesized that these stabilization processes are realized in multiple attractor states at various levels of organization (Ingber 2008; Huang and Ingber 2000; Huang 2011). Against this background, microenvironmental factors mediated by epigenetic mechanisms acquire a major causal relevance in the onset of cancer (see also Capp 2006). In this way, cancer can be said to involve a deviation from the range of normal functional states of an organism’s developmental trajectory.

This relational perspective also casts light on the ongoing debate between two main positions that compete in explaining carcinogenesis: somatic mutation theory (SMT) and tissue organization field theory (TOFT). The former considers the neoplastic process to be triggered by genetic mutations that lead to alterations in **(p.328)** cellular behaviour, while the latter locates the origin of cancer in the deterioration of tissue organization (Sonnenschein and Soto 1999; Soto and Sonnenschein 2005). Broadly speaking, SMT models adopt a reductive approach to biological explanation: higher-level phenomena are explained in terms of the properties and interactions of their parts, and changes at higher levels are traced to changes at the lower level. Those who reject this reductionistic viewpoint typically accept so-called downward causation, that is, casual explanation of the behaviour of parts in terms of autonomous causal powers of the whole (Noble 2008). As we have discussed, the processual view presented here takes carcinogenesis to involve the disruption of processes at multiple levels of organization, which mutually regulate and stabilize each other and which, collectively, constitute the lifetime process of ontogenic development.

We thus reject the reductionist presuppositions often associated with SMT. At the same time, however, we do not endorse an exclusive holistic focus on tissue organization of the kind that proponents of TOFT seem to support.[5] Instead, we propose a *pluralistic* explanatory approach. Because cancer is a multilevel phenomenon, we believe that what is needed is the deployment of a variety of models which address using different methodologies and over different timescales the effects of the same overall process on various biological entities (genes, cells, organs, etc.).

Overall, SMT is incapable of providing a satisfactory explanation of the characteristics of tumour cells, as well as of the neoplastic process as a whole. In principle, SMT is not incompatible with an explanation of cancer that construes it as an aberrant process of development, or as the disruption of the homeostatic mechanisms governing the normal proliferation of the cells (Hahn and Weinberg 2002a, 2002b). However, it does not possess the explanatory resources needed to account for the multiple levels at which neoplastic processes act and interact. As we have argued, a tumour is formed when a metazoan cell undergoes aberrant changes in the coupling of processes that normally regulate organic growth.

Defining carcinogenesis in terms of mistakes in the proliferation of cells, or as genetically programmed apoptosis, is to construe it as an autonomous cellular process, depending upon the intrinsic (mainly genetic) properties of cells (Weinberg 2006; Hanahan and Weinberg 2000, 2011). But, even if this understanding is not deemed to imply a form of genetic determinism, its exclusive focus on intrinsically driven cellular processes is problematic. Processes such as cell proliferation and differentiation are not self-sufficient, autonomous determinants of development and growth. Development is a

multifactorial process, dependent on both external and internal factors (as emphasized for many years now by developmental systems theorists; see e.g. Griffiths and Gray 1994 and chapter 11 in this volume). These cellular processes are both causes of and caused by the developmental processes of which they are part.

The processes of cell division and differentiation that lie at the basis of healthy morphogenesis and are pathologically disrupted in carcinogenesis are not autonomous and internally generated, but are inextricably dependent on the wider context **(p.329)** in which they act. For instance, a stem cell, which is usually considered the paradigmatic source of biological differentiation, is highly dependent upon its spatio-temporal position in the organism (Fagan 2013). Once extracted from its ‘biological context’, the cell loses its pluripotency and undergoes a process of proliferation and differentiation, like any other somatic cell. In other words, it loses the asymmetry that characterizes the divisions of stem cells. This point illustrates the inadequacy of a further reductionistic perspective, termed ‘biological atomism’ (see Nicholson 2010), which attempts to derive all organismic activity from the activity of fundamental biological units, in this case cells.

