Chapter 1
An Introduction to the Semiotic Approach to the Placebo Responses

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Today, the placebo effect is the Cinderella of a new medical world; a phenomenon which in one night turned from a platitudinous problem and paternalistic sham in practice and a disturber factor in clinical trials, to meaning response, spirit of practice and an extremely valuable subject for research. The word "placebo" is rooted in the Latin Psalm phrase "*placebo domino in regione vivorum*" – I will please the Lord in the land of the living (Kradin 2011). The word itself has been used in medical literature for centuries, but the first clinical trial was conducted in 1799, in which the author stated: "[A]n important lesson in physic is here to be learnt, the wonderful and powerful influence of the passions of the mind upon the state and disorder of the body" (Price et al. 2008). From the middle of the twentieth century, conventional medicine began using placebos as methodological tools to distinguish between specific and non-specific ingredients in treatment (Papakostas and Daras 2001). The placebo was first introduced as an inert agent solely prescribed for pleasing the patient. There was a paradoxical conceptualization in this way of thinking because doctors used placebos on one hand as an element with no therapeutic effect, but on the other hand, it did show some response in the patient. This paradox resulted

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F. Goli (ed.), *Biosemiotic Medicine*, Studies in Neuroscience, Consciousness and Spirituality 5, DOI 10.1007/978-3-319-35092-9_1

in the shift from focusing on the inert content of placebos to the concept of an active therapeutic agent within a psychosomatic context.

Until recent years, placebos had a bad reputation amongst health care professionals. To some who are involved at the clinical level, it is a kind of "trick" to make the patient feel better by utilizing the power of positive expectations. It is the last chance of a doctor who has no other scientifically rational options for the treatment of the patient. In this situation, he or she administers an inert drug. The patient assumes that it is a potent pharmacological agent, and experience has shown that this belief in the potency of the drug is indeed beneficial and can lead to the patient experiencing an improvement in his/her condition.

As placebos are chemically inert and have no specific biological target in the body, it is generally believed that the effects induced are non-specific. But a closer look at the mechanisms involved shows that it is not as simple as it seems. In fact, placebo effects are specific to the therapist's latent and active inductions, and the patient's anticipations and interpretations, which can form the complex and hermeneutic response to the therapeutic communication which is called "Meaning Response" (Moerman 2006).

Now, more than ever, the paradoxical nature of the placebo response has manifested itself in the medical community. One can find a vast number of articles which introduce placebos as a chemo-physical (non-specific) effect or a semantic/cognitive (specific) effect; as noise of biomedical studies or a signal of doctor-patient communication; as a very beneficial, safe, and common therapeutic agent, or as immoral interventions which ignore the principle of autonomy. One can infer that there are very serious dilemmas in this field of practice and research: pragmatic (specific and non-specific), methodological (desired and undesired), and ethical (beneficence vs. autonomy). Introducing these dilemmas shows the paradoxical and complex nature of placebo responses and also addresses the clinical and paradigmatic opportunities and restrictions. We will discuss these topics and their biosemiotic explanations further in the following chapters.

1.1 The Pragmatic Dilemma: Non-specific or Meaning Response

As Moerman and Jonas (2002) explain, different elements of medicine are meaningful for the patients and are unrelated to the intentions of doctors and other health care professionals. A fitting example is the so-called "white-coat hypertension". Studies show that the environment of a hospital and the white coat typically worn by doctors is a trigger for elevated blood pressure in some patients (Pickering and Friedman 1991; Bügel 2004). Like doctors' white coats, many other elements present in the clinical context have meaning for the patient. Doctors' behavior, facial expressions, gestures and language, as well as the devices, colors and shapes in the hospital all are meaningful and play a part in the process of treatment. Paying

attention to these factors and analyzing them make these seemingly non-specific effects specific. Moerman and Jonas also mention that the placebo response may even be stronger in surgical interventions because the rationale behind these interventions fit better to the mechanistic mind of modern man. In other words, it is easier to assign a meaning to a surgical intervention. A good example is a study that evaluated the effectiveness of binding internal mammary arteries to reinforce the blood supply to partially occluded coronary arteries. In the study, this technique was compared with a sham surgery in which only a skin incision was performed and the internal mammary arteries were not ligated. The results showed that there was no difference between the intervention group and the group of patients on which sham surgery was performed (Bügel 2004). Especially today, with new insights and developments in medical ethics, it is not possible to design such studies for evaluation of surgical procedures, because the patient would bear the burden of a surgical operation. There are, however, similar recent studies like one that evaluated the effectiveness of arthroscopic removal of osteophytes in patients with osteoarthritis. In this study, the results showed that there was no difference in the outcome between the patients with actual removal of osteophytes and the patients with a sham surgery, in which only an incision on the skin was done and no osteophyte removal was performed (Kradin 2011). Although the placebo effect is not specific like the effect of pharmaceutical agents designed to target specific chemical interactions or molecules, they have specific effects via the meaning that treatment produces for the patient and the direct and indire ct suggestions that they produce in the clinical setting.

