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Abstract	Semiotic concepts such as 'sign' and 'symptom' have been applied in medicine since ancient Greece. Against this background, a semiotic perspective on nosology may be relevant and informative, particularly regarding the recognition of diseases. This chapter provides an overview of key works in semiotics on the study of medicine in general and nosology in particular. It presents a biosemiotic perspective on human health, starting with the 'Umwelt,' the organism's subjectively experienced lifeworld, and ending with 'endosemiosis,' the sign processes that are internal to the body and relate to somatic phenomena. The chapter contributes to biosemiotic medicine by commenting on how such an approach can be understood as process-based medicine, the way in which it can bridge human and animal health studies, and how it can be understood as involving a conception of the human being as a system of interrelated sign systems. It concludes by discussing how organ crosstalk can be understood within a biosemiotic framework.	
Keywords (separated by " - ")	Biosemiotics - Endosemiosis - Umwelt - Biosemiotic medicine - One health - Nosology - Semiotics	

Chapter 1
Nosology and Semiotics

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1.1 Introduction

The central medical terms 'sign' and 'symptom' are semiotic concepts, with symptoms being a class of signs. There are both natural signs, which are typically exchanged within or between bodies, and conventional (human-made) ones, such as words and cultural imagery. In this chapter, I explain how semiotics, the theory of signs, is relevant for medicine and health studies. I make use of a perspective that draws heavily on biosemiotics, which can be understood as the part of semiotics which is concerned with the study of signs in the realm of the living (biology).

The broad relevance of semiotics for natural science has been emphasized by several scholars [1–3]. In this context, particular attention has been devoted to application of semiotic ideas and models in the study of biological phenomena. However, the acknowledgement of the semiotic nature of the realm of the living is even better established in the context of various human phenomena, ranging from psychological and social to cultural phenomena. An important aim for biosemiotic medicine should be to integrate our knowledge about human biology and medicine with our knowledge about these other human phenomena in so far as they make a difference for disease and health phenomena, within a comprehensive semiotic framework.

Nosology is the theory or study of diseases, or more specifically "the scientific study and classification of diseases and disorders, both mental and physical" [4]. As such, it is related to the concept of *diagnosis* and the practice of *diagnostics*, where making a diagnosis often, and historically, entails recognizing a disease or condition by its signs and symptoms. Classification of diseases has changed considerably over time. Attempts at developing classifications of diseases go all the way back to ancient Greece, but "the first serious attempt to develop a comprehensive approach

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C. G. Musso, A. Covic (eds.), *Organ Crosstalk in Acute Kidney Injury*,
https://doi.org/10.1007/978-3-031-36789-2_1

to the classification of disease" was made in the sixteenth century [5].[1] Since the eighteenth century, it has been recognized that many diseases affect particular organs, and since the middle of the nineteenth century, there have been international classifications of diseases.[2] Even so, there is no general agreement in contemporary philosophy of medicine about what constitutes disease or health [6]. In psychiatric nosology, there is substantial disagreement about if or to what extent classification of diseases should refer to natural kinds, social constructs and/or practical kinds [7].

The condition that today goes under the name acute kidney injury (AKI) has been subjected to numerous different terms throughout history [8]. While competing definitions of AKI have been developed and applied clinically, establishing an ideal, universal definition of AKI has proven challenging, as AKI is a syndrome of many causes [9]. The fact that AKI can result in multi-organ dysfunction or be a first indication of a more complex clinical picture has made scholars study AKI in light of organ crosstalk [10, 11].

'Organ crosstalk' refers to "the complex and mutual biological communication between distant organs mediated by signaling factors" [12].[3] The term has received increasing attention over the last 10 years or so, as several new types of organ crosstalk/interaction have been identified. In the context of nephrology, this includes cardio–pulmonary–renal interactions, hepato-renal (kidney–liver) crosstalk, heart–kidney crosstalk, kidney–brain crosstalk, kidney–gut crosstalk, kidney–lung crosstalk, the cardio–renal axis, kidney–bone crosstalk, and muscle–kidney crosstalk.[4] While under normal circumstances neurons and bloodstream facilitate "interaction between the organs for maintaining an adequate homeostasis," the communication entailed in organ crosstalk can also facilitate "the spread of damage mediators" [10].[5]

As Danesi and Zukowski point out, "despite the fact that the discipline of semiotics traces its roots to the medical domain in the ancient world," medical semiotics "has never really gained a foothold in either semiotics itself or medical science" [13]. They define medical semiotics as "the study of the connection between the biosphere and the semiosphere in all areas of health and disease."[6] Current research which can be categorized as 'medical semiotics' does not systematically cover all major areas of medical research. However, Tredinnick-Rowe and Stanley claim that there are "many areas of clinical practice in which semiotics could be applied," and argue that a semiotic approach in medicine could function "as a qualitative counterpoise to existing bio-statistical approaches in medicine and healthcare" [14].

[1] 2011:9.

[2] 2011:9,10.

[3] 2019:825.

[4] 2019:827.

[5] 2019:2203.

[6] 2019:4.

Biosemiotic medicine has been approached from different angles, including body language and interpersonal interaction [15], patient agency and subjective aspects of symptom formation [16], and the interaction of biological and cultural factors of health and illness [13]. The approach of Musso et al. [11] builds on the recognition of a semiotic network which links the whole body and can be conceptualized as a 'biosemiotic plane' that is intimately related to the body's 'structural plane.' In this perspective, diseases should be reconceptualized as disorders on the biosemiotic plane involving pathogenic biosemiosis (i.e. biological sign exchange), since damage on the structural plane is typically preceded by abnormal processes on the biosemiotic plane.