The shortcomings of this atomistic approach highlight the fact that distinguishing tumour cells from normal cells, or tumour cells among themselves, is far from trivial, since not all of the tumour cells have the same proliferative and invasive capacity. The aim of these distinctions is to characterize cells in terms of their activities, as processes. And it is generally supposed that this can be done by characterizing their internal structure, just as one describes the essential features of an object. However, as is so often the case in biological systems, in which the behaviour of an entity invariably depends on its role in a wider context, it appears highly doubtful that this reduction of process to object can be accomplished. The shift in perspective from object to process, from internal structure (the nature of stem cells) to external environment (the ‘stemness’ of a cell under specified circumstances), draws attention to the more transitory, for example epigenetic, effects of the environment—effects that are often described in terms of networks (Giuliani et al. 2014).

4. Morphogenetic Fields

The claims we have advanced in the previous section reinforce the idea that in the onset of the neoplastic phenotype the balance between cell proliferation and cell differentiation is disrupted. As we have seen, molecular elements alone do not offer a satisfactory or sufficient causal explanation of cancer. Something further is needed that can illuminate the structuring of developmental patterns and the coupling of the relevant processes at a variety of spatial and temporal scales. In this context, we believe that it may prove helpful to appeal to an

explanatory notion that is commonly used by scientists but which remains virtually unexplored by philosophers.

In the early decades of the twentieth century, organicist theoretical biologists Joseph Needham (1936) and Conrad Hal Waddington (1935) already speculated that cancers represented an escape from the control of a *morphogenetic field*. With the advent of molecular biology, this perspective was abandoned. Only when 'morphogen' gradients became visualized in the 1990s did developmental biology resuscitate this old concept. Morphogens are diffusible substances that contribute to orienting the cell differentiation process and thus to determining the pattern of tissue development.[6]

(p.330) In more recent literature, this concept has re-emerged in various authors who refer to 'fields of cancerization': these are groups of cells from which specific morphological structures develop in response to biophysical and biochemical cues, generally mediated by epigenetic changes. In cancer, these epigenetic changes are aberrant (Ushijima 2007). Such aberrant epigenetic fields of cancerization promote carcinogenesis (a) by inducing epithelial cell growth, angiogenesis, degradation, and remodelling of the extracellular matrix and basal lamina; and (b) through paracrine signalling that induces epithelial cells to secrete further tumour-promoting factors. More generally, it appears that developmental, regenerative, and cancer biology requires a focus on 'the spatially distributed nature of instructive patterning signals' (Levin 2012: 244). The multilevel phenomenology of cancer involves organizational dynamics that are progressively compromised in the transition to a neoplastic process. The concept of a morphogenetic field aims to make sense of such organizational dynamics.

From this emerging field perspective, cancer is primarily characterized by an unspecific progressive disorganization, which can result from the impairment of the coherent dynamics at some specific level. The multiple interactions both within and between levels that constitute the impaired functional field make it difficult to identify a unique causal factor; the impairment may be induced by multiple, causally interconnected disruptions of the dynamics of the system. For example, damage to oxidative respiration and prolonged dependence on glycolysis may induce structural abnormalities in the mitochondrial inner membrane; it may also severely disturb cell homeostasis, and it will generally lead to genomic instability (e.g. Plankar et al. 2012). Epigenetic instability, which may be caused by stochastic perturbations, can result in a range of genomic changes (e.g. variation in gene expression, chromosomal instability, activation of mobile genetic elements, etc.), any of which may eventually translate into instability of the genome itself. In fact, it has been known for some time that environmental stress can induce genomic rearrangements (Ingber 2008; Levin 2012). One last important factor that should be mentioned in the context of the integrated nature of the functional field is the cytoskeleton (Nelson and Bissel

2006), which integrates many signalling pathways, influences gene expression, coordinates membrane receptors and ionic flows, and localizes many cytosolic enzymes and signalling molecules, ultimately forming an integrated system throughout the tissues and organs (Plankar et al. 2012).

Overall, the concept of field integrates various kinds of phenomena, providing a theoretical principle that can account for different aspects of carcinogenesis from both biological and physical perspectives. Specifically, the term ‘field’ as it is used in the literature denotes ‘a construct that encapsulates key properties of instructive growth and patterning control’ (Levin 2012: 243). This is probably why this term is so often used to describe features of the biology of cancer.

