Biological Theory (2020) 15:180–187
https://doi.org/10.1007/s13752-020-00365-4

CLASSICS IN BIOLOGICAL THEORY

Revisiting D.W. Smithers's "Cancer: An Attack on Cytologism" (1962)

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Published online: 2 November 2020

Abstract
David Waldron Smithers was, among other things, a physician and a pioneer of cancer radiotherapy and a well-respected figure in British medicine and public health. From the 1940s until his retirement from medical practice in 1973, he was the director of the Radiotherapy Department at the Royal Marsden Hospital and London University Chair of Radiotherapy at the Institute of Cancer Research. Using massive amounts of clinical observations, which he interpreted from an organicist viewpoint, and his impressive synthetic thinking, he proposed a coherent alternative perspective to the somatic mutation theory (SMT) which was then, and still is, the dominant theory of cancer. The purpose of this essay is to acquaint the modern audience with his seminal paper, published in 1962, because it deserves to be recognized as a true classic. In it, he examined the lack of fit between clinical observations and the SMT and proposed the rejection of this reductionist perspective. In addition, he built an organicist alternative in which carcinogenesis is seen as a problem of biological organization. His conceptual contribution to the cancer problem has inspired us and other authors over the last two decades. His essay "Cancer: An Attack on Cytologism," originally published in *The Lancet* in 1962, is available as supplementary material in the online version of this article.

Keywords Cancer · Organicism · Reductionism · Somatic mutation theory · Tissue organization field theory

Some ideas are dangerous—not so much intellectually but socially because they threaten the status of science—and so they cannot be allowed to get off the ground.

Michael Ruse (2020) The Quarterly Review of Biology 95:132

Introduction

A quarter century ago, when we were writing our book *The Society of Cells* (Sonnenschein and Soto 1999), we found David W. Smithers's article "Cancer: An Attack on Cytologism" referenced in Leslie Foulds's 1969 book *Neoplastic Development* (Foulds 1969). We considered Smithers's views on carcinogenesis original and impressive. His ideas about reductionism and cancer are as valid today as when they were first published in 1962; indeed, this essay merits being labeled as a classic.[1] We leave it up to historians of biomedicine to place it in its proper context in the field of the biological sciences. In hindsight, we regret not having focused more extensively on this remarkable paper at the time of our first reading. We gladly welcome this opportunity to now revisit Smithers's views in light of additional evidence collected in the last half century on carcinogenesis and related subjects.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13752-020-00365-4) contains supplementary material, which is available to authorized users.

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[1] Smithers's essay "Cancer: An Attack on Cytologism," originally published in *The Lancet* (1962a), is available as supplementary material in the online version of this article, as part of the journal's "Classics in Biological Theory" collection.

Fig. 1 Portrait of Sir David Waldron Smithers by Elliott & Fry, bromide print, 14 June 1948. Photographs Collection, National Portrait Gallery (London), NPG ×91,640 (reprinted with permission)

David Waldron Smithers, the Man and the Physician

David Waldron Smithers (1908–1995) was a British physician, a pioneer of cancer radiotherapy, and a well-rounded, cultivated person (Fig. 1). His peers considered him, first and foremost, a doctor who cared about patients; he insisted that they must be treated as people, not merely as patients. He played a major role in developing the medical oncology specialty. In particular, Smithers was instrumental in designing the Surrey branch of the Royal Marsden Hospital, which under his leadership became a major, prestigious cancer treatment and research institution. Smithers

> stressed the importance of a broadly based humanist education for recruits to the medical profession, and expressed his concerns about the danger that the modern intensive training of doctors may produce too narrow a specialist who is not able to take a broad view. (Henk 1995a)

Smithers was also a respected public figure—a member of the council of the Royal College of Physicians, president of the Faculty of Radiologists and of the British Institute of Radiology, chairman of the cancer advisory committee of the Ministry of Health, and a member of the council of the Royal College of Surgeons and of the Central Health Services Council. He was knighted in 1968, an honor previously shared by his father and grandfather, both Conservative members of Parliament. He was also made a knight commander of the Sovereign Military Order of Malta. Smithers was a prolific author of medical books; during his retirement, he wrote about historical subjects, physicians who became writers, Jane Austen, and other literary personages (Henk 1995b).