The chapter is structured as follows. I start by outlining a brief historiography of the interrelations between semiotics and studies of health/medicine and also present semiotic aspects of nosology. Next, I introduce fundamental elements of a biosemiotic perspective on human health, focused on the 'Umwelt' notion; a biosemiotic view of the relation between the body and the environment; a biosemiotic view of the relation between physiology, behaviour and perception; and the notion of 'endosemiosis,' encapsulating somatic sign processes. The final section of the chapter comprises contributions to biosemiotic medicine. These include discussing how such an approach can be regarded as process-based medicine, the way in which biosemiotic medicine can bridge studies of human and animal health, and how it can be understood as involving a conception of the human being as a system of interrelated sign systems. In relation to the latter topic, the human microbiome is discussed as a context for the way in which the human organism can be conceived of as an ecosystem. The section concludes by discussing how organ crosstalk can be understood within a biosemiotic framework.

1.2 A Brief Historiography of Semiotics and Health/Medicine

Through history, semiotic ideas and concepts have been applied in medical literature and contributed to our attempts at providing definitions and explanations of health and disease phenomena and identifying causes of diseases. In this section I outline a historiography of connections between semiotics on the one hand and medicine and health studies on the other.

At its historical beginning, semiotic discourse was indistinguishable from medical discourse. Danesi and Zukowski credit Hippocrates (ca. 460–377 BCE) for being "the founder of both medicine and semiotics,"[7] referring to his coining of the term *semiotiké*' meaning "medicinal diagnosis" [13]. In Greek Antiquity, the art of healing was called *techne semeiotike*, indicating a craft involving the skills to interpret signs [14, 17]. The term 'semiotics' itself is derived from the Greek word

[7] 2019:3,5.

for 'sign,' *sēmeion* (σημεῖον). As Deely [18],[8] cited in Tredinnick-Rowe and Stanley [14], observed, semiotics initially referred to "that specific branch of medicine concerned with […] symptoms, the signs of diseases". More than 500 years after Hippocrates lived, Galen (ca. 129–216) classified semiotics as one of the six principal branches of medicine [19].[9]

Through its central role in Greek Antiquity, semiotic terminology in medicine has also played a role in Roman times and the Middle Ages, as well as in later centuries. Hess outlines medical semiotics in the eighteenth century, as it facilitated combining empirically based rules of instruction with theoretical knowledge drawn from emerging sciences [20]. Traces of the Greeks' mixture of semiotic and medical thinking were still discernible in English language use in the nineteenth century. In *The Imperial Dictionary of the English Language* [21], 'Semeiotics' is said to have two meanings, firstly, "The doctrine or science of signs," and secondly, in pathology, "that branch which teaches how to judge of all the symptoms in the human body, whether healthy or diseased; symtomatology" (cited in Deely [18] and Tredinnick-Rowe and Stanley [14]).

In the early work of the theoretical biologist Jakob von Uexküll (1864–1944), the originator of the Umwelt theory, some views on health and pathology appear in his writings on Umwelt theory [22, 23]. "Die Biologie in ihrer Stellung zur Medizin" [24] reports from a lecture he gave on how biology relates to medicine, in which he does not appear to have addressed specifically medical questions, but argued for the relevance of his biological outlook.

More focused and in-depth work on medicine from a semiotic perspective was done by Jakob's son Thure von Uexküll (1908–2004). Towards the end of his life, Thure von Uexküll played a central role in the establishment of modern biosemiotics [25, 26].[10] Being a physician and professor of psychosomatic medicine, he had throughout his career pioneered and promoted psychosomatic medicine in Germany. In his writings that explicitly address connections between semiotics and medicine [27–29], Thure von Uexküll contrasts a semiotic approach to medicine with a mechanistic approach narrowly based on natural science. His basic premise is that behaviour should be seen as "the response to signs," while physical and chemical processes can serve as vehicles for transportation of meaning or information.[11] All cells in the human body are connected via sign processes.[12] With regard to the Umwelt theory's relevance for medicine, Thure von Uexküll indicated that medicine's inability to integrate physical and psychological aspects of patients' problems could only be overcome by showing interest "in the 'reality' in which the patient lives himself" (i.e. the patient's Umwelt) [30].[13]

[8] 2006:76.

[9] 2001:75.

[10] The latter includes a selected bibliography.

[11] 1999:649.

[12] 1986:204.

[13] 2004:374.

According to Thure von Uexküll, the need for sign theory in medicine is most obvious in psychosomatic medicine [27].[14] "The unique position of psychosomatic medicine in Germany" is "largely down to the continuous engagement of Thure von Uexküll" [31]. His legacy in the German context includes the fact that subjects such as psychology, sociology, and psychosomatic medicine are included in the undergraduate medical curriculum, and that several thousand hospital beds are reserved for patients with psychosomatic disorders. In Thure von Uexküll's view, "the progression of a disease depended just as much on the personality, attitude, and the social circumstances of a patient as on his or her medical condition" [31]. Moreover, he regarded "the human being as a system in the environment of other systems" [31], i.e. he contextualized human health in a social and ecological setting.

Tredinnick-Rowe notes that there is currently a "total absence of medical semiotics in the curriculum of medical schools in the English speaking world", and asks whether the works of Thure von Uexküll could "offer a possible step towards a resurrection of medical semiotics in clinical education" [32].[15] In their overview of contemporary research in medical semiotics, Tredinnick-Rowe and Stanley [14] mention work done in gerontology, immunology, psychiatry, psychosomatic medicine and public health. Explicitly semiotic methods are taught in clinical skills courses in psychiatry and neurology in the context of disease identification and categorization in Latin American countries.

While it can be argued that all human thinking and therefore also all psychiatric symptoms are related to the functioning or dysfunction of symbol processes, semiotic approaches to psychopathology have not had any major impact on psychiatry and psychology in recent decades [32]. In this context, Andersch argues that there is an unrealized potential for cooperation between the medical profession and established subfields of semiotics such as biosemiotics and neurosemiotics [33, 34].[16]

1.3 Semiotic Aspects of Nosology

As we saw in the last section, nosology has historically been associated with and made use of semiotic terms. The relevance of semiotics for nosology has also been emphasized by several contemporary scholars. In this section I outline semiotic aspects of nosology.

According to Staiano-Ross, the symptom, as a term, refers to a clinical, objective sign as well as the patient's subjective experience and interpretation of their own health [35]. It can thus be seen as a natural sign at the same time as it has cultural aspects. Rather than understanding symptoms merely as biologically coded events,

[14] 1982:212.