One important reason for shifting the perspective from the genetic to the morphogenetic field view is the apparent reversibility of carcinogenesis. The neoplastic phenotype of tumour cells can revert to a normal healthy phenotype when located in a healthy microenvironment (Mintz and Illmensee 1975; Hochedlinger et al. 2004; Kenny and Bissell 2003; Lotem and Sachs 2002; Erdo et al. 2003; Soto and Sonnenchein 2005). Clearly, this is hard to reconcile with the idea that there is some **(p.331)** intrinsic property of a cell—the cancer stem cell—that inexorably leads it to express the neoplastic phenotype. The breakdown in spatio-temporal organization of the morphogenetic field—in which cues from both lower (molecules, cells) and higher or functional (tissue, endocrine and nervous stimuli, dietary factors) levels converge—disrupts the coherence between the cell and the overall organismic functional dynamics, thereby contributing to the onset of cancer. According to this perspective, the dynamic switch towards different cell fates is ultimately under the control of a morphogenetic field. Indeed, studies in which cancer cells have been cultured in specific morphogenetic fields (3D, embryonic, or maternal) or by modifying supramolecular control factors (as the overall tissue stiffness or the endocrine stimulus) show how a strong, ‘normal’ morphogenetic field successfully induces the reversion of the tumour phenotype (see Bizzarri et al. 2012). On the whole, it is difficult to reconcile this heterogeneity with the hypothesis that there is some unitary unidirectional process that leads from a set of conditions internal to the cell to the full-blown phenomenology of cancer at a hierarchy of levels, without assuming a processual perspective on cancer itself.

5. Conclusions

There are various respects in which adopting a process-centred perspective can provide greater clarity in our thinking about cancer. The first step is to move from a simple contrast between a thing, the organism, and something that happens to it, the pathological process. From the point of view we are advocating, the organism itself is a process, specifically a developmental process. Development is not something that happens contingently to the organism; it is a core and structuring activity without which the organism could not be the kind of process it is. At a fine scale, the central constituents of the

ontogenetic process are the divisions, differentiations, and deaths of cells. Cancer is a disruption of this ontogenetic process. Given the complexity and multiplicity of the systems that are involved in the reliable regulation of the ontogenetic process, it is no surprise that there are ways in which this can go wrong, or that the longer the system persists, the more likely it is that the regulation of the underlying, ordered production and destruction of cell types will fail.

There are various ontological and epistemological implications of this processual viewpoint on cancer. First and foremost, there are serious limits to the possibility of explaining carcinogenesis in terms of the linear, bottom-up causal sequences that have been dominant in much of recent biology. A process ontology should qualify the way we think scientifically about biological entities at all levels. Neither the organism nor the organ whose pathology we are trying to explain, nor the structural elements (cells, genes, etc.) in terms of which we do so, are static and univocally defined entities. The extent to which they may seem to be static entities is a consequence of their status as processes dynamically stabilized over various, often very short, timescales. This stabilization is accomplished both by the interactions of parts and by the relations that constitute the parts as parts of a larger system. The proper sense in which ‘the whole is greater than the sum of the parts’ is that the parts are, to some degree, constituted as the kinds of entities they are by their relation to the whole.

(p.332) This network of relations in which stabilities emerge at multiple levels and are maintained by the simultaneous activities of entities at further multiple levels is a long way from the linear mechanistic causality in terms of which we are more accustomed to think. Nevertheless, it is what we must come to grips with if we are to understand the processes that maintain the stable features and the stable cycles of living organisms, as well as the ways in which these features and cycles can (too frequently) become disrupted. Some projects under the general rubric of ‘systems biology’ do appear to be heading in this direction.

