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ORIGINAL PAPER

Emergentism by default: A view from the bench

Ana M. Soto · Carlos Sonnenschein

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Abstract For the last 50 years the dominant stance in experimental biology has been reductionism in general, and genetic reductionism in particular. Philosophers were the first to realize that the belief that the Mendelian genes were reduced to DNA molecules was questionable. Soon, experimental data confirmed these misgivings. The optimism of molecular biologists, fueled by early success in tackling relatively simple problems has now been tempered by the difficulties encountered when applying the same simple ideas to complex problems. We analyze three examples taken from experimental data that illustrate the shortcomings of this sort of reductionism. In the first, alterations in the expression of a large number of genes coexist with normal phenotypes at supra-cellular levels of organization; in the second, the supposed intrinsic specificity of hormonal signals is negated; in the third, the notion that cancer is a cellular problem caused by mutated genes is challenged by data gathered both from the reductionist viewpoint and the alternative view proposing that carcinogenesis is development gone awry. As an alternative to reductionism, we propose that the organicist view is a good starting point from which to explore these phenomena. However, new theoretical concepts are needed to grapple with the apparent circular causality of complex biological phenomena.

Keywords Cancer theories · Carcinogenesis · Cell proliferation · Downward causation · Organicism · Reductionism

A. M. Soto (✉) · C. Sonnenschein
Department of Anatomy and Cellular Biology, Tufts University School of Medicine,
136 Harrison Ave, Boston, MA 02111, USA
e-mail: ana.soto@tufts.edu

A. M. Soto · C. Sonnenschein
Centre Cavaillès, Ecole Normale Supérieure, 29 Rue d'Ulm,
75005 Paris, France

C. Sonnenschein
e-mail: carlos.sonnenschein@tufts.edu

1 Introduction

Philosophers have been debating how to define emergent phenomena, whether emergence is an ontological or epistemological category (Bunge, 2004), and whether emergentism is a viable alternative to reductionism (Kim, 1999, this volume). Judging by some of the biological examples philosophers use to illustrate their positions regarding emergentism, we are concerned that our evaluation of their biological examples may be as harsh as their judgments about our incursions into philosophy. Hence, we will avoid this temptation and instead, look at the problem of reductionism/emergentism from our perspective as experimental biologists.

We can safely say that the overwhelming majority of biologists are materialists/physicalists. By this we mean that they take the ontological position that what actually exists is matter. Within this materialist stance, the dominant epistemology is reductionism. By that we mean that explanations are found at the lowest possible level of organization, so that biology can eventually be reduced to chemistry and physics. However, in practice, this reductive thrust stops at the level where "it makes sense." Admittedly, "what makes sense" is hard to define. Methodologically, it means something like "do not bring more details than those needed to construct an explanation." For example, biochemists studying the mechanism of action of a particular enzyme may describe their objects of study at the atomic and subatomic levels of organization. This is necessary for elucidating substrate-enzyme interactions resulting in the modification of the substrate. They are in fact working in the realm of chemistry. However, when questions are asked about cellular activities—for example, how a particular hormone "induces" a functional response in a particular cell type—the description of the "signal transduction" pathway is generally made at a higher level of complexity. These researchers concentrate on describing the sequence in which proteins interact in order to transfer information from outside the cell into an observable cellular response (Morange, 2003). They consider that a lower level of inquiry is not necessary to understand how the hormone elicits cellular behavior. Curiously, while biochemists do not strive to explain all phenomena at the lowest possible level of organization (i.e., a physical one), a great number of biologists insist that explanations should always be sought for at the gene and/or gene product level, regardless of the level of organization at which the phenomenon of interest is observed. This stance, genetic reductionism, predicates that everything in biology must be reduced to genes because the genome is the only repository of transmissible information. In this view, genes are the only units of selection (Dawkins, 1976) and development is just the unfolding of a genetic program. In sum, genes in this view are the building units of the organism.

Although prevalent, this is not the only way in which biologists deal with epistemology. Evolutionary biologists have a tradition of being philosophically literate and caring about epistemological issues. Biologists concerned with the study of multicellular organisms in general, and metazoa (multicellular animals) in particular (i.e. developmental biology, physiology, and cancer research) deal with epistemology in four different ways:

(1) They consider that "data talk" and data are theory-free.
(2) They adopt reductionism to study complex phenomena like carcinogenesis. By reductionism, we mean genetic reductionism, which in biology has mostly replaced physical reductionism. When the data contradict their hypotheses they usually invoke complexity and add *ad hoc* explanations to incorporate the contradictory

data. Eventually, they hope, everything will fall into its proper place. The original hypothesis is rescued by deciding a posteriori that the *ceteris paribus* clause did not apply to the set of troublesome data. Oftentimes, no attempts are made at rejecting any hypothesis (see below, under "The Somatic Mutation Theory").