[15] 2017:1.

[16] The latter offers a biosemiotic take on neurosemiotics.

she suggests looking at symptoms as indicative of the misadventures of a body and the condition of its associated Umwelt, and therefore as biocultural events. In a similar vein, Danesi and Zukowski, while acknowledging that all "species have a species-specific bodily warning system that alerts them to dangerous changes in the bodily states," stress that "in the human species bodily states are also representable and thus interpretable in culture-specific ways" [13].[17] This implies that both the definition of and the experience of diseases have a cultural aspect, and are related to cultural norms about what is regarded as healthy and sick. Relatedly, Kirmayer points out that "diagnoses serve to position individuals by assigning the sick role," which has personal as well as societal consequences [36].[18]

As Nessa notes, a medical consultation "often starts with the patient presenting a symptom, a bodily sensation of some kind" [37].[19] He portrays the clinical model at work in situations in which diagnoses are being made as involving the triadic relation Symptom–Disease–Diagnosis, corresponding to the semiotic structure Sign–Reference–Meaning).[20] According to Tredinnick-Rowe and Stanley, the physician must "link together signs, history and symptoms that are indicative of a particular pathology" by "weaving together facts into a strong inferential chain" [14]. Thure von Uexküll stresses that the physician is a meta-interpreter of the patient's symptoms, and that the physician and the patient must establish a common reality [29].[21] He sees symptoms as originating from "a disrupted flow of information in which objective and subjective evidences of an illness (signs and symptoms) appear" [28].[22] Burnum emphasizes that medical diagnosis always relies on interpretation of signs, and that getting it right requires recognition of relevant contexts [38]. As he notes, since "interpretation is subjective, it is subject to bias and to the constraints of personal experience" [38].[23] Soldati et al. emphasize doctors' use of abduction and various manipulative actions aiming at eliciting signs in the diagnosing process [39]. Thure von Uexküll cautions that such machine-supported capabilities, although they facilitate progress in medicine, do not eliminate the need for interpreting the patient's subjective signs [28].[24] An important task for the physician in his view is to carry out "the semiotic analysis of the subjective meaning which objective evidences of illness imply" [28].[25]

In their overview of contemporary research in medical semiotics, Tredinnick-Rowe and Stanley mention work done on aphasia, Alzheimer's, anorexia, autism, chronic pain, depression, dementia, fibromyalgia, HIV, obesity and schizophrenia

[17] 2019:86.
[18] 2005:193.
[19] 1996:364.
[20] 1996:368.
[21] 1999:653.
[22] 1986:215.
[23] 1993:942.
[24] 1986:205.
[25] 1986:215.

[14]. As this rather limited selection of medical conditions shows, research in medical semiotics does not to date cover all major diseases in any systematic and comprehensive manner, as a full-fledged research paradigm should. Tredinnick-Rowe and Stanley call for "a more comprehensive dialogue between biosemiotics and the use of semiotics in medicine," which may alleviate the situation [14].

1.4 Fundamental Elements of a Biosemiotic Perspective on Human Health

So far in this chapter, we have looked at interrelations between semiotics and medicine, and semiotic aspects of nosology. In so far as what we aim for is comprehension of bodily processes, within semiotics, biosemiotics is particularly relevant. In this section, I present fundamental elements of a biosemiotic perspective on human health, starting with the human Umwelt, i.e. the subjectively experienced lifeworld of human beings, and ending with endosemiosis, the most relevant category of signs in the context of bodily processes.

1.4.1 The Umwelt

A natural starting point for a biosemiotic perspective on human health is the notion of Umwelt. The Umwelt theory in its classical version was developed by Jakob von Uexküll, with major works appearing between 1909 and 1940 [22, 23, 40, 41]. In its updated version, Umwelt theory is a central part of the foundation of contemporary biosemiotics.

According to Uexküll, any animal is endowed with an Umwelt, i.e. a subjectively experienced lifeworld. In terms of biology, this includes the human being. The Umwelt is constituted by signs that are perceived as meaningful by the organism as a whole. What all creatures endowed with an Umwelt have in common is that anything that appears to the organism as meaningful does so within the framework of the Umwelt.

The Umwelt is the realm of our experiences as well as the realm in which our behaviour takes place. In Uexküll's view, behaviour is best understood as continuous response to what we experience. This is expressed by Uexküll's most famous figure, the so-called functional cycle (also called functional circle), where an act is depicted as the functionally justified response to some perceived object [41]. In Uexküll's view, the goal of any action is to make the perceived object disappear from the perceptual field by handling it appropriately. The most fundamental acts of animals include relating to some perceived objects as potential food, enemies or a sexual partner, and relating to the physical medium that the organism navigates within. The disappearance of perceived objects may imply, e.g., that a prey animal has been

caught and consumed, that a predator has been avoided, that a sexual partner has been approached, or that the animal has passed through a particular physical medium.

The Umwelt is constituted by the *Merkwelt* (perceptual world) and the *Wirkwelt* (operational world). At a lower level of biological organization these are in turn constituted by *Merkzeichen* (perceptual signs) and *Wirkzeichen* (operational signs). Operating at a cellular level, according to Uexküll such signs represent the biosemiosis, which is the foundation of consciously experienced phenomena.

The human Umwelt share basic features, such as the ones described so far, with the Umwelt of other animals, but is distinguished, first, by the way we humans make use of language and abstract thinking [42].[26] This in turn colours our perception even of tangible objects. No matter how distinct the human lifeworld may appear in comparison with the lifeworlds of other animals, we should not forget that when in crisis, human beings also tend to revert to more basic perceptions and actions. The logical starting point for any sound health care philosophy is thus to take care of fundamental bodily needs first.

When human beings relate to their own diseases, exactly what actions are required is not as straightforward as in the simpler cases of satisfying, e.g., hunger or sexual needs. The 'perceived object' may be complex, and it may not be possible to perceive it momentarily. Furthermore, the individual human being itself is not necessarily capable of perceiving the object satisfactorily. Appropriate actions may require the guidance of trained specialists.