From his obituaries, we learned that, "He disliked what he felt was the reductionist approach of much of the cancer research at that time" (Henk 1995a) and

> As a clinical scientist he concurred with the Austrian philosopher Karl Popper in the view that a theory must be testable by experiments designed to prove it false. He stressed in many writings that cancer is a disorder of organisation of the human body, rather than a defect of cells. In his controversial article in The Lancet in 1962 entitled 'Cancer - an Attack on Cytologism', he castigated the concept of cancer as a disease in which people are devoured by their own cells gone wrong, and criticised much of the cancer research of the time as based on this false premiss [sic] and lacking direction, thereby gaining the opprobrium of many in his own institute. (Henk 1995a)

It is not surprising given the novelty of his ideas, that his insight and courage to criticize the status quo were greeted with disapproval even when coming from a distinguished professor, clinical scientist, and an officer of high standing of several medical societies and councils.

"Discovering" Smithers While Developing a Theory of Carcinogenesis

For the last 100 years the dominant view of cancer has been (and still is) the somatic mutation theory (SMT), which originated in a book published in 1914, authored by Theodor Boveri, a German embryologist of great renown. Boveri claimed that cancer is a cell-based problem caused by unrestrained cell proliferation.[2] The two premises of the updated SMT are that (1) the constitutive state of cells in metazoans is proliferative *quiescence*, and (2) cancer is caused by DNA mutations in a founder normal cell that makes this cell able to multiply autonomously and become a cancer cell (Vogelstein and Kinzler 2004; Weinberg 2014a, b).

In the early 1990s the consensus remained that cancer is a cell-based problem of control of cell proliferation. When in the mid-1990s we decided to write a book on cell proliferation and cancer, we were adopting this perspective. Our

[2] He followed the lead of German pathologists who viewed cell proliferation as a constitutive state of cells. In Boveri's words, "I hold it to be without any doubt that the tendency to continued multiplication is a primordial quality of cells, which only becomes inhibited in many-celled organisms through environmental influences" (Boveri 1929, pp. 113–114; in original German, Boveri 1914, pp. 26–27).

point of disagreement with the mainstream was about the constitutive (default) state of cells in multicellular organisms. The mainstream thinking was then—and still is—that the default state in multicellular organisms is proliferative *quiescence*; by then, we had already concluded instead that it is *proliferation*. While writing the book, we were trying to make sense of the experimental and clinical data that did not fit with the mainstream view of cancer as a cell-based problem (Pierce 1967; Illmensee and Mintz 1976; Clark et al. 1995). For example, the Illmensee and Mintz (1976) paper on normalization of mouse teratocarcinoma cells injected into blastocysts made us think that the regulatory capacity of the embryo was not to make the teratocarcinoma cells stop proliferating or to undergo cellular differentiation, but to follow the path dictated by each cell's local position inside the embryo. Equally intriguing was the fact that the teratocarcinoma cells they used were obtained by placing a normal blastocyst under the kidney capsule of a mouse. Injecting a few of these same cells into the mouse peritoneum resulted in certain death of the host a couple of weeks later. Altogether, this data indicated that normal structures placed in a heterologous organ promoted neoplastic behavior, while placing neoplastic cells in a homologous environment (i.e., the blastocyst) "normalized" them and allowed them to become normal components of a variety of different tissues. From these experiments, we conceptualized carcinogenesis as development gone awry. However, there was still much to do to move from this notion to a theoretical construct.

Reading Smithers's paper at this point was inspiring to us for his bold rejection of "cytologism." On the one hand, his arguments strengthened our rejection of a cell-based perspective of carcinogenesis, and, on the other, helped us to answer the question, at what level of biological organization does carcinogenesis belong? We felt comfortable accepting his clearly organicist stance. The chapter of our book entitled "Introduction to Carcinogenesis and Neoplasia" ended with a section entitled "Are Carcinogenesis and Neoplasia Cellular or Tissue Based Phenomena?" In it, we reflected on Smithers's analysis, stating:

> In a cogent and impassioned analysis in 1962, Smithers raised most of the pertinent questions regarding the somatic mutation theory, or cytologism, as he called it. He offered a series of suggestions to remedy the impasse in this highly controversial field. Among several remarkable passages, we selected one that it is both intriguing and eminently valid as we approach the beginning of the next century: '*Observation has produced too many incompatibilities, and a vast research effort too little support, for conventional cancer theory to hope to hold its place much longer*' (our italics) (Smithers 1962a). The verdict of time has not been kind to Smithers, or others, who ventured into the realm of predictions in the field of cancer. With an additional four decades of intense efforts designed to vindicate the somatic mutation theory, the incompatibilities have been compounded and the uncertainties have multiplied. Has the time for a paradigmatic change in understanding carcinogenesis finally arrived? (Sonnenschein and Soto 1999, pp. 97–98)

Obviously, it had not.

The exhilaration we found in reading Smithers' analysis, the subject of this essay, was mitigated by the realization that his timely analysis was rejected violently by some of his prominent colleagues (see the exchange between H.B. Hewitt and Smithers; Hewitt 1962; Smithers 1962b) and otherwise largely ignored by most cancer researchers. In the following two chapters of our book, we postulated a new theory of carcinogenesis, the tissue organization field theory (TOFT) and gave examples of how this theory would change the way research had to be done if cytologism was to be rejected (Sonnenschein and Soto 1999).

Our theory moved the problem of cancer from a philosophical stance, organicism, to a theory that could empirically frame experiments. The postulates of the TOFT are that (1) the constitutive (default) state of *all* cells is *proliferation*, and (2) that cancer is a relational problem of interactions among the cellular and acellular components of the morphogenetic field. This is why the title of our book became *The Society of Cells*. In this view, cancer can regress by normalization of these reciprocal interactions, a well-documented phenomenon that Smithers analyzed in several publications.

To wrap up our encounter with Smithers, we agree with the philosopher Georges Canguilhem, who stated, "Theories never proceed from facts. Theories only proceed from previous theories, often very old ones" (Canguilhem 2008). Smithers's analysis of organicism in general and cytologism in particular on the one hand, and Immanuel Kant's and Paul Weiss's ideas on the other, were our main sources of inspiration when writing our book. Regarding the default state, we were inspired by the principle of inertia in classical mechanics (Longo and Soto 2016; Soto et al. 2016a, b) and the views of some 19th century German pathologists (Triolo 1965).

Smithers's Arguments for Organicism and Against Reductionism as Philosophical Stances in Biology

Organicism has its philosophical roots in Aristotle and Kant and their respective views of organisms. The vital force invoked by Kant's followers was comparable to that of universal gravitation—that is, mysterious but not necessarily contradicting physical principles. In the 20th century,

this "force" reappeared in a materialist frame conceptually related to self-organization. According to Gilbert and Sarkar, organicism is a materialistic philosophical stance that, contrary to reductionism, considers both bottom-up and top-down causation (Gilbert and Sarkar 2000). Other organicists have interpreted emergence without invoking downward causation, and thus have made organicism compatible with the dominant current of analytical philosophy (Mossio et al. 2013). Both interpretations of emergence postulate that properties that could not have been predicted from the analysis of the lower levels may appear at higher levels of biological organization (Soto and Sonnenschein 2018). Thus, explanations in biology should address phenomena happening at all relevant levels of organization. According to Nicholson and Gawne, what united the 20th century organicists "was a shared commitment to three general ideas…: (a) the centrality of the organism concept in biological explanation; (b) the importance of organization as a theoretical principle; and (c) the defense of the autonomy of biology" (Nicholson and Gawne 2015, p. 361). By all these criteria, we can confidently place Smithers among the organicists.

Practical and Logical Arguments Against a Cell-Centered View of Cancer

We infer that Smithers intended his 1962 paper to be both a manifesto and an invitation to adopt his ideas toward the construction of a theoretical proposal with the purpose of changing the perspective on cancer from cell-centered reductionism to that of organicism. Smithers offered two types of arguments, labeling them as "practical" and "logical." He also made clear that this perspective should be applied to all aspects of biology. Within this context, he examined the tenets of the SMT and showed the contradictions that made it flawed. While presenting a plausible alternative view, he left open the possibility that the theories proposed from this new perspective might be wrong and made it clear that simple propositions should be made so that they could be explored and rejected when proven unproductive.