(3) They adopt an organicist view and accept the existence of emergent phenomena. Parenthetically, organicism is also called materialistic holism (Gilbert & Sarkar, 2000). They choose to work at the level of organization at which the studied phenomenon is observed and gingerly venture into lower levels of organization. However, they do so gradually through the diverse hierarchical levels of complexity, rather than jumping from phenotype to gene. Moreover, since they acknowledge emergent phenomena, their incursions into lower levels must be followed by a synthesis of how lower level phenomena bear upon upper level phenomena.

Or,

(4) They adopt an instrumentalist stance and study phenomena using heuristic models for as long as they continue to be consistent with data. They adjust their models as problems arise and care neither about the unity of science nor the reality of the entities and processes their explanations postulate.

2 Reductionism versus organicism

In the 1960s, it seemed that genes (hitherto considered abstract and operational entities) were finally transformed into material, specific DNA sequences (Benson, 2001). Molecular biologists concluded that biology was at last being reduced to chemistry. However, the early optimism about reduction has proven premature. Hull was probably the first to call attention to the difficulties in achieving this reduction (Hull 1974). Additional arguments for the irreducibility of the Mendelian gene to the molecular gene were provided by the discoveries of the modular structure of the molecular gene and of alternative splicings of gene products. Modern genes resulted from the duplication and recombination of ancestral ones. For example, the part of DNA coding for a given protein is made up of modular "domains" which serve a particular biochemical function, i.e., having a given enzyme property, binding a given ion, recognizing a protein structure. The messenger RNA resulting from a particular DNA is "spliced" (cut and pasted) before leaving the cell nucleus. Thus, one gene may produce many different RNAs (Moss, 2003). These and other theoretical considerations implied that not all biological phenomena could be meaningfully reduced to the molecular level even when adopting a materialistic stance (Rosenberg, 1994). Nevertheless, the reductionistic approach prevailed. By conflating the Mendelian and the molecular gene, biologists adopt a genetic determinist worldview—genes are in the driver's seat (Moss, 2003). Development is therefore viewed as a set of "orders" given by a "genetic program" that unfold seamlessly from the zygote to the viable newborn organism and beyond.

Organicists work at the periphery of the reductionistic mainstream, continuing the tradition of Developmental Mechanics. They study self-organization, cell–cell interactions, tissue–tissue interactions, and organogenesis. They posit that the organism is the zygote that organizes itself into a newborn and beyond. By virtue of being an open system, the organism utilizes resources from the external world (environment) and the internal world (gene products and other chemicals synthesized by the

organism); there is no causal primacy to the DNA (Griffiths & Gray, 2000). As the reductionistic view became dominant in biology, the organicists still continued their studies of self-organization. Their explanations are operational—i.e., they are made in terms of how a cell (or a tissue) influences another cell's (or tissue's) behavior. In contrast, reductionist explanations are made in terms of material entities such as genes and their products. From this perspective, histogenesis and organogenesis were purported to be reduced to the phenomenon of differential gene expression, which was thought to be similar in bacteria and multicellular organisms. Hence the aphorism "if you understand the bacterium, you understand the elephant." The mechanicist rhetoric of geneticists won the day. Embryologists became second-class experimentalists who were simply engaged in doing "phenomenology" or "descriptive" science. In hindsight, we consider that all experimental biologists do "descriptive research" and provide explanatory narratives for the phenomena they study; this also applies to the research done by the genetic reductionists.

A main obstacle to the success of reductionism is the historicity of the organism, i.e., evolution and ontogeny. As Jacob noted, nature is not an engineer, but a tinkerer—a given molecule is put to different uses (Jacob 1982). The main problem posed by this evolutionary history is that the record of these transformations was lost with the extinction of over 95% of the species that once existed. We are forced to reconstruct this history from the organisms that exist today. A main effort is placed in reconstructing the evolution of particular genes by comparing their sequence and structure in these organisms. However, this difficult task is hindered by the fact that, even in the same organism, one protein may have different functions in different cells. For example, lactate dehydrogenase and crystallin are the same molecule; the former is an enzyme in muscle while the latter plays a structural role in the eye's lens. Beta-catenin is both a transcription factor and a cell-adhesion protein (Gilbert & Sarkar, 2000). In addition, a signal pathway effector may lead to the induction of different gene products and therefore different differentiation programs in different cell lineages (Brisken, Socolovsky, Lodish, & Weinberg, 2002). This lack of a unique correlation between a given protein and its function was addressed by Hull as the problem of "the many and the many" (Hull, 1974). In other words, one phenotype may result from several different molecular mechanisms, while a single molecule may be involved in different phenotypes. A clear example of this divergence is polyphenism, a single genotype producing different phenotypes. These cases (from single proteins with multiple activities to diverse phenotypes coexisting with a single genotype) make reduction difficult, if not impossible.