To incorporate all of these facts into a comprehensive framework, we need a new perspective towards the fundamental concepts in medicine, such as health, diseases, and healing. A semiotic approach can provide such a framework, especially for explaining psychophysical events which could not be demonstrated by linear causal models. As Eco states, until a short time ago, medical semiotics was the only research project in the field of sign studies (Eco 1979). His interpretation of signs has been a central issue in medicine since its beginning, and there existed a close relationship between medicine and semiotics. The German thinker and physician, Thure von Uexküll, who is considered one of the founders of psychosomatic medicine, believed that the biosemiotic approach is a good tool for describing what happens in the process of clinical encounters in real life. Semiotics is the doctrine of signs developed by the American philosopher Charles Sanders Peirce. With this perspective, there are three important components: sign, object, and interpretant. A sign is something that stands for another thing which is the object that it signifies. The sign represents certain meaning or understanding in the recipient. The recipient then acts based on the meaning it perceives (Meyer 1984; Walach 2011).

In other words, an object which represents a sign itself can be a sign for recipients, and as recipients have minds, they interpret the signs. The meaning that can be produced by the object is called “interpretant” and the individual who analyses the sign and object is the “interpreter”. When there is only one object that has one meaning, there is a causal relationship between the sign and meaning. A familiar example in the clinical setting is examining pulse. The pulse is a sign and the cardiac

function is an object. For instance, in the case of tachycardia, the accelerated pulse shows the increased rate of heartbeats and only one meaning arises from this sign (cause and effect). Now, this accelerated heart rate could be considered as a sign and the object could be anxiety, the increase of certain hormones like thyroid hormones, etc. It is the context that reveals which object is connected to this clinical sign.

In the biomedical paradigm, man is considered a biophysiological machine. The medical interventions are based on the causal relationship between interventions and the change of the system toward recovery. The interventions could be pharmacological agents which block or activate certain receptors, or physical and surgical procedures that rectify the pathological deviations. In this perspective, the patients are considered to be a passive receiver of treatment, for which there is no place for their feelings, thoughts, believes, emotions, intentionality, and agency. In this model we cannot explain how a positive anticipation or a healing intention can initiate a complex chain of physiological procedures (Lewith et al. 2010).

In the biosemiotic perspective, patients are seen as active agents who have their individualized interpretations of different interventions. Each intervention is, as a result, considered as a sign, which is meaningful for the patient. This sign could be interpreted as belonging to different objects (Miller and Colloca 2010). For example, if the patient believes that more invasive and painful interventions are more effective, then an injection will have a more substantial effect than a pill. Also based on previous experiences of the patients, the meaning and effect of the injection will be different. It should be mentioned that in this approach, the causal element of pharmacological properties of the agent are not ignored, but that the meaning that is created in patients as an active agent is something above the causal element.

A good replacement for causal model of placebo is the biosemiotic approach. As Wallach (2011) explained: "Placebo effects are real physiological effects. But they are not caused by a physical intervention but arise from the intrinsic meaning-making of an active organism that interacts with the environment." (p. 1874)

It is clear that placebo responses are not matter-specific, and, from the mechanical and linear causality viewpoint, can only be deemed as non-specific effects. Yet from a biosemiotic point of view, they are meaning-specific responses, and the semiotic formulation of each can affect the psychoneuroimmunologic state in a distinct manner. There is no limitation for biosemiotic formulations; they could be even paradoxical mixtures of salutogenic agents (placebo-anticipated positive effects) and pathogenic agents (nocebo-anticipative negative effects) which arise from a communicative context.

1.2 The Methodological Dilemma: Placebo, Noise, or Signal

Apart from the clinical impacts, placebo effects are also a dilemma in research. They are problematic for the most important tools in evaluating new treatments, known as randomized clinical trials (RCTs). Historically, the American anesthesiologist, Henry Knowles Beecher, became familiar with the power of placebos

during World War II. In a difficult situation in a hospital at Anzio Beachhead, Italy, there was shortage of morphine for the many wounded soldiers suffering from pain. Faced with a difficult situation, a nurse proposed injecting them with saline water, but telling them it was strong analgesic. Astonishingly, it was helpful. He was so fascinated by this that after the war, in 1955, he wrote a paper in the *Journal of American Medical Association* titled "The Powerful Placebo". He reviewed 15 published papers about different interventions and concluded that 35 % of the successes in treatment were due to the positive expectations of the patient, or the placebo effect. He later focused on the fact that in evaluations of effects of a pharmaceutical agent or a new procedure, it is difficult to differentiate between the healing effects of placebo responses and the genuine effects of the treatment. He went on to become one of the founders of double blind placebo-controlled RCTs, but did not explore the mechanisms of the placebo response itself. Today, RCT is the gold standard of evaluation of new treatments, and because researchers try to minimize the placebo response in their research, or in other words, get rid of it, it has also become a reason that there is a negative attitude towards placebo responses among health care professionals. In other words, Beecher experienced the placebo effect as a powerful healing tool in the clinical setting. He defined it as a noise in the research system of clinical trials; it is the unwanted and undesired part of research that should be eliminated in order to reveal the useful and therapeutic part of the study (Bensing and Verheul 2010). But in recent years, there are many studies that suggest this so-called "noise" or confounding factor that used to interfere with the physical and chemical interventions, which are designed based on precise pathophysiological knowledge, could be interpreted differently. Now, several studies show that placebo reaction is a healing message itself that can be explored and controlled for therapeutic purposes.