This has several implications. First, a human being needs perceptual assistance, as it were, in figuring out the meaning of the 'perceived object' which indicates the incidence of a disease. Within a psychosomatic framework, the patient's own experience nevertheless remains significant [35]. Second, the perception of the disease-related object thus turns into a group task. And third, the appropriate actions that follow from correct identification of a disease may or may not be carried out by the patient him- or herself; they may have to be carried out by an external party (e.g. a doctor or a nurse).

In line with Uexküll's model of the functional cycle [41], successful action against the perception of a disease should result in the disappearance of the perceived object, i.e. the perceived disease. In a psychosomatic perspective, the subsequent perception of the patient's condition following recovery may also be a group task.

[26] The latter includes discussion of different views on humans' capabilities and place in nature.

1.4.2 Body and Environment

In the time of von Uexküll's most intense theory development, many theories about biological holism were presented. Many of these theorists "used the model of an organism as a unifying explanatory tool for all levels of reality" [43].[27] To von Uexküll, the organism rather represented the centre of subjectivity and sentience.

By way of the functional cycle, the Umwelt theory aims to say something about the relation between an organism's body and the environment [41]. More specifically, the Umwelt theory stresses that what an organism perceives in its environment, and what it acts upon in its environment, contributes to the constitution of what we could call *the extended organism* (the organism-in-its-environment as a whole). Phrased differently: If you want to understand the perception and behaviour of an organism, you must study its perception and behaviour in its proper context, namely from the perspective of the extended organism. Physiological studies alone are not telling of behaviour; behavioural studies require an environmental perspective that goes beyond the physical organism itself. Hoffmeyer, referring to the fact that a human body has "perhaps as much as 30 km^2 of membrane structure," stresses "how the skin, on the one hand, makes us belong in the world, and on the other hand, is part of the huge landscape of membranes across which the semiotic self incessantly must be reconstituted" [44].[28]

Applied to the study of diseases, a biosemiotic perspective entails that a first step should be to identify the relevant environmental context of a disease. For complex diseases or disorders, this might have to involve the entire environmental context of a human individual.

Given the ubiquity of signs and sign processes, applying a semiotic perspective may be appropriate for the study of complex wholes in the realm of the living [16, 29]. Giorgi et al. thus suggest that the biopsychosocial model can be better understood if approached biosemiotically [45].[29] Relatedly, Grzybek (1993) suggests that empirical semiotics "may […] offer our first hope of a unifying methodology for the cognitive sciences" [46].[30]

1.4.3 Physiology, Behaviour and Perception

In a biosemiotic perspective, physiology, behaviour and perception should be studied in conjunction, since these phenomena are interrelated. Umwelt theory is founded on the combination of physiological and behavioural studies.

[27] 2008:379.

[28] 2008:175,169.

[29] 2020:369.

[30] 1993:1.

A central notion in Uexküll's work is that of the 'Bauplan' (literally: blueprint or construction plan), which is the organism's physiological and functional organization. Early on in his first major work, *Umwelt und Innenwelt der Tiere*, von Uexküll states that it is the Bauplan, depicted as a spatial scheme, that shows us how different parts of the organism, and different processes that take place within the organism, are connected [22].[31] This, however, does not establish the physical organism alone as a functional unit. But the Bauplan furthermore largely determines the exact nature of the Umwelt of an organism and directs it towards seeking out that in its physical environment which suits it given the way the organism itself is built.[32] And this is the proper context for organismic functionality—a functioning organism is an organism that is active in a suitable environment, and the organism as a functional unit is constituted by the organism and the environment in liaison.

As Brentari remarks, the Bauplan can in some cases be understood as "a structure which actually exists in the organism"—i.e. an ontological reality, but in other cases von Uexküll appears instead to refer to a scientific model reconstructed for the purpose of understanding an organism—i.e. an epistemological tool [47].[33] In his case-specific scientific work, von Uexküll often used the term "to refer to the structure and the organization of the animal itself" [47].[34]

Musso et al.'s conception of the organism's structural plane and biosemiotic plane [11] could be understood in light of von Uexküll's notion of Bauplan. In their understanding, not only the structural plane but also the biosemiotic plane should be understood in material terms, since the vital information flow on the biosemiotic plane typically involves exchange of signalling molecules such as hormones and neurotransmitters, cytokines and autacoids. Various flows of organic substances thus mediate sign exchange, with the sign processes having obvious material aspects. The vital information flow on the biosemiotic plane sustains and has an impact on the structural plane over time. Like von Uexküll's Bauplan notion, Musso et al.'s conception of the organism as having a structural plane which is integrated with a biosemiotic plane [11] also has both a material and a functional aspect, and explains functionality in terms of biosemiosis.

1.4.4 Endosemiosis

With signs permeating the realm of the living, we have good use of a distinction between sign processes that are internal to the body and those that are not. This is found in the distinction between 'exosemiosis' and 'endosemiosis,' where the suffix '-semiosis' means sign exchange or sign action [48]. Exo- and endosemiosis refer

[31] 1909:12.

[32] 1909:5.

[33] 2015:60.