A change in the perception of biologists has occurred during recent years regarding the success of reductionism when addressing complex phenomena. This is evidenced by a shift in strategy proposed by those who previously practiced genetic reductionism and now preach a "postgenomic" research program, whereby computer analysis will identify patterns of gene expression, which will be used for hypothesis building (Bassett, Eisen, & Boguski, 1999; Brown & Botstein, 1999). Others, being more philosophically inclined, propose a new epistemology instead of this brute force postgenomic approach. The following quotation illustrates the new thinking: "Isaac Newton might have liked the neat view of biological systems made up of dedicated components, with causal roles that can be studied in isolation, and in which particular starting conditions give rise to uniquely predictable responses. Charles Darwin, by contrast, might have felt more at home with the idea of a complex, emergent system made up of many non-identical components, with non-exclusive roles, non-exclusive

relationships, several ways of producing any given output, and a great deal of slop along the way. We have been Newtonians for the past several decades in our thinking about gene action. It is time to become Darwinians" (Greenspan, 2001).

In multicellular organisms, single cells do not have an existence independent from the whole organism; they are linked through their developmental history (ontogeny). Only in unicellular organisms that can facultatively associate into multicellular colonies can the part (one cell) exist independently from the whole (the multicellular organism). This means that the usual way of thinking about organisms as made up of cells that relinquished their independence is inaccurate. Rather, a zygote—which is a cell resulting from the union of a female and a male gamete—divides, producing more cells, which are organized in a tri-dimensional pattern. Both association patterns and cell types change as tissues and organs are formed. From the beginning of ontogeny, each cell undergoes "differentiation" under the influence of neighboring cells. This reciprocity makes it difficult to establish detailed cause and effect relationships, since "signals" are being sent from one cell to all its immediate neighbors, and vice-versa. This fact may also preclude individual cells in a dish from revealing their role in the organism. Acknowledging these problems is not an exercise in nihilism, but a first step in trying to devise ways of studying organisms while taking into consideration the problems posed by their historicity. Hence, the problem is to develop an epistemology that takes into consideration evolutionary and developmental history, elements that play a central role in biology but not in chemistry or physics.

3 Three examples illustrating the shortcomings of a reductionistic program

3.1 Nuclear transplantation experiments

"Cloning" of embryos through transplantation of somatic cell nuclei into enucleated oocytes yields a very low percentage of embryos that develop to term. In turn, a large percentage of these animals die soon after birth because of respiratory and circulatory problems and show increased placental and body weights (large offspring syndrome). These anomalies are thought to be due to the abnormal expression of imprinted genes, i.e., genes that are modified in a reversible way, such as methylation). Imprinting of certain specific genes takes place during gamete maturation; this process is believed to be necessary for the success of embryonic development. As expected, many imprinted genes are misregulated in the tissues of the surviving cloned mice. However, this research found that there was no correlation between the abnormal expression of any single imprinted gene and the degree of anomalous fetal overgrowth (Rideout, Eggan, & Jaenish, 2001).

In a complementary study, Jaenish's group investigated global gene expression of a set of more than 10,000 genes by microarray analysis of RNA isolated from the placentas and livers of neonatal cloned mice derived by nuclear transfer from both cultured embryonic stem cells and freshly isolated cumulus cells (somatic cells from the ovarian follicle) (Humpherys et al., 2002). The expression of 400 genes (4% of those analyzed) was significantly altered in the placentas; however, the pattern of gene expression did not correlate directly with the macroscopic anomalies found in some placentas. Moreover, the pattern of misregulated genes in the placenta and liver was dissimilar. These data suggest the coexistence of apparently normal organs at the morphological level of organization (anatomical, histological and cellular archi-

tecture) with significantly altered gene expression. This demonstrates a great degree of tolerance of abnormal gene expression consistent with normal development. This fact is difficult to reconcile with a reductionistic view in which precise alterations at the molecular level should translate into precise alterations at higher levels of organization. One can postulate redundancy when the altered expression of a single gene, or multiple genes pertaining to a given pathway, does not cause a distinct phenotype; however, the experiments being discussed here involve 400 apparently unrelated genes. The coexistence of grossly altered patterns of gene expression with normal development is instead consistent with the "Darwinian" views proposed by Kupiec (1997) and by Greenspan (2001), who posit a probabilistic rather than a deterministic relationship between these different levels of organization. This brings us to another problem, namely, whether a probabilistic treatment is just instrumental (and hence a practical tool for the analysis of phenomena that are in essence deterministic) or whether the phenomena studied are really of a stochastic nature. From the pragmatic view of experimentalists, the only option is to handle this phenomenon as if it were probabilistic.