It is a well-known fact in medicine that the relationship between the therapist and the patient has a healing effect. Balint (1957) considers the doctor as the most potent drug. As Bensing and Verhul state (2010), although the two fields of placebo research and doctor-patient research were generally separate, they are converging and demand exploration of the mechanisms by which placebo effects are produced by doctor-patient communication. Adopting an analytic approach to medical investigations as a modern tradition obligates us to eliminate the placebo effect in order to distinguish the chemophysical effectors, but as a complementary approach, we can also have a synthetic approach to develop the psychosomatic dynamisms (an interactive intentional-physical network) for establishing more effective and humanistic health services which are not necessarily quantitatively and analytically well-defined. Knowing these healing pathways allows us to control and expand them, and make doctors aware of the powerful healing tools that they possess in clinical encounters.

1.3 The Ethical Dilemma: Beneficence vs. Autonomy

One of the barriers of using placebos in a clinical setting is the ethical problem associated with their administration. From the perspective of medical ethics, there is a conflict between two of the basic ethical principles in the treatment of the patients with placebos. These two principles are autonomy and beneficence (Miller and Colloca 2011).

On one hand, based on the autonomy principle, the patient has the right to accept or reject a treatment so he or she must clearly be informed of the safety, efficacy and nature of the therapy. And according to the beneficence principle, it is the duty of the therapist to act in the best interest of the patient in the safest and most efficient way possible. Upon first sight, placebo therapy seems fundamentally paternalistic and we also know that placebos are extremely safe, but here the question is: Are placebos really beneficial to the patients?

There is enough evidence in the literature that shows the power of placebos. A variety of health conditions, like heart failure, pain, Parkinson's disease, and schizophrenia, were responsive to placebos. There is a special interest in placebo responses to pain, and it has been shown that there is a real effect, the magnitude of which however differs vastly (Bensing and Verheul 2010).

Here, there is an ethical dilemma for doctors and health care professionals. On one side, the placebo effect is quite safe and helpful, and although it is chemically inert, the patient feels better after its administration. Alternatively, if a patient realizes that there was no rational and scientifically valid reason for the use of that drug (or procedure), a negative feeling will develop due to the patient feeling "deceived" or "tricked" which could possibly disturb the rapport. This issue in particular has become an increasingly serious concern, as it is generally accepted that the patient, from an ethical point of view, should be aware of the treatment process and informed about all drugs administered and procedures used by means of the autonomy principle; patients should give consent for all treatments applied. Another pertinent ethical issue in researching placebos is the potential danger for patients in specific circumstances. When effective treatment already exists, waiting for the assessment of the effectiveness of a placebo is unethical because it can cause irreversible changes in patients, placing them in danger. For instance, when treating myocardial infarction, some cancers and some infectious diseases, placebo-controlled trials are not moral.

In spite of these ethical concerns, placebos are used regularly in the clinical setting. In a study which has been done on American internists and rheumatologists, around half of the participants used placebos regularly in their practice. Most of them use placebos for chronic pain patients if they think it is beneficial, and a significant number believe that it is ethically justifiable (Tilburt et al. 2008). Many physicians prescribe antibiotics, sedatives, vitamins, and physiotherapy as placebos, and, especially in the case of antibiotics, it is the source of new problems like the development of multi-drug resistant types of bacteria (Miller and Colloca 2011).

Because of these issues surrounding the concept of placebos, it is a concept that doctors are not inclined to deal with. But is there a way out of this problem?

The point that helps us solve the problem is mentioned by Moerman and Jonas (2002) and is based on the fact that placebos are inert. We know that there are no chemically and physically-induced therapeutic changes by placebos, and that there are other related mechanisms that are involved in the formation of the healing response. That being said, the solution would then be to focus on psychoneuroimunological mechanisms of the placebo effect instead of focusing on the placebo itself. A great amount of empirical evidence supports three main mechanisms in the emergence of a placebo response: (1) conditioning, (2) The Expectancy Theory, and (3) The Affect Theory. It should be mentioned that there is an overlap among these mechanisms. Each of them can also be influenced by a doctor's behavior, which in turn shows the importance of doctor–patient relationship in this issue (Price et al. 2008; Bensing and Verheul 2010).