In case this characterization of the complexity of biological processes in general and of cancer in particular is discouraging, we end with a more optimistic thought. In exploring regularities at various levels of organization, from patterns of evolutionary adaptation to patterns of gene expression, it seems that outcomes are frequently more robust than the processes that produce them. It is plausible that this is a necessary requirement in order for systems to exhibit both high complexity and high stability; which is to say, a requirement for life. One way of expressing this requirement is in terms of the concept of an ‘attractor state’, a state that the system has a tendency to reach one way or another. If the state of a properly functioning cell is an attractor state, then presumably cells are capable of reaching many such states, as demonstrated by the processes of cell differentiation. Cancer could then be seen as providing a

new, dysfunctional attractor state or, perhaps better, as breaking down the processes that lead the cell to the contextually correct state (as in the extreme case of the teratoma, in which different parts of the tumour mimic bits of different organs).[7]

We describe this as an optimistic thought because, unlike a linear path that has been lost, a scenario in which there may be no attainable way of rejoining it, there is no reason why the locally healthy attractor state would be lost just because the cell has found its way to another. This thought leads to another. It is common to think of medicine as engaged in trying to restabilize a system that some injury or insult has destabilized. But in the case of cancer, at least, the aim, paradoxically perhaps, should be to destabilize rather than stabilize the system. An attractor state, after all, is by definition something stable. States in its vicinity will revert to it; small perturbations will not lead the system away from an attractor. If cancer itself is a stabilized state, a pathological attractor state, then it may be that a large shock is needed to destabilize the system, in the hope that the healthy state will be regained. Perhaps this is a general explanation of why the standard treatments for cancer, the familiar repertoire of slash, poison, and burn, are sometimes successful.

This last thought is of course speculative, but some empirical studies seem to point in this direction (e.g. Cirkel et al. 2014). What we hope it illustrates is that ontological reflections on the nature of cancer, which in turn will require ontological reflections on the nature of living systems more generally, can profoundly affect how we think of the medical problems of oncology. If we are right that living systems are dynamically stabilized processes, this will have profound consequences on how we attempt to keep that process running for an optimal period in a desired condition.

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Notes:

([1]) If and to what extent this assumption, and the following discussion, can be fruitfully extended to a metaphysics of life in general and to a revision of the classical notion of substance is beyond the scope of this chapter. One of the authors, however, is committed to a more general extension of this sort (Dupré 2012 and chapter 1 of this volume, co-authored with Daniel Nicholson), while the other has shown why a mereological framework is not adequate to account for cancer and how a processual perspective also makes sense of scientific practice (Bertolaso 2016).

([2]) For a detailed processual account of organismic lineages and their evolution, see Dupré 2017.

([3]) For a broader and more comprehensive historical review of theories of carcinogenesis, see Loeb and Harris 2008; Bizzarri et al. 2008; Bertolaso 2009, 2016; and Weinberg 2006.

([4]) Synchronization is defined as a natural tendency of biological systems to adjust their internal rhythms to a collective operational regime due to their mutual interactions, and it has become one of the main areas of research in non-linear science. Synchronous behaviour of coupled elements enables a powerful response of a system to external stimuli, efficient coordination between different systems (e.g. temporal compartmentalization), and information encoding; it also maximizes energy and information flow throughout the system, thereby increasing the organizing potential of biological processes. There is no gene for the rhythm of a pacemaker, or coherent brain oscillations, which represent a dynamic physical basis of cognition. In the same way, there is no gene or genetic pathway for cancer, because cancer is, like any physiological rhythm, a dynamically emergent process (Plankar et al. 2012; Winfreee 1967; Haus and Smolensky 2006).

([5]) For a discussion of TOFT’s merits in opening up a new view regarding the importance of a field theory of development, and on the epistemological implications of adopting this perspective, see Bertolaso 2016.

([6]) For a historical review of the origin and use of the morphogenetic field concept, see Soto and Sonnenschein 2006. For a contemporary methodological overview of its use in biological modelling, see Levin 2012. For a discussion of its explanatory import, see Bertolaso 2016. For a deeper analysis of the relationship between the neoplastic process and embryogenesis, see Bizzarri et al. 2011.

([7]) See Huang 2011 for a more detailed attempt to characterize cancer along these lines.