3.2 The specificity of signal transduction pathways

The "instructive" hypothesis of differentiation proposes that hormones determine a specific phenotype in target cells by inducing a lineage-specific gene-activation program. However, recent data are inconsistent with this view. For example, precursor erythroid cells, which generate red blood cells (erythrocytes) were engineered to lack the erythropoietin (EPO) receptor (EPO receptor$^{-/-}$, or EPO-knock-out). As expected, these cells failed to generate mature erythroid cells. In order to further test the specificity of this process, EPO receptor$^{-/-}$ cells were engineered to express the receptor for the reproductive hormone prolactin, which normally plays no role in the development of erythroid cells. The rationale behind this experiment was that the intracellular portions of these receptor molecules were about 20% homologous, and that the signal transduction pathway for both hormones contained many similar proteins. These EPO receptor$^{-/-}$ precursor erythroid cells, now bearing the prolactin receptor, were able to produce normal red blood cells in response to the hormone prolactin (Socolovsky, Fallon, & Lodish, 1998). The authors of this experiment further investigated whether it was possible to obtain similar results using the natural target cells for prolactin, namely, the epithelial cells in the mammary gland. Epithelial cells are tightly connected to one another forming sheets (skin) or tubes (mammary gland). Prolactin receptor$^{-/-}$ mammary gland epithelial cells were placed into the mammary glands of normal mice. As expected, these cells failed to develop into alveoli when these animals underwent pregnancy; this is the natural way of exposing these cells to prolactin. To test for the specificity of the response, these prolactin receptor$^{-/-}$ mammary gland epithelial cells were made to express a fusion protein having the extracellular portion of the prolactin receptor and the intracellular portion of erythropoietin receptor. This fusion protein was able to restitute normal alveolar development when these cells were transplanted into the mammary fat pad (Brisken et al., 2002). As mentioned above, many of the downstream signal transduction effectors are shared in both erythroid cells and mammary epithelial cells; however, the genes that are expressed after the activation of the signal transduction pathway are entirely different. In other words, these hormone-regulated pathways seem to be "generic" rather than specific. Hence, their role may be permissive rather than instructive,

allowing a predetermined differentiation pattern to be expressed. The specificity of the response therefore does not reside in the hormone, its receptor, or the signal transduction pathway; it would be determined by an unrelated differentiation process. Again, we observe the lack of a unique correlation between a given protein and its biological function. The promise that the specificity of the effect of a given hormone could be understood by the study of interactions between the receptor and the hormone, and the subsequent activation of the transduction pathway downstream, could not be fulfilled. Specificity is to be sought elsewhere.

3.3 Carcinogenesis

The development of the cell theory and advances in microscopy during the first half of the 19th century allowed for the first time the study of cancer as both a disease and a biological phenomenon. A great part of this research was done in Germany under the influence of Kant's philosophy about circular causality in living organisms, being both the cause and effect of themselves (Moss, 2003). From this point of view, the directedness of development was considered as an unknown "force." The research program that was followed to study development concentrated on the description of the phenomena caused by this putative "force" while being agnostic about the nature of the "force" (Moss, 2003). The net result of this program culminated in the cell theory and the flourishing of embryology. The organism was considered as a whole and carcinogenesis was viewed as an alteration of development and of organization.

Only with the advent of genetics in the early 20th century did the first cell-centered theory of cancer emerge. Boveri postulated that cancer was a problem of unequal distribution of chromatin (and hence, of genetic determinants) between the daughter cells. Boveri borrowed this concept from the Weismannian theory of embryonal differentiation that explained the acquisition of phenotypic diversity as a result of unequal segregation of genetic material during morphogenesis. Remarkably, at that very time, Weissmann's theory was being undermined by experimental data from H. Driesch, who showed that isolated cells (blastomeres) from early embryos were able to generate full organisms (Gilbert, 1997).

Genomic equivalence of somatic cells was experimentally demonstrated in 1960s in amphibians and in 1990s in mammals (Gurdon, 1968; Wilmut, Schnieke, McWhir, Kind, & Campbell, 1997). Different phenotypes were expressed in cells that shared the same genotype. Thus, even though the concept of mutations in carcinogenesis had lost its original explanatory power (since mutations ceased to be the only way to explain different phenotypes), it nonetheless became the dominant idea in cancer research for the remainder of the century and beyond.

3.3.1 The somatic mutation theory

In the last 50 years, the prevailing paradigm in the field of carcinogenesis has been the *Somatic Mutation Theory (SMT)* (Curtis, 1965; Hahn & Weinberg, 2002b). Its fundamental premise is that cancer is derived from a single somatic cell that over time has accumulated multiple DNA mutations. This implies that cancers are monoclonal, i.e., they are all derived from a single faulty, mutated cell (Weinberg 1998). A second implicit premise adopted by those who favor this theory is that the default state of proliferation in multicellular organisms is *quiescence* (Alberts et al., 2002). By default state we mean the state under which cells are found when they are freed

from any active control (Sonnenschein & Soto, 1999; Soto & Sonnenschein, 2004). A third premise of this theory is that cancer is a disease of cell proliferation and that cancer-causing mutations occur in genes that control cell proliferation and/or the cell cycle (Alberts et al., 2001).