In conditioning, a natural stimulus is repeatedly associated with an unconditioned stimulus (e.g. active drug), where the natural stimulus with time can act as a conditioned stimulus. An empirical study shows the conditioning mechanism in the clinical setting very well. Goebel and his colleagues (2002) conditioned subjects in four sessions in a double-blind study. They paired an immunosuppressive drug (unconditioned stimulus) with a specific flavored drink (conditioned stimulus) and gave them to the subjects every 12 h. After 1 week, subjects again received the flavored drink that now contained merely placebo capsules that were free of active substances, and the patients interestingly showed further suppression of the immune system. The conditioning phenomenon happens in clinical settings consciously or unconsciously. Warm and empathic communication with a physician can be coupled with a patient's recovery from previous health problems, and this conditioning would also affect the patient's future experiences with medical problems and occurs often as an automatic unconscious process.

Expectancy is defined as a patient's expectation of response following administration and is, in contrary to conditioning, always a conscious process. Expectancies could be patients' beliefs about the effects of treatment or about the ability of themselves in fighting a disease and controlling or coping with it. It has been shown *in vivo* that this phenomenon induces endogenous opioid release. Additionally, expectation can be reinforced by previous experiences, verbal suggestions, and the stronger desire of a patient to reach positive goals. Several studies show that when patients are aware of the type and exact time of drug administration, the drug's effect is greater and faster (Meissner et al. 2011).

Bensing and Verheul (2010) consider affect manipulation as another mechanism in placebo response. It is defined as the influence of different methods of treatment administration on patients' affective state. They believe that positive affect and lower levels of stress and anxiety would facilitate the treatment. Affect can work through mediators like self-efficacy, adherence, and self-disclosure. The doctor's attitude towards the patient has also an important role in assembling a positive view in the patient about his/her disease.

Based on neurobiological studies on placebo effects, the reduction of neural activity can be seen in the parts of brain which are responsible for pain and anxiety. The increase in brain activity in emotion regulation areas has also been shown to exhibit a placebo response (Price et al. 2008; Flaten et al. 2011). Despite the fact that these mechanisms are well known in psychology, and many psychoneuroimmunological studies revealed the details of this phenomenain biological and physiological levels, the use of treatments based on these processes is not well established in clinical practice. In other words, although there is rich literature on the importance and efficacy of psychophysiological pathways, the application of these mechanisms is underscored in the clinical setting.

Now the question is: Why is this happening? The answer goes back to the ethical dilemma of placebos. As mentioned, the main problem in using placebos in the clinical setting is the contradiction between "beneficence" and "autonomy". This inconsistency emerges based on the assumption that if the doctor does not lie to the patient, there would be no placebo response. Based on this assumption, if the physician informs the patient that the prescribed drug has no pharmacological properties, the drug would then have no effect on the patient. Montgomery and Kirsch conducted a study on pain and analgesia with an artificially induced pain in their laboratory and showed that when the participants were merely told that they were not receiving a real drug and the cream applied was inert, the drug (placebo cream) had a little or no effect in pain reduction (Kirsch 1997). This study supports the idea that a placebo is only effective when the patients are not aware of the drug's contents.

In contrast, Kaptchuk and his colleagues (2010) questioned the explained assumption on the placebo effect. They did a randomized controlled trial on Irritable Bowel Syndrome (IBS). In their research, they presented the placebo pill to the patients as "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes" (p. 1) and the results showed significant improvement in the placebo group. Although in this study patients were aware that the drug has no pharmacological agent, identical to the former study, the results were completely different solely due to the different methods of information disclosure. In other words, the important point here is that the way that treatment intervention is described affects symptom relief and patient experiences (Miller and Colloca 2011). This point can facilitate solving the ethical dilemma of placebos regarding autonomy and beneficence.

The other way out of this ethical dilemma is by emphasizing the mechanisms involved in the formation of a placebo response instead of the placebo itself. We saw that the placebo itself is inert and that the psychological mechanisms in fact activate the process of healing. These mechanisms could be activated by doctor-patient communication and different psychological intervention (Miller and Colloca 2011). For example, expectancy is an important component of treatment in hypnosis. The suggestions which are given to the patient have a healing impact, and the physiological changes which occur through hypnosis are the result of expectancy mechanisms (Kirsch 1994, 1997).

Conditioning, which is the other proposed mechanism for placebo response, is well known in behavioral medicine (Mommaerts and Devroey 2012). Different treatment methods have been developed based on this mechanism in this approach.

Justman (2011) explored the relationship between psychotherapy and placebo effects. According to Justmsn, sychotherapy as one of the psychological treatments is widely used in the treatment of psychosomatic medicine. In psychotherapy, emotion is a core concept and affect manipulation plays an important role in the process of this treatment.