[34] 2015:77.

to semiosis that is external and internal to the body respectively. Specifically, von Uexküll T and Geigges define endosemiosis as referring to "processes of sign transmission inside the organism".[35] They describe the cell as the "most elementary integrating unit" of biosemiosis, and observe that "all sign processes occurring in multicellular organisms are 'endosemiotic,' no matter whether we look at fungi, plants, animals, or humans".[36] The authors operate with a hierarchical system of different integration levels, starting with microsemiosis (sign exchange within cells) and proceeding to cytosemioses (sign exchange between cells) and organ semiosis. A fourth integration level involves the immune system and the nervous system, which envelop the whole body and together constitute the inner world of the organism.[37] In the context of the immune system, they remark that as "a transport system for sign vehicles, the bloodstream is considerably slower" than the nervous system.[38]

"All endosemiotic sign processes" are said to be "indirectly linked to phenomena in the organism's environment," with the link between the nervous system and the locomotor apparatus exemplifying how the inner world of the organism (the 'Innenwelt' in Jakob von Uexküll's terminology) reflects its Umwelt [48].[39] Von Uexküll T and Geigges support the pragmatic idea that signs are generally "for somebody."[40] On the most basic level, this implies that the cell is the interpreting unit in the case of microsemiosis. They are somewhat reluctant, however, to attribute subjecthood at levels in-between the cell and the organism, stating that "[d]ifficulties arise […] if it has to be decided whether a cell aggregation, a tissue, or an organ should be regarded, in an endosemiotic sense, as the addressee "for whom" certain sign processes may possess a pragmatic meaning."[41] There is in their view no "one-dimensional hierarchical order" for endosemiotic processes, "but several ramified orders and numerous feedback loops between them" [48].[42]

This foundational understanding of endosemiosis is supplemented by Sebeok, who states that various biological codes, characterized by Sebeok as "syntax-controlled semiotic systems," play an important role in regulating and directing several forms of endosemiosis [49].[43] He specifically mentions the genetic code, neural code, immune code and metabolic code.

A contemporary contribution to biosemiotic medicine which may inform our understanding of endosemiosis is provided by Nowlin, who investigates the role of dysfunctional signalling processes in human pathology within a biosemiotic

[35] 1993:283.
[36] 1993:283.
[37] 1993:286.
[38] 1993:302.
[39] 1993:283.
[40] 1993:299.
[41] 1993: 299.
[42] 1993:300.
[43] 1996:107–108.

framework [50]. In immunology, it is well established that allergies are related to inappropriate defence reactions of the immune system. Nowlin's core hypothesis is that *errant defense*, far from being limited to immunology, "is a universal physiological phenomenon that can occur with any system in the body," and "results from dysfunctional signaling processes which alter stimulus interpretation, leading to erroneous perception of threat."[44] She argues that identification of threats is a primitive function that occurs in all animals, and that "living systems in the body have evolved with defense mechanisms" to protect the integrity of cells and organs.[45] Defining errant defence as "any negative, pathological or abnormal physiological reaction to a benign stimulus," she explains such reactions as the response to a system's negative valuation of a stimulus, with the purpose of the defence reaction being to "preserve the 'self'" of the system [50].[46]

1.5 Contributions to Biosemiotic Medicine

After having presented the fundamental elements of a biosemiotic perspective on human health in the previous section, I now proceed to make a few more explicit contributions to biosemiotic medicine. This will include approaching biosemiotic medicine from different angles, namely in its character of being process-based medicine, and in providing a bridge between human and animal health studies. It will further include presenting a conception of the human being as a system of interrelated sign systems, and a framing of the human organism as an ecosystem in the context of the human microbiome. To draw the chapter to a close, some remarks are made on how organ crosstalk can be understood within a biosemiotic framework.

1.5.1 Process-Based Medicine in Light of the Ontogeny of the Human Being

According to Musso et al., modern medicine suffers from an overreliance on physiological and physiopathological points of view and neglect of processual perspectives [11]. In their view, both the structural plane and the biosemiotic plane of an organism can be regarded as temporal, developing entities, with the structural plane having a slow pace (slow and in some cases permanent changes) and the biosemiotic plane a fast pace (rapid and more dynamic changes). Instead of basing diagnoses on identification of damaged organs, we should in this view aim for earlier diagnoses based on early detection of pathogenic crosstalk. They call this

[44] 2021:155.

[45] 2021:158.

[46] 2021:158,157.

'biosemiotic process medicine' [11, 51]. In a somewhat similar manner, von Uexküll T and Geigges refer to 'semiotic anatomy,' with 'anatomy' denoting "dynamic structures being constantly constructed and transformed," and "the vital relations between the organism's cells and organs […] established and maintained by information transmission through signs" [48].[47]

It is an established fact that any organism's body takes shape gradually in the course of the organism's development until it reaches the stage of the adult organism [52].[48] This is naturally the case for the human body as well—including organ systems, such as the urinary system. The coming to be of a body clearly demonstrates that physiology has processual aspects. However, conceiving of an organism's body as a mature body *only* simplifies the understanding of the body to an unwarranted extent. Neither is the perspective of the origination of adult organisms always sufficient to understand the health condition of adult organisms.

In the context of process-based medicine, it is worth noting that the term 'ontogeny' can be applied to two different temporal perspectives: either the development of an organism from an egg to an adult organism, or the development of an organism throughout its lifespan. In the latter sense, ontogeny covers any organismic development whatsoever, and in this perspective, it becomes clear that organisms are subject to processes of change throughout their lives, and not only in their initial, forming, developmental stages. For instance, normal development of the urinary system involves the emergence of voluntary control of urination. But in some cases, humans lose this function at some later life stage. As all individuals who are fortunate enough to die of old age demonstrate, processes of change, including physiological ones, occur at all life stages.

The idea that physiology, behaviour and perception should be studied in conjunction—an idea which is prominent in biosemiotic thinking, among other strains of thought—has implications for the understanding of process-based medicine. In the same vein, it also has implications for our understanding of biosemiotic medicine as process-based medicine. Beyond the processual aspects of human ontogeny, which have already been mentioned, there are further processual aspects to physiology as well, related to the integration of physiology with behaviour and perception. The functioning of a living body is intimately related to the perceptual and behavioural repertoire its physiological makeup enables at any point in time. This functioning is not static, but subject to change throughout the lifespan—potentially at any given moment. Whenever diseases or disorders affect the functioning of specific organs, they tend to affect the functioning of the body as a whole as well. When physiological malfunctioning occurs, the patient's perception and behaviour are often immediately affected.

[47] 1993:284.

[48] The latter offers a portrayal of human ontogeny in an Umwelt perspective.