Genetic determinism is the dominant stance among cancer researchers, particularly among those supporting the SMT. On the pragmatic side, the linear organization of DNA, its great stability and the immensely powerful tools that were developed to study nucleic acids suggested that the study of Nature could be conducted as if it was chemistry. The lack of ambiguity about the precise chemical sequence of nucleic acids gave an aura of certainty seldom before found in biological studies. However, while there is no ambiguity in a DNA sequence, its transcription into RNA and translation into protein, as mentioned above, are not always straightforward. From genotype to phenotype, the picture remains as messy as ever.

The cancer research program practically abandoned animal models and centered on the search for oncogenes, defined as genes that produce cancer by causing excessive cell proliferation. Most of this research was conducted using *in vitro* models, like established cell lines, whereby organismic phenomena were purportedly reduced to cellular phenomena. The tri-dimensional tissue entities called cancers were reduced to "transformed" cells and carcinogenesis was reduced to enhanced proliferation of cells in a dish (Sonnenschein & Soto, 1999).

Oncogenes were defined operationally as DNA that when transfected (introduced) into normal cells resulted in a "transformed" phenotype. The discovery that oncogenes were mutated versions of normal genes resulted in the conceptualization of the cancer problem as a result of mutations in genes that control cell proliferation by affecting pathways that regulate proliferation and the cell cycle. The study of heritable cancers, however, pointed in another direction—the gene alterations found were deletions, and cancer was therefore inherited when the genes were rendered inactive, rather than super-active as proposed by the oncogene theory.

After remaining dominant for over 20 years, the oncogene theory has lead to the identification of more than 100 oncogenes and 15 suppressor genes (Weinstein, 2002). The search for unifying rules seems to be thwarted by reports from within the oncogene paradigm. "Oncogenes and tumor suppressor genes are important not only for cell proliferation but also for cell fate determination [differentiation, senescence (loss of the ability to proliferate), and apoptosis (cell death)], their effects often depending on the type of cell in which they are expressed. Thus, overexpression of a given oncogene can enhance growth in one cell type but inhibit growth or induce apoptosis in another" (Weinstein, 2002). This assertion is in direct contradiction to the experiments that had given rise to the concept of oncogenes, which were so named because of their presumed "dominant" behavior. At first, it was expected that only one oncogene was needed to achieve the expression of a "transformed" phenotype, as in the case of Rous sarcoma viruses on primary cultures of chicken cells. As time went by additional oncogenes were purportedly needed to produce transformation (Elenbaas et al., 2001). Moreover, normal human diploid fibroblasts are refractory to oncogene-mediated transformation (Akagi et al., 2003). Furthermore, the presumed association between the pattern of mutated oncogenes and the cancer type is yet to be found (Hahn & Weinberg, 2002a).

These lacks of fit are now being acknowledged by the supporters of the SMT: "For those who believe in the simplification and rationalization of the cancer process, the actual course of research on the molecular basis of cancer has been largely

disappointing. Rather than revealing a small number of genetic and biochemical determinants operating within cancer cells, molecular analyses of human cancers have revealed a bewilderingly complex array of such factors" (Hahn & Weinberg, 2002a). The SMT now has the structure of pre-Copernican astronomy. When something does not fit, a new epicycle is added. These continuous additions of interpretations of convenience lead to a situation in which any possible conclusion is valid. No hypothesis is ever refuted. If something does not work as expected, it is blamed on its particular context and unfathomable complexity.

We conclude that, like Ptolomean astronomy, the SMT is resorting to *ad hoc* explanations because its premises are wrong. Cancer is neither a genetic nor a cellular problem, but rather a tissue organization problem.

4 An organicist view of carcinogenesis: The tissue organization field theory

Developmental mechanics, the forerunner of modern developmental biology, established the concept of "fields of organization" or "morphogenetic fields" (Needham 1931). These entities were defined as "a collection of cells by whose interactions a particular organ formed" (Gilbert, 2003a). The morphogenetic field became the basic paradigm of embryology. In the 1930s, Needham (1936) and Waddington (1935) proposed that neoplastic development resulted from alterations of the normal interactions that occur in those morphogenetic fields. In other words, carcinogens, as teratogens—i.e., agents that interfere with normal embryonic development—would disrupt the normal dynamic interaction of neighboring cells and tissues both during early development and throughout adulthood.