Generally, it can be said that in different mind–body interventions, like acupuncture, relaxation therapy, yoga, meditation etc., there is a component that is common with the mechanisms involved in the formation of the placebo effect (Brom 2012; Stefano et al. 2001). Considering these facts, it might be appropriate at this stage to think about the possible ways out of the mentioned dilemma.

1.4 The Way Out of the Dilemma

As discussed, the mechanisms by which a placebo effect is mediated are not unknown. But why, in today's medicine, is their use so limited? And why have they not become incorporated in the main treatment protocols of health problems?

The basic answer to these questions is hidden in the way that the current model of medicine; namely that biomedicine, defines the patient. As its name biomedicine implies, a person is a biological and at most physiological entity. The main focus of interventions in this approach lies in the subpersonal levels and the physiological mechanisms involved in the formation of different problems (Kihlstrom 2008; Gaines and Davis-Floyd 2004). In this framework, the mental phenomena like thoughts, feelings, beliefs, and imagination, although possibly considered as effective or functional in the process of treatment, are not considered tools for designing and developing new interventions. Any intervention developed based on these phenomena is in turn considered to be alternative, adjuvant, or secondary to biomedical interventions.

In biomedicine, the "signs and symptoms" have become separated and there is a split between hard and soft data in clinical encounters, but from a systemic viewpoint between hard and soft reality (Nessa 1996). As we see in the case of placebo responses, in the clinical context as well as in the very process of healing response formation, emotions, feelings, beliefs, and the patient's (and therapist's) personal experiences play a critical role. As a result, in order to solve these dilemmas, we require a broader perspective. A new framework is needed in which the phenomenal experiences of the individuals involved come to play their role and are considered as real but non-linear causal factors in the maintenance of health and development of disease. In this view, disease is not merely considered as a derangement of a physiological or biological organ, neither coincidentally nor because of an unknown reason. Instead, it is a malfunctioned pattern of behavior developed in the context of

a person's life, world, and lifestyle with all of the biological, psychological, and interpersonal interactions and complexities.

There were clinicians who recognized this problem and attempted to develop an alternative framework to gain a broader view which could explain both the mechanical (hard) and semantic (soft) aspects of human systems; a systemic approach which would provide an integrated model for consciousness–information–energy–matter interchanges and interactions. Evidently, it would be an ambitious goal for us even now after decades of systemic speculations and trials, but nevertheless, the theoretical and practical impacts of systems theory have formed a vast variety of the current theories and methods in psychology and medicine. Developed by the American psychiatrist George Engel, the biopsychosocial model might be one of the most successful and influential views in this field.

1.5 Biopsychosocial (BPS) Model

In 1977, George Engel published a paper in Science Magazine titled: "The need for a new medical model: A challenge for biomedicine" and attempted to explain the deficiencies of the biomedical model and the advantages of the model he proposed (Engel 1977). His new model was developed based on Ludwig von Bertalanffy's General Systems Theory (GST) (1956). In GST, von Bertalanffy tried to develop a general model for the systems in different fields that is neither reductionist nor mechanistic. In this model, we deal with different systems from micro to macro with hierarchical organization. Engel applied this model to the human and considered a hierarchy of organization of the different systems in man. This hierarchy begins with the level of molecular interactions and extends to higher levels corresponding with cells, tissue, organs, nervous system, person, two persons, family, and community. He claims that in biomedicine, the emphasis is mainly on the subpersonal levels and the trend is to more highlight the cellular and molecular levels, with the assumption that all human phenomena can be reduced to underlying biological procedures.

He addresses that in practical clinical encounters, we deal with the personal level, of course by highlighting the behavioral aspect of this level and ignoring the experiential aspect; the mental activities and states such as intentions, thoughts, emotions, feelings and beliefs. These mental phenomena are the superimposed, emergent modes of this level which cannot be inferred or predicted from the underlying levels. As such, the analysis of a system, like that of a human being, could be helpful but insufficient. One must study the whole system's behavior and experience in order to synthesize a systemic approach and understand the irreducible properties of the system.

Engel explains that when a pathological change emerges in one of the levels of the hierarchy, the problem would not remain confined to that especial level; changes also take place in the upper and lower levels. For example, when a myocardial infarction occurs in the level of cardiac muscles, it raises concerns, fear, and anxiety

in the personal level; new patterns in the relationship dynamic of the two person level; strain, anxiety, new tasks and roles in the family; and the use of medical-social and other recourses in the community level. Similarly, changes happen in the downward direction. The sympathetic system is activated and there is a neurotransmitter release from the nerve endings. There presents then a risk of damage to the other organs like the kidneys and liver. Ischemia and infarction are seen in tissues and the signs of cell damage could be seen in the cellular and molecular level. Engel suggests that in the treatment of a patient, all of these changes in the different levels should be considered and that the intervention should not be confined to the level in which the primary pathology has emerged. He also states that as we deal with the personal level of patients in the clinical setting, the communication skills and attention to patient concerns, emotions, feeling, and beliefs are of great importance.

