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WHAT TUMORS TEACH US

PARALLELS IN CELL AND HUMAN BEHAVIOR

Jana Šmardová

MUNI
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To my daughters Anna and Daniela

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PARALLELS IN CELL AND HUMAN BEHAVIOR

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A. Introduction

Ethologist and Nobel Prize winner Konrad Lorenz wrote in his book *Civilized Man's Eight Deadly Sins*: "Far from being an insurmountable obstacle to the analysis of the organic system, a pathological disorder is often the key to understanding it. We know of many cases in the history of physiology where a scientist became aware of an important organic system only after a pathological disturbance had caused its disease" (Lorenz, 1974, p. 5). For tumors – currently one of the most common disorders of the human body – this is the perfect truth. Understanding the rules broken by tumors and followed by healthy cells provides an important insight into the fundamentals of healthy multicellular organisms. It is the tumors that remind us how perfectly organized the healthy body is, and how breathtakingly sophisticated is the scenario that makes all these incredibly different, diverse, yet interconnected cells coexist and work together in harmony.

And that is exactly what tumors teach us. Or they can teach it. They show us clearly and painfully what the violation of basic rules means for coexistence and cooperation in the community of cells that make up the multicellular organism. Perhaps they can also teach us something about the rules of coexistence and cooperation in our human community. Or at least, perchance we can get some insightful and playful suggestions to improve or correct the way humans live together and cooperate. In the pages that follow, I will refer to these free analogies as "overlaps."

The development of a tumor begins inconspicuously, just as a cluster of several proliferating cells. Cells that gradually multiply and, step by step, acquire more and more properties that increasingly distinguish them from healthy cells. The pathological behavior of these cells is reminiscent of the behavior of us – humans. Considering the harmonious perfection of a multicellular organism and the dramatic effects of tumor development, one begins to wonder if cancer is really just a disease and a matter of cells. What if cancer represents a more general principle? A more general failure of complex, multi-layered systems? Perhaps tumors thrive not only in our bodies, but also in our lives and in society as a whole. If so, it might be worth investigating whether the characteristics and behaviors that distinguish tumor cells from healthy cells are not parables or analogs for the characteristics and behaviors of us humans. And do they not then represent such characteristics or behaviors that pose a threat to society as a whole?

It can be argued that simple transfer of knowledge from biological to social systems is foolish, just as the functioning of living systems cannot be explained solely on the basis of understanding physical and chemical processes. This is undoubtedly true.

However, this book does not intend to provide a literal and authoritative transfer of knowledge from biology to the social sciences. It is more like an experiment, a trial, a game. We can use the biological system here as a starting point, as inspiration for analogies and reflections on human behavior. And what is the point? Some do not find one. Some may even see this book as pure nonsense. On the other hand, if only some of the findings about tumors and cancer were more generally applicable, and we were aware of all the limitations and simplifications we are making, the conclusions could be extremely useful to human society. While we already know the consequences of cancer and its effects in cells and multicellular organisms, it is difficult, if not impossible, to assess the behavior of people in society that we might label as "cancerous." We already have a lot of experience with the diagnosis and prognosis of biological tumors. We have developed tools to intervene in their further development and cure them. In contrast, our experience with human "tumor behavior" is very limited. The "overlaps" of biological knowledge with the human world could help us to become more sensitive to the "cancerous behavior" of people, groups, and especially ourselves in our own lives. And awareness of the possible consequences of human cancerous behavior could inspire, stimulate, and motivate us to become less tolerant and supportive of conduct that has bad consequences for ourselves and others. This awareness could help free us from many prejudices and from what we think are the unchangeable conditions of our time.

B. Overlaps

Is it appropriate to think of overlaps?

American writer, theorist, and essayist Susan Sontag would probably disagree. In her book *Illness as a Metaphor: AIDS and its Metaphors*, she writes: "But the modern disease metaphors are all cheap shots. The people who have the real disease are also hardly helped by hearing their disease's name constantly being dropped as the epitome of evil. And the cancer metaphor is particularly crass. It is invariably an encouragement to simplify what is complex and an invitation to self-righteousness, if not fanaticism" (Sontag, 1989, p. 85). Nevertheless, tumors and cancer are used as metaphors. And quite often and in a wide variety of contexts. And this is not a modern phenomenon. Already Publius Ovidius Naso used cancer as a metaphor in his Metamorphoses, written in around 8 AD, in the second book, in a chapter called "Envy and Aglaur":