In this context, Orr postulated that the target of carcinogens was the stroma (Orr, 1955, 1958; Orr & Spencer, 1972). Classically, the "stroma" has been considered the support tissue of organs and "parenchyma," the component responsible for the distinctive functions of each particular organ. Nowadays it is accepted that because of their reciprocal interactions both tissues should be considered as a functional unit. Using a clever transplantation model, Orr's group claimed that normal skin epithelium (epidermis—the parenchyma) combined with carcinogen-treated dermis (the stroma) resulted in skin (epithelial) cancer. The recombination of normal dermis with carcinogen-treated epidermis did not (Orr & Spencer, 1972). However, these experiments were criticized on the basis that epithelial cells from hair follicles could have remained embedded in the dermis and, hence, these may have been the cells that originated the cancer (Steinmuller, 1971). The option proposed by Orr was discredited and only a few researchers kept it alive under a variety of guises (Dawe, Morgan, & Statick 1966; Tarin, 1972; Pierce, Shikes, & Fink, 1978; Fujii, Cunha, & Norman, 1982).

In the alternative view of molecular biologists, tissues were reduced to collections of independent cells and explanations of carcinogenesis were sought primarily at the cellular, subcellular and molecular levels of organization. The morphogenetic field was overcome by the operon to explain differentiation and epigenesis. An operon is a group of genes all controlled by the same regulatory gene. Nonetheless, the morphogenetic field hypothesis was not disproved—it was just forgotten (Gilbert, 2003a). Only when "morphogen" gradients were visualized in the 1990s did developmental biology resuscitate this old concept so central to its previous success (De Robertis, Morita, & Cho 1991). Morphogens are diffusible substances that "determine" the differentiation that cells "perceiving" this information will undergo (Gilbert, 2003a).

As briefly referred to above, despite the dominance of the reductionistic program, a few research groups studied the expression of the neoplastic phenotype in a developmental context. For example, when cells from early embryos were placed into ectopic places (under the kidney capsule, or the peritoneal cavity) they behaved like malignant neoplasms called teratocarcinomas. When teratocarcinoma cells were injected into early embryos (blastocyst stage) they generated normal tissues and organs. In fact, these cancer cells became gametes (oocytes and sperm cells), which in turn generated normal progeny. Thus, embryonal cells produced neoplasms when misplaced in adult tissues, and reverted to normalcy when placed in an early embryo (Stewart & Mintz, 1981). Along the same lines, when nuclei from frog Lucke renal carcinoma cells were transplanted into enucleated and activated ova they reached the swimming tadpole stage (DiBerardino, Orr, & McKinnell, 1986). Finally, transplantation of tissues from these tadpoles into normal recipients generated normal tissues that were indistinguishable from those of the host (McKinnell et al., 1993). These data contradicted the view that cancer was caused by DNA mutations, since the neoplastic phenotype could be normalized at a frequency much higher than that needed to revert a DNA mutation back to the wild-type. Hence, the dictum "once a cancer cell, always a cancer cell" was invalidated while the data suggested instead an epigenetic control of the expression of neoplastic phenotypes (Pierce, 1978).

Meanwhile, pathologists viewed neoplasms as a problem of tissue organization, since for the most part, they retain the distinctive characteristics of the organ of origin (Foulds, 1969; Clark, 1991). Some neoplasms tend to arise in areas of contact between two types of epithelium. Metaplasias, which are normal-looking tissues in an abnormal location, are frequently observed in these areas. Barrett esophagus, located near the area of transition between stomach and esophagus, is one of the most conspicuous examples. An epithelium resembling the lining of the stomach or intestine is found in the lower portion of the esophagus. Similarly, cancer arises in the uterine cervix at the "transformation zone," the region where metaplastic tissue is often observed. These examples point toward an instability of dynamic stroma-epithelium interactions in these areas of abrupt change of tissue organization (Rao & Reddy, 1996).

During the second half of the 20th century, a handful of biologists concerned with the post-natal development of hormone-target tissues (e.g. mammary gland and prostate) maintained the organicist tradition of tissue recombination and transplantation while describing the "inductive" role of the mesenchyme (precursor of connective and other tissues) and stroma on epithelial morphology and function. Induction means interaction at close range between two or more cells or tissues of different histories and properties (Gilbert, 2003b). Those developmental biologists established the fact that these stromal-epithelial interactions were active during adult life (Cunha, Bigsby, Cooke, & Sugimura, 1985). Starting in the 1970s, extracellular matrix research contributed significantly to the understanding of tissue organization. Mina Bissell's laboratory showed that extracellular matrix proteins provided a substratum for the tri-dimensional self-organization of mammary epithelial cells in culture (Bissell, 1981; Weaver et al., 2002). Her extensive work clearly showed that tridimensional organization suppressed the neoplastic behavior of "malignant" cells (Weaver, Fischer, Petersen, & Bissell, 1996; Weaver et al., 1997, 2002).