On one hand, the Biopsychosocial model was very influential and many have tried to apply it to real life situations in medicine and other related fields like sociology and health psychology. This group believes that the assumptions of this model are still relevant and could be further developed with new ideas (Adler 2009). On the other hand, there are debates about its applicability and there are some who criticize it. For example, the psychiatrist Tavakoli (2009) believes that this model in practice confuses the students and residents who are learning the different psychiatric problems and creates an arbitrary separation between biology and psychology. Additionally, he claims that the use of this model in psychiatry and other fields of medicine such as surgery and medicine makes students frustrated and avoidant. We think that this confusion arises from a fundamental question which is not only present in medicine, but also in other fields which deal with mental phenomena like psychology and sociology. This is the basic philosophical question of the relationship between mind and body, or in a wider view, mind and matter. In medicine, it is a critical question, but in the field of psychiatry, it is more tangible because patients have mental problems. Developments in neuroscientific studies of psychiatric disorders have shown the patterns of change of neurotransmitters in the central nervous system in the course of these problems (Trimble and George 2010). On the other hand, plenty of studies show that the psychosocial context is important and plays a crucial role in the emergence of these disorders (Wallace and Gach 2008). At first sight, these findings seem controversial, but if we can rid ourselves of the linear causality framework, we will at least see a causality network in which the psychosocial and/or physical parameters can initiate and/or accelerate a mental/physical illness or healing response. The BPS model illustrates this circularity in the form of mutual interactions of different organizational levels. For example, a change in the personal level (experience and behavior) leads to changes in the subpersonal (molecular, cellular and vital systems) and also the suprapersonal levels (two-person, family, community, etc.). This model therefore shows interchangeability and merging of hard reality and soft reality, but what about translatability of these two worlds? How can we follow the energy-information flow through the levels of organization? And how should we manage the semiotic and mechanical consequences of each health event?

In any case, the BPS model is an appropriate theoretical framework for the enrichment of patient-doctor communication, elaboration of clinical reasoning, and also interdisciplinary research and development. Yet as an explanatory model, it has certain shortcomings and ambiguities, especially in exploring the mutual translation of the mental and the physical. The emergency principle of the BPS model is a good departure from the reductionism of biomedicine and its limitations but the embodiment principle of BPS model could not appropriately overcome the mind–body dichotomy (Schwartz 1982). According to the embodiment theory, mental procedures are embodied as neural processes (MacKay 1978). This means that mental activities are nothing but brain function, but it could not explain how a symbolic agent such as "this is a pill for pain relief" can control the neuroimmunologic responses (Sperry 1980). In fact this theory is not able to explain how signs flow through the human systems in the forms of molecules, cells, bioenergetic pulsations, sounds, writings, icons, and intentions, nor how these heterogeneous signs are transformed and translated to each other. For instance, pressure – point massage, NSAID pills, hypnotic suggestions, sugar pills, behavioral change, healing touch, mindfulness trainings, and corticosteroid injections can control or even treat inflammatory arthritis, but each one initiates the healing response from one level of organization with different sorts of signs and materials; energetic, informational and mindful.

We were unable to verifiably find a type–type identity between the mental and physical phenomena, and as one can see, a diversity of anisotropic, semiotic, and mechanical agents achieves an anti-inflammatory response in a joint. According to the American philosopher Donald Davidson (1970, 1994), there is no psychophysical law, and there are only token mental events which are identical to token physical events. From this viewpoint, it is not possible to produce a generalized map for all mind–body interactions in a case of a disorder because of anomalous monism in the mental and physical phenomena (Davidson 1970, 1994).

In addition to a bigger picture of human systems, which BPS has outlined, we need a common language to be able to translate signs of various levels of organization to each other; a systemic language which can illustrate microvessels of the psychophysical body, indeed in the unique, dynamic, and chaotic clinical contexts. Some of the BPS reformers such as Aviel Goodman have identified these pitfalls of the BPS model and tried to make light of them.

Goodman (1991), in the organic unity theory, tried to merge mental–physical identity and BPS theories to establish an integrative model which resolves the problem of translatability. This theory presents a satisfying solution for the problem, but relies on an abstract concept; "the pure psychophysical event," which is the unique reference of both the physical and mental phenomena. From this view, physical and mental events are originally psychophysical events which are described in mental and physical terms. The pure psychophysical event is a good assumption, but the parsimony principle necessitates lesser assumptions, of course if it were possible.

According to Thure von Uexküll and a great many pioneers of psychosomatic medicine, biosemiotics can play such a mediating role between the systems (Meyer 1984). They believe that the emerging discipline of biosemiotics is able to cast new

light on the meaning and nature of biological survival and also properly translate the mind–matter interactions away from common-sense mind–body dichotomy. Could this be what we are looking for in a BPS model; a concrete psychophysical reference which can be expressed in the terms of the mental or the physical?