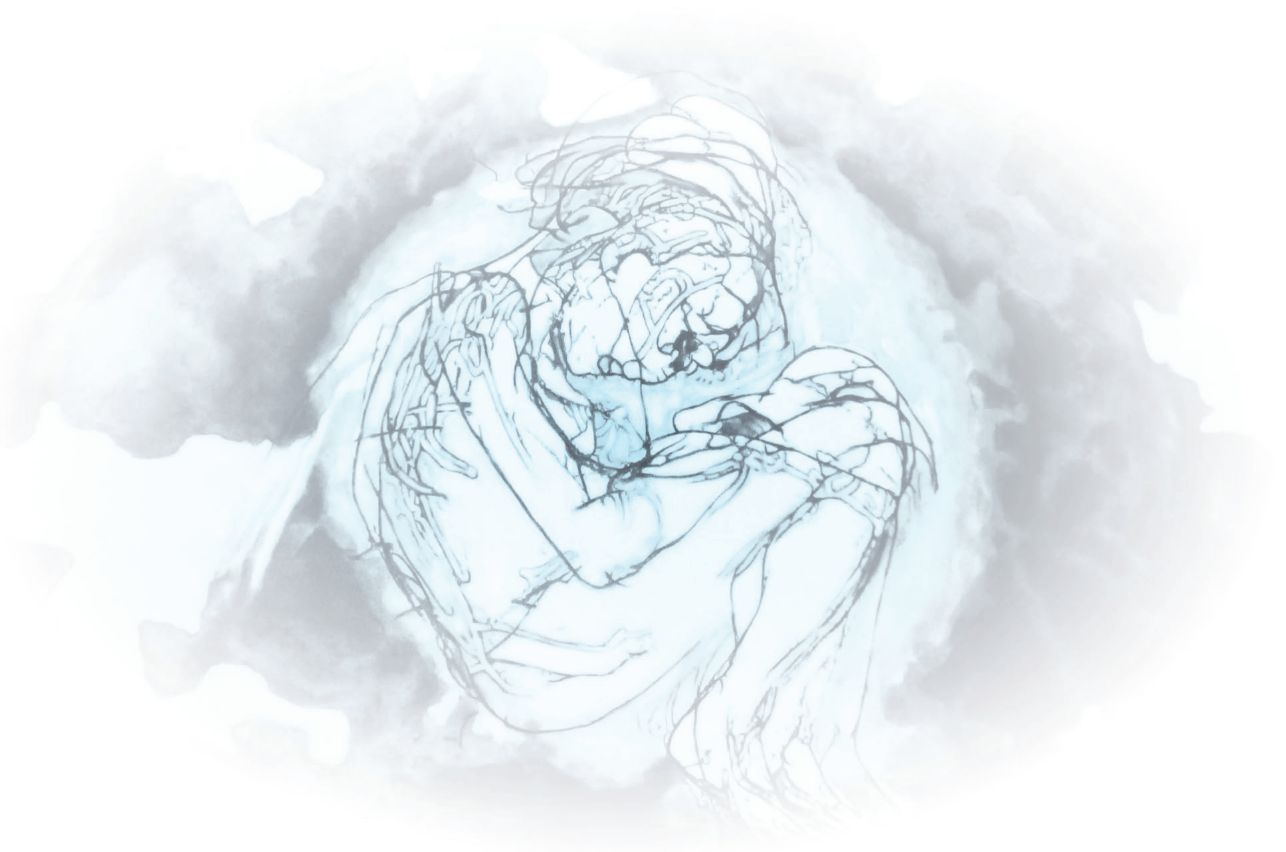
> *Strenuous she strives to raise her form erect,*
> *But stiffen'd feels her knees; chill coldness spreads*
> *Through all her toes; and, fled the purple stream,*
> *Her veins turn pallid: cruel cancer thus,*
> *Disease incurable, spreads far and wide,*
> *Sound members adding to the parts diseas'd.*
> *So gradual, o'er her breast the chilling frost*
> *Crept deadly, and the gates of life shut close…*
>
> (Ovidius Naso, 1974)

But let us return once again to Susan Sontag. She writes elsewhere in her book: "To describe society as a kind of body, a well-disciplined body ruled by a 'head', has been a dominant metaphor for the polity since the days of Plato and Aristotle, perhaps because of its usefulness in justifying repression… Rudolf Virchow, the founder of cellular pathology, furnishes one of the rare scientifically significant examples of the reverse procedure, using political metaphors to talk about the body. It was the metaphor of the liberal state that Virchow found useful in advancing his theory of the cell as the fundamental unit of life. However complex their structures, organisms are, first of all, simply 'multicellular' – multicitizened, as it were; the body is a 'republic' or 'unified commonwealth'. Among scientific-rhetoricians Virchow was a maverick, not least because of the politics of his metaphors, which, by mid-nineteenth-century standards, are antiauthoritarian" (Sontag, 1989, pp. 6–7). This raises the question of what is actually the appropriateness of using metaphors. Which ones are acceptable? And when, in what context?