From all this background, it followed that carcinogenesis resulted from the disruption of the reciprocal interactions between stroma and epithelium. This is one of the two basic postulates of the *Tissue Organization Field Theory (TOFT)* (Sonnenschein & Soto, 1999). The other fundamental premise is that the default state of *all* cells is

proliferation (Sonnenschein & Soto, 1999). The importance of this premise has been explored elsewhere (Soto & Sonnenschein, 2004).

4.1 Mammary gland carcinogenesis

The development of mammary carcinomas in susceptible strains of rats following administration of the chemical carcinogen nitrosomethylurea (NMU) is a widely accepted model for the study of chemical carcinogenesis (Gullino, Pettigrew, & Grantham, 1975). NMU reacts with a variety of cellular components, including DNA. From the SMT perspective, NMU is considered a "direct carcinogen" since it does not need to be metabolized in order to form DNA adducts. According to the SMT, NMU-induced mammary gland carcinomas (epithelial cell neoplasms) are due to the accumulation of mutations in the DNA of epithelial cells of this gland (Gould, 1995; Guzman et al., 1992). From the TOFT perspective, NMU would induce mammary gland carcinomas through its non-genotoxic properties, altering the interactions between the stroma and the epithelium. In order to test whether the primary target of NMU is the epithelium (consistent with both hypotheses), the stroma (consistent with the TOFT and inconsistent with the SMT), or a combination of both (consistent with the TOFT), we have used a rat mammary tissue recombination model under a theory-neutral experimental design. NMU was chosen as a carcinogen because it has a very short half-life (about 15 min) (Swann, 1968); this minimizes the risk of inadvertent indirect exposure during recombination of stroma and epithelium. Neoplastic transformation of epithelial cells occurred when the stroma was exposed to NMU, regardless of whether or not the epithelial cells were themselves exposed to the carcinogen. Remarkably, no tumors were observed when only the epithelial cells were exposed to NMU. These findings indicate that the stroma, rather than the epithelium, is the primary target of the carcinogen, as first proposed by Orr. Moreover, as there is no evidence of a mechanism by which DNA mutations in the stromal cells could be transferred to the DNA of epithelial cells, this experiment strongly contradicts the SMT.

4.2 Biological complexity and emergence

Mayr remarked that, for most biological phenomena, exploring levels of complexity lower than that at which the phenomenon of interest occurs usually adds little to what was learned at the original level of inquiry (Mayr, 1982). For example, understanding the structure of the muscle protein myosin has not significantly helped in the understanding of how the heart works as a pump.

Cancer is diagnosed by the pathologist looking through an uncomplicated light microscope at a biopsy of the suspected neoplastic tissue. Hence, carcinogenesis should be studied at the level where it is identified, i.e., at the tissue level of biological complexity.

The TOFT postulates that carcinogens act initially by disrupting the normal, reciprocal interactions that take place among cells in the stroma and parenchyma (usually an epithelium) of an organ (Waddington, 1935; Needham, 1936; Orr, 1958; Sonnenschein & Soto, 2000). This disruption results in a lessening of the cells' ability to "read" their positional and historical background. The initial alteration of the stroma/epithelium interaction would result in an epithelial hyperplasia within the affected field. Next, the tissue's organizational pattern would become disrupted, as in dysplasia, or would even adopt a different tissue type (metaplasia), and finally, this

pattern of progression may result in a carcinoma in situ. Central to this dynamic process is its reversibility (Clark, 1991). The neoplastic phenotype can be experimentally reversed through cell–cell interactions as demonstrated for embryonal carcinoma cells injected into blastocysts (Illmensee & Mintz, 1976), hepatocellular carcinoma cells injected into normal livers (McCullough et al., 1998), and by modification of the extracellular matrix components (Weaver et al., 1997; Bissell & Radisky, 2001). This evidence supports the notion that the cancer phenotype is an emergent phenomenon occurring at the tissue level of organization and is susceptible to being normalized.

Is it necessary that researchers reject one of the two opposing theories to unravel the mechanism of carcinogenesis? From the TOFT perspective, the effects of carcinogens on subcellular structures and organelles (including genomic mutations), while variably deleterious to each cell in the host, are not viewed as directly responsible for the development of neoplasms (see below). Instead, only those carcinogen-induced changes resulting in altered cell-to-cell or tissue-to-tissue interactions would be relevant. Thus, we favor discarding the SMT on the grounds that its niche is at the subcellular level of biological complexity, a level that appears irrelevant to carcinogenesis (Sonnenschein & Soto, 2000). We concur with biologist and philosopher L. Moss' conclusion that "... the somatic mutation hypothesis, fueled by a conflationary conception of the gene (i.e., the gene of transmission genetics and the gene as a DNA sequence) has unexpectedly provided some of the strongest evidence on behalf of the anticonflationary, epigeneticist critique" (Moss, 2003). Organicism, by admitting the existence of emergent phenomena and reciprocal, apparently non-linear relationships, is better suited to study these complex phenomena.