1.5.2 Biosemiotic Medicine Within and Beyond Human Health Studies

Over the last few years, the One Health agenda has increasingly been recognized, for instance by the World Health Organization. The core idea of the agenda is that human and animal health should be seen in context, and that professionals in human medicine and veterinary medicine should interact and learn from each other. As Day points out, the contemporary One Health agenda has deep historical roots in comparative medicine and comparative anatomy through centuries of work, including that of classics within infectious disease research [53]. Zinsstag et al. refer to developments over the second half of the twentieth century and 'One Medicine' as a precursor to One Health [54]. Since the 1980s, an increasing international focus on sustainable development has stimulated interest in relations between human and animal health and ecosystems.

A key issue related to connections between human and animal health is zoonotic diseases, which often involves a "transmission chain from wildlife to livestock and to people" [54].[49] Zinsstag et al. call for simultaneous studies of zoonoses in people and animals and an integrated health system addressing health issues across species [54]. Wondwossen et al. address how a 'global One Health paradigm' can improve the tackling of infectious diseases, especially in low-resource settings in poorer countries [55]. Writing 5 years before the Covid-19 pandemic, they state that 75% of newly emerging infectious diseases are zoonoses, and that the top 56 zoonoses cause 2.5 billion cases of human illness and 2.7 million deaths per year. Wondwossen et al. argue that an integrated surveillance system drawing on reports from environmental monitoring as well as human and animal health diagnostic systems is required to better tackle infectious diseases [55].

In extension of the One Health agenda, Pinillos et al. have suggested a One Welfare agenda where human and animal welfare are studied in conjunction [56]. They argue that interdisciplinary collaboration would deepen our understanding of the interconnections of human, animal and environmental factors, and benefit both animal welfare and human wellbeing. In the context of diseases, Pinillos et al. point out that "poor animal welfare result[s] in increased release and virulence of a number of zoonotic diseases" [56].[50]

With its foundation in biosemiotics, which involves a semiotic perspective on issues in biology at large, biosemiotic medicine is well positioned to contribute to comparative studies of health issues in humans and animals. If developed further, it even has the potential for contributing to establishing a more comprehensive theoretical framework for the One Health agenda. Similar claims could be made with regard to the One Welfare agenda. As Danesi and Zukowski indicate, medical semiotics can draw on Jakob von Uexküll's idea that "organisms are distinguished by semiosis," implying that "a species interprets symptoms, and reacts to them, in

[49] 2005:2143.

[50] 2016:413.

its own peculiar biologically-programmed way," in accordance with its exact anatomy [13].[51] There is thus a potential for comparative studies with animal health issues whenever human anatomy resembles animal anatomy.

This applies to acute kidney injury as well as to any other disease or health issue that is rooted in anatomical factors which can be studied in a comparative perspective. Given that all vertebrate animals—i.e. all mammals, birds, reptiles, amphibians, and fish—have kidneys, the potential for comparative studies of AKI and similar health issues across species is considerable. Rather than limiting such studies to applying animal models to human cases of AKI, a One Health approach implies that learning should go both ways in-between human and animal medicine [54].

1.5.3 The Human Being Conceived of as a System of Interrelated Sign Systems

In biosemiotics, it is commonplace to frame the operation of signs in terms of sign processes and sign systems. As stressed by Sharov and Tønnessen, semiosis, or the use of signs, should always be associated with, and understood in light of, the semiotic agents that control or perform the semiosis [2]. The human being as an individual organism is one such semiotic agent which is endowed with what we can call 'semiotic agency,' i.e. the ability to make use of signs. In addition to being a semiotic agent at the organismic level, any organism incorporates a number of subagents, which can be understood as involving autonomous sign systems operating at sub-organismic levels of biological organization. We can therefore understand the human organism—and any other organism—as a system of interrelated sign systems [2].

This perspective on the human organism stresses the importance of a semiotic approach to health issues, and the systemic and organized nature of most sign processes. In the context of biosemiotic medicine, the conception of the human being as a system of interrelated sign systems provides a theoretical framework for studying the interrelation between different somatic sign processes. As Thure von Uexküll writes, "for the introduction of semiotics into the science of medicine, it is essential to describe the connections that exist between the different levels and their sign processes" [28].[52] This is relevant for the study of organ crosstalk on one condition, namely that we can conceive of human organs, or at least organs involved in organ crosstalk, as subagents of the organism-level semiotic agent, and therefore as involving their own organ-specific autonomous sign system. More specifically, organs are subagents that partake in an organ system, which can likewise be understood as a subagent of the organism-level semiotic agent. For clarity, we may distinguish between the different organizational levels of subagents in this context

[51] 2019:30.

[52] 1986:211.

by referring to first-order and second-order subagents, with first-order subagents representing the highest level of organization. In this view of the human body approached as an organism endowed with semiotic agency, the kidneys constitute a second-order subagent partaking in the urinary system as a first-order subagent of the human organism.

An organ is commonly defined as a collection of tissues that are joined in a structural unit to serve a common function. The study of organ crosstalk is particularly relevant for understanding the function and dysfunction of organs that can be explained by reference to endosemiosis occurring between organs. In the conception of Musso et al., the organism is formed by the combination of a structural plane and a biosemiotic plane [11]. In this view, flows of various signalling molecules that act as biosigns functionally connect vital organs, and organs may be seen as both anatomical structures that produce crosstalk and as products of such crosstalk [11]. This is also in line with von Uexküll T and Geigges' conception of "semiotic anatomy" [48].

Drawing on "the biosemiotic position which recognizes cells and organs as semiotic systems," Nowlin portrays the body as "a community of living systems within living systems, or selves within selves, each with their own boundary and need to interpret and respond to the surrounding environment" [50].[53] Organs are living systems in this sense [2, 50]. Each system "must be able to respond to a quasi-negative environment that includes increasingly complex and every-changing stimuli," and given that "interpretive systems are not always accurate" and that "fallibility is a basic feature of semiosis," any "system in the body is capable of reacting inappropriately to a harmless stimulus, exogenous or endogenous," and thus of enacting what Nowlin calls errant defence [50].[54]

While some of the functions of an organ system are performed locally, others may require coordinated whole-body action performed at the level of the organism. In the context of the urinary system, urination is an example of a function that requires organism-level action. Urination occurs as a reflex in infants, but by voluntary action in healthy children and adults. In the perspective of Umwelt theory, it is worth recalling that the 'functional cycle' applies to any act performed by the organism as a whole [41]. Within this framework, the act of urinating can be understood as an act that is tailored to neutralize the individual human being's sensation that the urinary bladder is full.[55] After emptying the bladder and thus disposing of waste from the body, the sensation vanishes, and the individual can proceed to focus on other tasks. While the cognitive mechanism involved is likely quite straightforward, the act of urinating nevertheless requires the participation of the brain, the nervous system and muscles, and thus coordinated whole-body action.