1.6 Biosemiotics and the Biopsychosocial Model

The German medical doctor and philosopher Thure von Uexküll was the son of eminent biologist and philosopher Jakob von Uexküll and, in fact, throughout his professional life, he tried to develop and apply his father's ideas in medicine (Kull and Hoffmeyer 2005). Jakob von Uexküll was a biologist who conducted numerous studies on the interaction of animals with their environments, the result of which was a theory that explains the development of the subjective internal world of an organism by the interaction with its environment. In this theory, his goal was to explain how an organism, based on its instinctual needs and biological structures, gives meaning to the perceptual cues from the world around it and acts according to this meaning. This action is the basis for the meaning that has been assigned to that entity, and this cycle occurs again and again, ultimately solidifying its meaning. This theory was called Umwelt, the German word for "environment" (Deely 2004; Rafieian 2010). Jakob von Uexküll did not use the terminology of semiotics in this model, but what he described as perceptual cues is practically the same as the signs in the semiotic framework. He was, because of this, called a cryptosemiotician by other semioticians like John Deely (1990, 2004). Among other efforts, like the development of the philosophical school of biosemiotics, Thure von Uexküll introduced the foundations of psychosomatic medicine in Germany. To provide a better theoretical framework, he tried to merge the principles of the biopsychosocial model and biosemiotics. As mentioned, the problem with the biopsychosocial model was that when one goes from the micro levels to the macro levels, it is not entirely evident how these different levels are connected. Uexküll believes that semiosis is the translator of the events from one level to another (Uexküll and Pauli 1986; Rafieian 2012). Semiosis is the milestone of life and life is actually defined by semiosis. To fully understand this idea about the process of translation, consider the following example: Imagine a situation in which a shouting person raises the heart rate of the other. In this situation, the shout is perceived as a sign and interpreted in his or her mind as a result of connections in the brain to memories and other signs coming from the context of the environment. Impulses are then sent to the heart and neurotransmitters are released from the nerve endings releasing hormones into the blood stream. The neurotransmitters and hormones attach to the receptors on the cells and convey a message. In today's biology, it has been shown that the metaphor of a key and lock is not an appropriate model for the way that hormones act at the level of receptors. Hormones are proteins with complex three-dimensional structures and the way they attach to the receptors and the affinity of the molecule for the receptor depends on the context in which this attachment occurs (Sivik and

Schoenfeld 2006). The message conveyed and the ultimate effect on the cell is then dependent on this context of attachment. Here again, the hormone acts as a sign which is interpreted by the cell resulting in a change inside the cell.

Uexküll with the help of Thomas Sebeok defined the Biosemiotic School in philosophy of biology. In this school, the ideas of the American philosopher Charles Sanders Peirce were used to provide a new framework for the biology. I n the biosemiotic perspective, all living organisms are living in a semiosphere and sign interpretation is present wherever life is present (Sebeok 2001). In addition, Peirce tried to categorize the signs and created detailed classification of signs, in which three main categories can be determined: indexes, icons and symbols (Colapietro and Olshewsky 1996).

Index is a sign that has an actual connection with the object. For example, when we see smoke we become aware of the presence of fire. Or in medicine, the pulse and its connection with the heart function is an indexical relationship. Icons are pictorial signs. The icon has a resemblance or likeness with the object. Any portrait of a person is an iconic sign of that person. In medicine, an X-ray radiography of an organ could be considered as the iconic sign of that organ. The third group of signs is symbols. Symbols are the signs that have an arbitrary connection with the object. For example, any word is a symbol of what it refers to in the real word. There is no real connection with the word "water" and the water that is present in the tap. There is only a convention that makes the connection with the word water and the real water in nature.

In biomedicine, every doctor is thoroughly familiar with the use of indexes and icons. Taking the pulse auscultation and percussion are all examples of the use of indexical signs of objects inside the body and cannot be directly visualized. With the advance of technology in medicine, many indexical items have been replaced by new iconic signs. Doctors today depend on echocardiography signs of a cardiac valve stricture or insufficiency for a diagnosis instead of merely confining themselves to findings in an auscultation. Similarly, new methods of imaging like the CT scan and the MRI give new information via the iconic signs they provide. In the case of symbols, doctors use symbolic words of language to provide information about the signs and symptoms in the process of history taking (Nessa 1996). But because in biomedicine, the focus is on the biologic and physiologic levels, the use of language and communication is limited to the process of gathering information related to the biological and physiological functions of the organ in which the pathology has been developed. Humans are the only animals that have the ability to use symbolic signs as means for assigning a new meaning to an entity in the physical world. This ability to create new meanings and the power of semiosis as the translator of events between the levels of hierarchy of existence provide a great therapeutic tool, freedom of action, and creativity in clinical context. As mentioned, Balint has noted that in clinical practice, the doctor himself or herself could be as effective as a drug and many physicians in their daily practice have indeed experienced this occurrence (Balint 1957). To be as effective as a drug, a good rapport with the patient is needed; communication here is a semiotic enterprise. The tone of the voice, facial expressions, and gestures could all be meaningful and could have a placebo or nocebo

effect. In fact, here is the point of intersection between placebo research and research in the doctor–patient relationship as different types of meaning effect. It is the semiotic analysis of this relationship that makes non-specifics specific and provides the doctor with the power of healing in the very context of clinical encounters.