This question has been asked by Bruce H. Lipton, an American biologist and teacher whose research mainly deals with the development of muscle cells. In his book *The Biology of Belief*, he describes his educational experience. "I had been fascinated by the idea that considering cells as 'miniature humans' would make it easier to understand their physiology and behavior," he says. But he is aware of the risks of such a comparison: "Trying to explain the nature of anything not human by relating it to human behavior is called anthropomorphism. 'True' scientists consider anthropomorphism to be something of a deadly sin and ostracize scientists who knowingly employ it in their work" (Lipton, 2005, p. 35). He himself uses the opposite approach in his book, which he calls "cytomorphism" or "subcellularization," and explicitly states that we can learn much from cells. He believes that "cells teach us not only about the mechanisms of life, but also teach us how to live rich, full lives" (Lipton, 2005, p. 27). By conceptualizing his "cytopomorphism," Bruce Lipton fulfills to some degree the ideas and challenges of Carl Richard Woese (1928–2012). Woese was an American microbiologist known for constructing a prokaryotic phylogenetic tree based on sequence comparisons of ribosomal RNA and defining the new kingdom of Archaea. He was involved in introducing the theory of the RNA world and brilliantly interpreted new phenomena in biology throughout his long life. In his extensive essay on the future of biology published in 2004, he wrote: " Biology today is at a crossroads. The molecular paradigm, which so successfully guided the discipline throughout most of the 20th century, is no longer a reliable guide. Biology, therefore, has a choice to make, between the comfortable path of continuing to follow molecular biology's lead or the more invigorating one of seeking of a new and inspiring vision of the living world, one that addresses the major problems in biology that 20th century biology, molecular biology, could not handle and, so avoided. The former course, though highly productive, is certain to turn biology into an engineering discipline. The latter holds the promise of making biology an even more fundamental science, one that, along with physics, probes and defines the nature of reality. This is a choice between a biology that solely does society's bidding and a biology that is society's teacher." He believed that "the main task of biology is to help us understand the world, not to change it. The greatest task of biology is to teach us" (Woese, 2004).

Is it reasonable to think of overlaps?

And is it useful to ask this question? Is it even important to look for an answer to it? Overlaps are not science! And they do not even want to play on it! In this book, the term "overlaps" refers to facts based on the science described in the chapters on tumor biology (Chapters A). Overlaps (Chapters B) are just free analogies, metaphors, ideas, topics to think about, to inspire or to teach. According to Carl Woese, this is the task of the "New" Biology. According to Bruce Lipton, cells have this potential. And perhaps Susan Sontag would accept the overlaps. But who knows? We will not ask her again. She herself died of cancer…



1A. The healthy multicellular organism

The incidence of tumors in humans is not uncommon, nothing rare. It seems that the very basis of the human body, the way it was created and the way it functions, carries the potential for tumor formation.

A healthy multicellular organism is a harmonious community of a large number of cells. Each cell has its function, which it performs at a particular time and place for the maximum benefit of the organism as a whole. The individual cells of the organism are not in competition with each other. On the contrary, they support each other and work together.

The life of every human being begins in the same way: with one cell – a zygote, which is formed by the fusion of two germ cells – sperm and egg. From it, through repeated rounds of cell division and differentiation, gradually develops the embryo, the fetus, the newborn – and the baby then gradually develops and matures into an adult human being (Fig. 1). The body of an adult human is a complicated multicellular system. What do we know about this system?

How many cells are there in the human body?