Under the subtitle "The Logical Argument," Smithers defined "cytologism," namely, the idea that everything in biology is due to processes internal to cells. In his own words,

> It does not therefore follow that, because organisms are the product of interacting cells, they must be governed by organismal laws which are ultimately reducible to the laws of cytology. This false doctrine—that all the events of organismal life (including its psychology) must be the outcome of individual cell initiative—may be called cytologism …. (Smithers 1962a, pp. 496–497)

We consider these objections as powerful arguments against reductionism and of what he called cytologism.

In the section of the paper entitled "Intracellular Initiative or Organismal Organisation?" Smithers makes a typically organicist argument:

> A fertilised cell, which carries the whole inheritance of a new individual, can by reaction with its environment form a collection of cells, each carrying this unique inheritance, which is developed by organisation into a functioning, sentient, human being. We all have a constancy of form, with only an occasional malformation, which is the remarkable achievement of this process. This performance is continued in renewal and repair throughout our lives. It is not the doing of individual cells acting alone, whether by accident or intent; nor is it a conspiracy of powerful groups of cells within the body, for it is not governed by the direct design of cells at all. It is the indirect outcome of cellular action, a side-effect arising from the performance of units which are themselves the product of organised life. (Smithers 1962a, p. 497)

Felicitously, using elegant prose, Smithers illustrates this reductionist fallacy with an excellent example:

> A lifetime of study of the internal-combustion engine would not help anyone to understand our traffic problems. The causes of congestion can be many. A traffic jam is due to a failure of the normal relationship between driven cars and their environment and can occur whether they themselves are running normally or not. (Smithers 1962a, p. 497)

Smithers analyzed the reductionist views under the subtitle "The Traditional Ideas." We will not go over them in detail as they were summarized above when describing the SMT. Subsequently, he announced that the time had come to drop the SMT. He offered what he called "The Practical Argument" when he wrote,

> The horrible position of having to adjust oneself to a new situation, giving up ideas which were hardly won, of altering practice convenient to one's skills and inclinations, and of having to think again, is only forced on the unwilling when the case against the conventional view at last becomes overwhelming. Until that moment, resistance usually hardens as the established position is attacked, arguments in favour of popular belief are paraded, authority quoted, and irrelevant complexities scattered profusely around.

> Once old ideas are seen to be no longer defensible in sanity, they are, however, quickly allowed to subside into obsolescence, and the new becomes, for the time being, the conventional wisdom. Practice may lag some way behind this change in ideas, being liable to last-ditch stands on the grounds that "it has always worked very well in my hands", until younger men take over. (Smithers 1962a, p. 495)

Smithers's critique of social mores within science relates to Thomas Kuhn's views on how the accepted paradigm tightly constrains the judgment of practitioners during periods of "normal science." Smithers makes very real the defense strategies used by the "establishment" in its diverse guises bent on neutralizing threats to its dominance. Incidentally, both Smithers's paper and Kuhn's influential book were published in 1962 (Kuhn 1962).

Smithers then examined "a list of incompatibilities" between data and the SMT that are still pertinent today. Among those, he mentioned the regressions of neoplasms. Regression is not just the disappearance of the neoplastic tissue; an overt neoplasm may undergo a path to tissue normalization. For example, a malignant neuroblastoma spontaneously becomes a benign ganglioneuroma, a phenomenon repeatedly documented since 1927 (Smithers 1969). He also referred to the conditional persistence of some tumors as an incompatibility. He was probably referring to the tar-induced tumors in rabbits (Rous and Kidd 1941; Smithers 1969) and/or the Scharlach orange-induced tumors that regress when the stain is removed by macrophages (Bullock and Rohdenburg 1915).

Proposing an Alternative: "A Revised Cancer Image"

Smithers considered that clarity and simplicity in the expression of concepts are a prerequisite for proposing "a logical argument."