5 Conclusion: Thinking about emergence

Philosophers debate whether emergence is a real phenomenon, or just an epiphenomenon (Kim, 1999). A main concern of philosophers about emergentism is "downward" causation. As stated by Kim about synchronic emergence: "... apart from any recondite metaphysical principle that might be involved, one cannot escape the uneasy feeling that there is something circular and incoherent about this variety of downward causation" (Kim, 1999). In a general and perhaps trivial sense, molecules mediate these high-level phenomena. However, there are many interactions that occur simultaneously to maintain the structure of a tissue; hence, it is practically impossible to sort out causes and effects in a way that would precisely reveal whether emergents have true causal agency. Hence, biologists who take for granted that emergent phenomena exist adopt an organicist stance; alternatively, those that assume a reductionist stance hope that eventually a neat, linear causal chain will be identified.

The claim by genetic reductionists that morphogenesis is controlled by the genetic patterning of the body plan through a gene-induction cascade is now being modified to include mechanical forces. The unidirectional flow from genes to shape is being modified to include cell movements which cause "physical stress" in neighbor cells inducing specific gene expression (Farge, 2003). This causal chain, from a molecular event to physical stress inducing the next molecular event appears as an emergent (an increased number of cells moving) acting as a downward cause.

Perhaps the problem centers in the literal way in which cells are taken as "low level" parts of the higher level "tissue." Historicity is of the essence here. A tissue results from a long series of interactions during which cells move around in relation to one

another and change in the process. By the time the tissue is formed, the "parts" that we identify in them are no longer the parts that interacted in their formation. The cellular components present now did not pre-exist the tissue itself—they are interacting now in a particular way that is reciprocal. When we artificially separate the components of the tissue, for instance the cells forming epithelium and its subjacent stroma, the cells cease to perform the functions they executed when together in their proper tri-dimensional arrangement. However, when recombined, they form a tissue similar to the one from which they originated. Parenthetically, this is an oversimplification; as previously stated, neither the parenchyma nor the stroma exists in isolation from one other.

Recombining stroma and parenchyma (usually epithelium) from different organs has provided some hints about the inductive role of the stroma over the epithelium, as well as some indications that the epithelium possesses some degree of cellular identity that is not influenced by the stroma. As researchers tend to think that the important part of the tissue is the parenchyma, no one really searched for subtle reciprocal changes in the stroma. Interestingly, the basement membrane that is interposed between the epithelium and the stroma is made "in collaboration" by the stroma and the epithelial cells. Notably, when epithelial cells are placed in a plastic culture dish, they form a flat layer, quite different from the epithelium of origin. If instead, they are placed in a similar dish coated with basement membrane proteins they associate and recover the original tri-dimensional architecture of the epithelium of origin, i.e., they attach to each other forming either sheets or ducts). Moreover, the individual cell shapes also change, as does the intracellular placement of their organelles. How can causation be studied here? Is the tissue causing the formation of a basement membrane? And then, is the basement membrane causing the normal architecture of the epithelium- and thus the tissue? This looks like circular causation.

Limb development also offers an example of apparent circular causation. The skeletal structures of the limb are initiated by the expansion of precartilage condensations within the mesenchyme. Proteins of the transforming growth factor beta (TGF-β) family regulate this process (Downie & Newmann, 1994) through a positive autoregulatory pathway (van Obberghen-Schilling, Roche, Flanders, Sporn, & Roberts, 1988), namely, cells in these precartilage condensations secrete TGF-β, and TGF-β in turn makes them secrete more of it.

Tooth development offers other examples of quasi circular causation. The mandibular epithelium "causes" the underlying mesenchyme to condense (i.e., it appears more cell-dense at the microscope). If the epithelium is recombined with other kinds of mesenchyme at this stage of development, it induces the generation of tooth structures. Soon thereafter this "inductive" potential is lost. If the condensed mesenchyme from underneath the mandibular epithelium is now recombined with other epithelia, the recombinant generates tooth structures. Moreover, the gene products involved in early tooth development are also involved in mammary gland development and in hair follicle formation. Hence, in order to understand how form is generated in these diverse structures, it may be more productive to concentrate on the higher-level phenomena (cell movement, cell proliferation, and cell death) than exclusively on patterns of gene expression, which, at the beginning are almost the same.

In sum, we think that at best, several levels of explanation are necessary for complex biological phenomena. Development and cancer will not be reduced to complex series of protein interactions, but rather a multilevel explanation will be required. In some instances, molecules will do the explanatory job, in others physical forces, but at

the core they will remain a problem of tri-dimensional tissue organization. To pretend that technological innovations will enable the understanding of these complex phenomena is just wishful thinking. Instead we need a novel way of thinking about these problems.

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