[53] 2021:158.

[54] 2021:176,158.

[55] Urination is also performed by voluntary control in many animals. In some species, such as wolves, dogs, rats and mice, urination has additional functions beyond disposal of waste material, in that urine is left at specific locations as a sign with social or practical significance, for their own perusal or that of fellow specimen.

As this fact illustrates, even though the urinary system for the most part functions as an autonomous subsystem of the organism as a whole—encompassing a first-order subagent of the human organism—the urinary system regularly involves the organism as a whole in its functioning as well. This involvement is induced by way of signals communicated via the nervous system. From a semiotic point of view, we can observe that the body, as a system of interrelated sign systems, relies on coordinated dynamic interaction between different levels of semiotic agency.

1.5.4 The Human Microbiome: The Human Organism Conceived of as an Ecosystem

In the previous subsection we discussed how the human organism can be conceived of as a system of interrelated sign systems, with organ systems and organs acting as first-order and second-order subagents of the human organism as a whole. In this subsection, the human microbiome—involving microorganisms that utilize various body sites in the human organism as habitat—is approached as exemplifying that the human organism can in some contexts serve as an ecosystem for other species.[56] Despite the radical difference between conceiving of the human organism as an agent and individual and conceiving of it as an ecosystem, the two perspectives are compatible and are in effect in operation simultaneously.

As noted in Sect. 1.4.2, "Body and Environment," rather than an isolated organism, a functioning organism is a whole constituted by the organism-and-its-environment. Recent investigations into the nature of the human microbiome, which involve bacteria, archaea, fungi, protists and viruses that permanently live in a human body, are informative in this regard [57]. As Knight et al. recount, improved methods for DNA analysis have in recent years made microbiome research possible that is now reshaping our understanding of human biology. This includes "rapid discovery of new links between diseases and the microbiome," e.g. on the gut–brain axis, and investigations of "crosstalk between the microbiome and epigenetic regulation" which "may also modulate disease susceptibility" [57].[57]

It is by now well established that the development of human infants and children relies on the maturation of the infant's microbiome, which is significantly affected by whether birth occurs vaginally or by cesarean section [57].[58] It is likewise well established that antibiotics usage can have a long-term detrimental effect on the gut microbiome [57].[59] However, only a fraction of the 2 kg of microbial biomass in a typical adult, which likely has a gene content "exceeding the ~20,000 human genes

[56] Parasites are another example of organisms that can take up residence in the human body.

[57] 2017:75,78.

[58] 2017:72–73.

[59] 2017:73.

by at least a factor of 100," and which includes an estimated 39 trillion microorganisms in the gut alone, has been studied [57].[60]

The existence of the microbiome implies that the human organism as a coordinated whole has to relate not only to its own bodily subsystems, but also to a number of other internal agentive powers in the form of microbes. The human microbiome can be regarded as an interface between the human organism as conceived of in species-specific terms and our actual ecology, where we as humans co-exist with several other species, some of which we depend on for our normal functioning. More specifically, the human microbiome can be seen as the microbic ecology we carry with us, in us or on us, as organisms. This perspective shows us that a living human body is in fact a multi-species entity, that the human species is not self-contained, and that no sharp distinction can be drawn between the human body or organism and the environment in which we live. The human microbiome supplements the human organism's own complexity in intricate ways and contributes to making the study of health and diseases even more challenging.

1.5.5 A Biosemiotic Understanding of Organ Crosstalk

A biosemiotic view on organ crosstalk can build on conceiving of organs and organ systems as semiotic subagents that operate within the biological context of the human organism and that each involves sign systems that are specific to organs and organ systems. Combined with a conception of the human organism as a system of interrelated sign systems, this opens a research avenue in which the interrelation of various somatic sign systems can be studied, including in the context of organ crosstalk.

In this view, each organ engages in two kinds of endosemiosis, with one occurring internally within the tissues of the organ itself, and the other occurring in-between the organ and other organs within the organism. We can call these two kinds of endosemiosis 'intra-organ endosemiosis' and 'inter-organ endosemiosis' respectively. The latter is particularly relevant for the study of organ crosstalk. Intra-organ endosemiosis is most relevant for understanding functions that organs can perform locally, and may relate, e.g., to signalling within the tissues of an organ. Any organ system relies on some inter-organ endosemiosis occurring between the organs involved in the organ system. Furthermore, inter-organ endosemiosis should always be taken into account when studying organ functioning that requires involvement of the organism as a whole. In humans (and all sentient animals) this often involves signalling via the nervous system. In cases where inter-organ endosemiosis interferes with functioning that is normally performed locally within an organ, it becomes relevant in studies of such functions as well.

[60] 2017:66,78.