It is no surprise to anyone that our bodies are made up of a large number of cells. But how many? The bodies of multicellular organisms differ in size and therefore in the number of cells that make them up. From tiny multicellular organisms we can deduce that the number of cells in their adult bodies is not random but on the contrary perfectly regular and accurate. For example, the body of the adult nematode *Caenorhabditis elegans* consists of 959 cells (Potts, Cameron, 2011). Counting the exact number of cells in the body of an adult human is, of course, impossible. In 2013, an Italian-Greek-Spanish research team attempted to make the most serious and rigorous estimate possible. The researchers used a model of an average person – a 30-year-old young adult who weighs 70 kg, is 172 cm tall and has a body surface area of 1.85 m^2. They admitted that the number they calculated is inherently inaccurate and varies from person to person. Their final estimate of the number of cells in the body of an adult

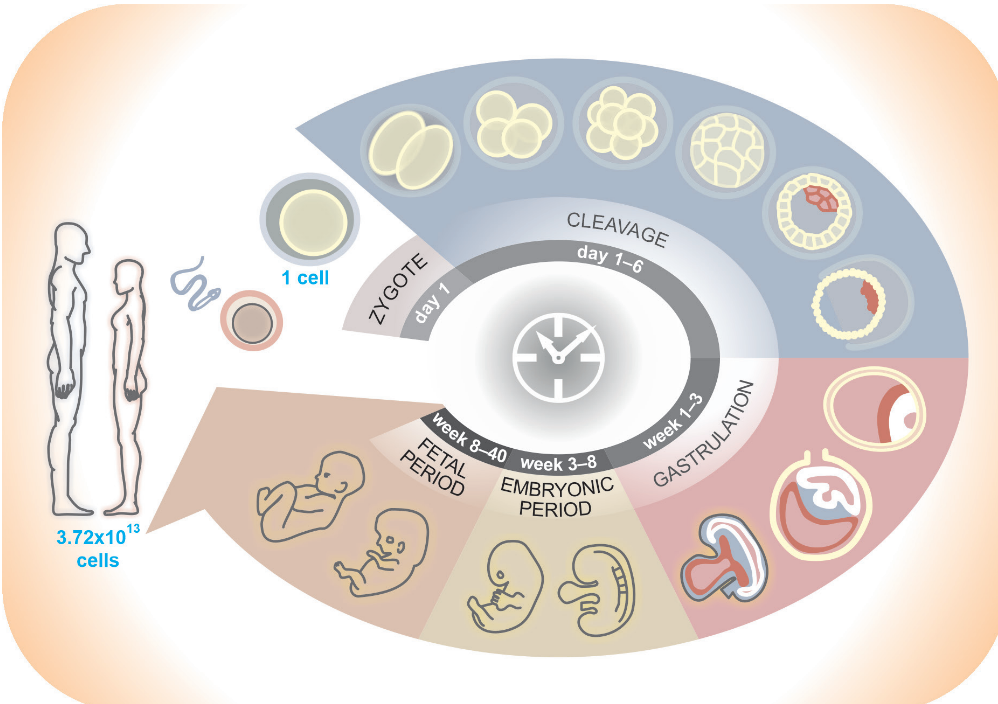


Fig. 1 Development of the human being
The life of a multicellular organism begins with the fusion of egg and sperm into a zygote. It divides again and again, the number of cells increases, the cells gradually differentiate, arrange themselves and form more and more complex structures. The stages of development after fertilization, which last about eight weeks, are called embryogenesis. Around the 56th day of development, when the foundations for all organs have been laid, the human embryo transforms into a fetus and fetogenesis begins. The body of an adult human consists of approximately 3.72 ± 0.81 × 10^{13} cells, which are differentiated into more than 200 different cell types.

human was 3.72 ± 0.81 × 10^{13} (Bianconi et al., 2013). This is a staggering number. Just for comparison, there are nearly 8 billion (7.86 × 10^9) people currently living on our planet. This means that there are 5,000 times more cells in each human body than there are people on Earth.

How many different cell types do we have in our bodies?

A typical feature of multicellular organisms is diversification. Cells differentiate into various specialized forms. We are naturally aware of this fact. We know that there are different cells in our body, such as blood cells (of which there are several types), neurons, muscle cells, epithelial cells covering the external and internal surfaces of organs, liver cells, and many others. But how many different types of cells are there in our bodies? The most common estimate is about 200 to 400 types. For example, the “Cells of the Adult Human Body” catalog published by Garland Science lists 210 clearly distinguishable cell types that can be determined by conventional histological examination techniques: that is, based on microscopic analysis of morphology (shape and structure) and staining. However, this list is not exhaustive as most cell types can be further subdivided into clearly distinguishable subtypes by other methods, e.g. physiological characteristics, degree of differentiation, developmental capacity, and so on. However, even the number 210 is overwhelming and reflects the considerable diversity of cells in our bodies. All these different cells are urgently needed by the body. Each is essential for survival and smooth functioning of the whole. Moreover, each type of cell must be present in a very specific quantity, and even a small deviation from the optimum threatens the viability of the body. Neither a deficiency nor an excess of cell types is tolerated. Deviations from equilibrium in either direction seriously disrupt the harmony of the whole.