> This attempt to rewrite the theory must be kept to simple terms which can the more easily be demolished. It must not be so hedged about by compromise and obscurity that it cannot be seen for what it is. This is the present state to which the conventional image has been reduced and one of the reasons why it can still resist attack. (Smithers 1962a, p. 498)

This comment reminds us of the physicist Richard Feynman's argument that a vague theory cannot be disproven. For the new image, Smithers proposed ten items, among them, that cancer is a disease of organization; thus, tumors may progress and regress. And "there is no such thing as a cancer cell—only cells behaving in a manner arbitrarily defined as being cancerous" (Smithers 1962a, p. 498). This is perhaps one of the boldest of Smithers's statements; it means that the organization state of the tissue determines the behavior of the cells inside it. In fact, this was demonstrated years after the publication of Smithers's paper in various experimental models, including teratocarcinoma, seminomas, melanomas, mammary cancers, hepatocellular carcinomas, and so on (Sonnenschein and Soto 2016). We buttressed this view in an essay entitled "The Death of the Cancer Cell" (Sonnenschein and Soto 2011).

"A Change of Emphasis": Is This an Invitation to Develop a Theory of Organisms?

Smithers stated:

> What we need most at present is to develop an autonomous science of organismal organisation, the social science of the human body: a science not so naive as to suppose that its units, when isolated, will behave exactly as they do in the context of the wholes of which they form a part, and willing to recognise that whole functioning organisms are its proper concern. It will try to explain normal growth, differentiation, maintenance, and repair, as well as their disorders. It will take biological orderliness in action as its field of study. It lies, in wait for a name, between cytology and sociology. It is much more than oncology, for it is the study of the organisation of whole organisms as well as that of disorganisational tumour formation. It is biocybernetics, the science of organismal organisation, the study of the foundation of life. It is this subject which must take over from 'cancer research', which—by its very title—proclaims its limitations and which, through lack of fruitful governing ideas, has become too diffuse to be effective. It is in any case only the tail end of a subject and one which has lost its way searching for a non-existent goal. It must restate the very aims to which it is committed. (Smithers 1962a, p. 498)

Smithers correctly mentioned the need to "develop an autonomous science of organismal organization" (Smithers 1962a, p. 498). For over almost six decades since the publication of this manifesto, an organicist school of thought has reintroduced in biology classical concepts shunned by the ascent of genetics (Moss 2003) and molecular biology (Soto and Sonnenschein 2018, 2020). For example, the idea that teleology could be replaced by the notion of program is now being rejected (Longo and Montévil 2011; Soto and Sonnenschein 2020). Also, philosophers and theoretical biologists of the organicist persuasion are now reintroducing the concept of "organism" that was considered superfluous by some

molecular and evolutionary biologists (Pepper and Herron 2008; Baedke 2019). Additionally, the concepts of agency and normativity have been reintroduced in organismal and evolutionary biology (Moss 2003; Moreno and Mossio 2015; Walsh 2015; Soto et al. 2016a, b). After reading Smithers's paper, our interests slowly grew from just cancer, to the whole organism where cancer may arise. Where would a theory of cancer be anchored if not on a theory of organisms? We took on this challenge several years ago by proposing principles for a theory of organisms (Soto et al. 2016a, b).[3] Those principles are: (a) a principle of biological inertia, i.e., the constitutive or default state (proliferation with variation and motility) (Montévil et al. 2016a, b; Soto et al. 2016a, b); (b) a principle of variation (Montévil et al. 2016a, b); and finally (c) a principle of organization (Mossio et al. 2016). The default state of cells provides a link between the theories of organisms (ontogenesis) and of evolution (phylogenesis). These principles provide a framework whereby normal development and its alterations, including carcinogenesis, can be conceptually understood, experimentally explored and mathematically modeled (Montévil et al. 2016a, b).

Where Is the Field of Carcinogenesis Today?

In Smithers' time, the SMT was practically "the only game in town." Currently, the situation is different in three aspects, namely, (1) the SMT is collapsing and is being only partially mended with ad hoc patches (Sonnenschein and Soto 2018, 2020; Aitken et al. 2020); (2) criticisms from within, namely, the SMT remains essentially unchanged despite clear admissions by its followers of its inadequacies to explain carcinogenesis and of a lack of effective therapeutic overtures (Weinberg 2014a, b; Sonnenschein and Soto 2017); and (3) acknowledgment of alternative theories, namely, there are now two acknowledged main types of theories of carcinogenesis, one cell-centered, the SMT, and another one that is tissue-centered and organicist, the TOFT (Sonnenschein and Soto 2020). In addition, there are a number of theories that take selected elements of both, specifically, the default state of quiescence, the centrality of the mutated cancer cell, and the importance of its microenvironment (Hanahan and Weinberg 2000, 2011; Capp 2005; Radisky and Bissell 2006; Bissell and Hines 2011; for further discussion on theories of cancer see Bedessem and Ruphy 2015; Bizzarri and Cucina 2016; Montévil and Pocheville 2017; Sonnenschein and Soto 2020). Like the SMT they attribute a causal role to mutations; new findings such as cancers without mutations (Versteeg 2014) and the presence of the same mutations in cancer and normal cells (Martincorena and Campbell 2015) challenge such a causal role.