Table 1.1 Typology of biosemiosis in relation to organs t1.1

Level of organization	Semiosis internal to unit	Which may be equal to …	Semiosis between units	Which may be equal to …
Cell	Intra-cellular endosemiosis		Inter-cellular endosemiosis	Intra-tissue endosemiosis Intra-organ endosemiosis **Intra-organ system endosemiosis** Organismic endosemiosis
Tissue	Intra-tissue endosemiosis	Inter-cellular endosemiosis	Inter-tissue endosemiosis	Intra-organ endosemiosis **Intra-organ system endosemiosis** Organismic endosemiosis
Organ	Intra-organ endosemiosis	Inter-cellular endosemiosis Inter-tissue endosemiosis	**Inter-organ endosemiosis**	**Intra-organ system endosemiosis** **Organismic endosemiosis**
Organ system	**Intra-organ system endosemiosis**	**Inter-cellular endosemiosis** **Inter-tissue endosemiosis** **Inter-organ endosemiosis**	**Inter-organ system endosemiosis**	**Organismic endosemiosis**
Organism	Organismic endosemiosis	Inter-cellular endosemiosis Inter-tissue endosemiosis **Inter-organ endosemiosis** **Inter-organ system endosemiosis**	Exosemiosis	Ecological semiosis Social semiosis

As shown in Table 1.1, a typology of biosemiosis can be built on the commonly held conception that an organism is constituted by cells that make up tissues, that in turn make up organs, that in turn make up organ systems, that in turn make up the organism. In the table, types of semiosis that are particularly relevant for organ crosstalk are highlighted using bold font. The dynamic interaction between different levels of agency at different levels of organization is accentuated by indications of how semiosis internal to a unit at one level may be equal to semiosis between units at lower levels of organization (third column). Likewise, it is also indicated how semiosis between units at one level may be equal to semiosis internal to a unit at

higher levels of organization (fifth column). In many cases, one and the same sign process can be approached from different perspectives, depending on the level of organization that is emphasized. The two most relevant types of biosemiosis in the context of organ crosstalk are inter-organ endosemiosis and intra-organ system endosemiosis. However, considering the dynamic interaction between different levels of agency, such endosemiosis may involve sign exchange within an organ system or within the organism as a whole (in the case of inter-organ endosemiosis), as well as sign exchange between cells, between tissues and between organs (in the case of intra-organ system endosemiosis).

Endosemiotic sign exchange often takes the form of cell signalling. This may involve, e.g., autocrine signalling in an intracellular context, and paracrine signalling or juxtacrine signalling in a local intercellular context. Longer-distance sign exchange typically involves endocrine signalling via the endocrine system or neurocrine signalling via the nervous system. Also relevant in the context of cell signalling is signal transduction, which concerns cells' utilization of signals originating from outside the cell.

Most of the human body's organs are engaged in endosemiosis only—in other words, the sign processes they are involved in are limited to occur within the physical organism. In contrast, the sense organs related to the external senses—namely the skin, eyes, ears, nose, mouth and vestibular system—are primarily engaged with exosemiosis. The sign processes they are involved generally play a role in receiving and interpreting external signals from other organisms or from the external environment. Moreover, organs involved in whole-body expressive actions, such as the larynx and voluntary muscles involved in the musculoskeletal system/human locomotor system, may also play a part in exosemiosis, by contributing to communicative acts. The sense organs that are related to the internal senses are engaged in endosemiosis on par with most of the other organs.

With regard to the term 'acute kidney injury,' George [8] raises the question of whether 'injury' is really "a preferable term by which to describe acute impairment of renal function?"[61] As he points out, 'injury' typically refers to physical damage, and using this term therefore in effect "poses a structural term to convey the meaning of a syndrome of malfunction."[62] In doing so, we are "describing a physiological *process* in anatomical words" [8].[63] This is a pertinent point to make in light of our earlier discussion of biosemiotic medicine in its aspect of being process-based medicine (cf. Sect. 1.5.1). As stressed there, the functioning of a living body is not static, but subject to change throughout the lifespan. If diseases or disorders affecting specific organs can be explained by organ crosstalk, malfunction will be best understood in a processual perspective. Understanding organ crosstalk within a biosemiotic framework likewise aligns with a processual perspective on organ

[61] 2018:5.

[62] 2018:5.

[63] 2018:5, emphasis added.

functioning and malfunction, since it involves what we can understand as a flow of semiosis which may change over time.

Whether the context is AKI or health care more generally, proper patient care requires that attention is paid to the first-person experimental perspective that is encapsulated in the Umwelt notion, and the implied change in Umwelt experience [58].[64] While AKI has multiple features, many of which are not experienced directly by the patient, a key measure of successful treatment of AKI must be an improvement in the patient's experience of health and disease before vs. after the treatment. Given a biosemiotic perspective on organ crosstalk, this requires seeing connections between the endosemiosis occurring in the kidneys and the kidneys' interrelation with the human organism as a whole. Such connections may become discernable in the disturbance of a regular function, such as urination, or in various AKI-related symptoms (e.g. nausea, fatigue, irregular heartbeat, shortness of breath) that trigger the patient to perform perceptible whole-body actions and responses. What disturbance in functions that are performed voluntarily and symptoms that affect the perception of the body as a whole have in common is that they significantly impact the patient's experience of his or her life, and thus the patient's experienced quality of life. While the problems may in a sense be 'located' in the kidneys, they may be caused by dysfunctional organ crosstalk involving other parts of the body. When the health issues are severe enough, there is a risk that one dysfunctional organ can dominate the patient's attention and experience, thus further distressing the human organism as a whole.

Nowlin's theorizing on the errant defence reactions of various systems in the body [50] is informative in the context of organ crosstalk. As she points out, in some cases where errant defence reactions occur, "medical tests are unable to detect a physical cause," but this may be because "the cause is semiotic: the reacting system is 'perceiving' a harmless stimulus as a threat and responding inappropriately."[65] A better understanding of what occurs at what Musso et al. call the biosemiotic plane [11] is then required. Nowlin speculates that "endogenous signals from the body's various systems can become associated with unconditioned stimuli," and indicates a need for research on the role of the Sympathetic Nervous System "in the defensive reaction of specific organs or systems" [50].[66]

The main pillars of a biosemiotic theoretical framework for understanding organic crosstalk are already in place. More empirically oriented research is needed on several fronts, ranging from endosemiotic sign exchange, the connections between different somatic sign systems, and organ-related defence reactions, to patients' Umwelt experience and sign-based doctor–patient interaction. Further theoretical refinement is also needed, to improve our understanding of how various sign processes are at work in the context of medicine.

[64] The latter addresses 'Umwelt transitions.'

[65] 2021:160.

[66] 2021:168,174.

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