A multicellular organism is a highly organized system of different cells

Not even the right amounts of the right types of cells is sufficient for the body to thrive. Also, all cells must be in the right place. Liver cells must not be in the muscles; muscle cells would not serve well in the brain or blood circulation. The nervous system would not be efficient if all the nerve cells were concentrated only in the brain and did not form a network running throughout the body, or if that network was broken somewhere. And the right placement, as well as the right connections – both structural and functional – are much more subtle than the examples given. A closer look at any piece of tissue would show that the order created by the cells in the body is enormous and the tolerance for deviation is low. Every part of the structure must be perfectly placed and arranged.

Considering the large number of cells in the human body, their diversity, and the need for their precise numerical representation and perfect distribution in the organism, two things might interest us. Both are well known, but we are seldom amazed by them. The first is the already mentioned fact that at the beginning of the development of an extensive, highly organized cell community there is always only one fertilized egg (Fig. 1). The nucleus of this cell contains genetic information that largely predetermines the morphology, physiology, and properties of the entire future organism that emerges from it. The second fascinating and also well-known fact is that the individual cells in the body, although so different from each other, all carry almost the same genetic information. This raises extremely interesting questions. How do the individual cell types develop? How do they differentiate? How do they find their place in a complex organism? How does a multicellular organism gradually grow and how is order created? And how is this perfect order maintained throughout the life course? Who or what drives the whole system and its development?

Development of the multicellular organism

Ontogenesis is the process of individual development from the beginning of the embryo until the death of the organism (Fig. 1). The actual beginning of the development of a new individual is fertilization. This is the moment when the germ cells, i.e. the unfertilized egg and the sperm, fuse, resulting in the formation of a fertilized egg or zygote, as mentioned earlier. After fertilization, the egg divides several times. The first division produces two daughter cells, the second produces four, then eight, sixteen, and gradually the number of cells in the developing embryo increases. These first divisions of the zygote are called cleavage. The cells formed at this early stage, the blastomeres, create a structure resembling a mulberry called a morula. A morula is a developmental stage consisting of up to 16 blastomeres. They are in close contact and constantly communicate with each other through a variety of molecular signals. They are similar, function similarly, and send similar signals.

Later, fluid enters the spaces between the blastomeres and the morula develops into the blastocyst. As the number of cells in the embryo increases, the different groups of cells begin to develop differently. Cell division comes under control and the first differentiation takes place. The outer layer of cells, called the trophoblast, surrounds the entire embryo and forms the basis of the future placenta. The embryoblast is an inner cell mass at one pole of the embryo that develops into the new individual being. During the differentiation of the embryoblast, which originally consisted of the same cells, groups of cells are gradually formed that differ from each other and give rise to the so-called germ layers: endoderm, ectoderm and mesoderm. The formation of the germ layers is called gastrulation. A very extensive rearrangement of cells occurs, as the basic orientation plan of the body and the foundations of organs and organ systems are laid (organogenesis). The individual parts of the embryo gradually become more finely specified, and complex tissues are formed, composed of many different types of cells to perform specific functions (histogenesis). While the cells in the morula and blastula still have considerable developmental flexibility and plasticity – they develop according to their position in the embryo – they lose this during gastrulation and acquire a clear and unchanging determination of their fate.

Morphogenesis as a process of formation of body structures has its molecular, cellular and organic levels. At the cellular level, this process includes proliferation, i.e. multiple rounds of cell division; gradual cell differentiation, i.e. diversification and specialization; and also programmed cell death, i.e. termination that accompanies development and occurs at a predictable time and place. At the organ level, cells move and arrange in three dimensions, establishing (and also breaking) mutual physical and functional connections. At the molecular level, these processes correlate with the regulation of gene expression, i.e. the turning of specific genes and gene groups on and off (Vyskot, 1999; Carroll, 2010). Even this brief overview of developmental processes in multicellular organisms raises the question: what drives such a complicated process?