Meanwhile, theoretical biology is flourishing by adopting an organicist perspective that incorporates evolution, functional biology, and development (Longo and Montévil 2014; Noble et al. 2014; Moreno and Mossio 2015; Walsh 2015; Soto and Longo 2016; Bizzarri et al. 2017; Sonnenschein and Soto 2018). However, in biomedical research, when competing for research funds reductionist approaches are favored over organicist ones. In this way, the "establishment" maintains the status quo.

Conclusions

Using only clinical observations and impressive synthetic thinking, Smithers correctly defined what kind of disease cancer is. He did it by showing the contradictions and lack of fit of the still hegemonic SMT and by proposing an organicist perspective from which to start building a new theory of cancer. The limited impact of his enlightened and elegant analysis of carcinogenesis and cancer treatment deserves to be studied by specialists under rigorous historical, sociological, and political perspectives. A citation search in Web of Science revealed that one-third of the journal articles citing his paper were published in the last decade, probably an indication of a shift in the appreciation that organisms, both in health and disease, cannot be reduced to the cellular level of organization (Moss 2003). Some of these papers call for new thinking in cancer research (Wion et al. 2015; Axelrod and Pienta 2018), and others propose new systemic views of cancer (Levin 2012; Bizzarri and Cucina 2014). Thus, we can assert that Smithers's legacy is assured at least among a minority of researchers who criticized the reductionist viewpoint and decided to explore new systemic approaches. From our vantage point, we attribute the retention of the SMT by the mainstream to the still prevalent reductionist stance in current experimental biology and the pervasiveness of genetic determinism in biomedical research at large (Krimsky and Gruber 2013). Smithers convinced us that the inertia to change one's modus operandi, be it on the ideological or practical front, was already an important factor at the beginning of the molecular biology era (see the section "Practical and Logical Arguments Against Cell-Centered Cancer"). The persistence of reductionist and gene-determinist stances may be due to additional sociological factors. Lately, an appraisal of the introduction of neoliberal ideas in the practice of scientific research at large, and in biomedicine in particular, calls attention to the shift in academia from the

[3] This work was developed by the ORGANISM group, comprising biologists, philosophers, mathematicians, and physicists. It was established during Ana M. Soto's tenure as Blaise Pascal Chair of Biology 2013–2015 at the École Normale Supérieure (ENS, Paris, France). The ORGANISM members are G. Longo, P.A. Miquel, M. Montévil, M. Mossio, N. Perret, A Pocheville, C. Sonnenschein, and A.M. Soto.

freedom to explore one's ideas to a system where funding is the foremost goal and a measure of prestige (Mirowski 2018). The "market of ideas" has become the arbiter of funding and thus of excellence in science (Mirowski 2012; Lazebnik 2015, 2018). This sociopolitical change does not totally obliterate organicist experimental research programs but certainly does not provide a balanced playing field either. Ultimately, a redirection of science objectives and funding might finally benefit the acknowledged target of this undertaking, that is, the cancer patient.

Acknowledgments We wish to thank Richard Gawne and Stuart Newman for providing us with the opportunity to discuss Smithers's seminal paper and for their constructive suggestions on the manuscript; Cheryl Schaeberle and Victoria Bouffard for their critical reading of the manuscript; and the National Gallery of Portraits, London, for their permission to publish D.W. Smithers's portrait. We gratefully acknowledge support by the US National Institute of Environmental Health Sciences Grants ES030045 and ES026283. The funders had no role in the content of this essay, and it does not necessarily represent the official views of the funding agencies.

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