As one can infer from the above discussion, the framework thinking about key concepts in health such as health and disease, and, healing and person are very important. And in order to change the way in which medicine is practiced, these concepts need to be revised. As philosopher of science Ludwig Fleck stated, it is the thinking style of the scientists in a field that defines the rules and structures of that field (as cited in Cohen and Schnelle 1986; Zajicek 1995) and in a similar manner, Thomas Kuhn (1992) speaks about the concept of paradigms and the fact that a scientific discipline is developed based on a group of axioms. The paradigm of that discipline then emerges by the activities of the scientists in that field. The paradigm remains stable only until the time in which the number of unexplainable anomalies remains unsubstantial. After that, a paradigm shift occurs (Anderson and Funnell 2005). As discussed, the results of research on placebos and related fields show that there is a need for a more comprehensive perspective in medicine. Engel found the systemic view useful because it provides the possibility for the thinker to cover a wide range of aspects of the person but as mentioned, the need presents itself for the different levels to be connected. As previously stated, Uexküll incorporated semiotics into Engel's systemic model and developed it further but there were other new ideas emerging parallel to it in the twentieth century that could expand our understanding, making the model more comprehensive. Søren Brier tried to incorporate these concepts in the Cybersemiotics model and develop a non-reductionistic model of consciousness, cognition, communication, and meaning that has been applied in medicine (Brier 1999a, b, 2008, 2010; Rafieian 2010). Here we will briefly outline the model and its application to medicine.

1.7 Cybersemiotic Medicine

As discussed, the main deficiency of the biomedical approach in modern medicine which results in avoidance of researchers and clinicians from dealing with placebo responses and its mechanisms is that a placebo response and its mechanisms are mediated by patients' feelings, beliefs, and emotions. In other words, because patients' phenomenological and first person experiences are important in exploring the placebo response, biomedicine's dualistic and reductionist approach to the mind–body relationship and its framework cannot define a research project for exploration of this issue. In fact as Brier (2010) explains, this ignorance of the first-person experience and the consciousness of an embodied person can also be seen in other fields of the natural and social sciences and humanities in today's world. Cybersemiotics is an effort to incorporate this phenomenological experience in a theory of cognition, knowledge, and understanding.

The two pillars of the Cybersemiotic model are cybernetics and Peircian (bio)semiotics. Until now, we have discussed biosemiotics and its function for systemic thinking. Cybernetics is derived from a Greek word that means "the art of steering". Cybernetics was originally developed by the mathematician Norbert Wiener as the science of control of animals and machines (Masani 1990). His aim was to develop a science for prediction and control of complex systems. The main concept of cybernetics is a feedback mechanism that helps the system to self-regulate. Shortly after its development, researchers from different disciplines grew interested in it because it was able to explain the mechanisms of system control in different disciplines from micro to macro levels (François 1999).

An important thinker, Gregory Bateson (1972), made further developments. He was an interdisciplinary researcher with contributions in different fields from anthropology and linguistics to psychiatry. After the emergence of cybernetics, he became fascinated in its ideas, and in collaboration with others from other disciplines developed the second-order cybernetics. In cybernetics, there is an observer who studies the behavior of systems. In second-order cybernetics, it is the very observer that is considered as the system under study. In other words, here the observer is observed.

In his career, Bateson (1979) was searching for the "patterns that connect". Cybernetic rules were one kind of these connecting patterns (like semiosis as discussed above). He also has been considered as one of the pioneers of biosemiotics, as his research about communication and information has been influential in different field s. For example, his double bind theory for the development of schizophrenia was based on his understandings about different levels of communication. His achievements in this era led to the development of family therapy as a method of psychotherapy.

From a medical perspective, cybernetics concepts are familiar for doctors. Any medical student is familiar with the feedback mechanisms that control different physiological functions in the body, like the level of electrolytes and hormones and coordination of the muscles. But again, like the territory of signs, the territory of feedback loops is not confined to the body. The interactions of the people in the interpersonal space and family, groups and organizations are also regulated by circular recursive feedback loops.

Cybernetics, like biosemiotics, then provides the patterns observed by Bateson that connect different levels of the hierarchy of existence of human organization. The other aspect that has influenced thinking about the way we gain knowledge in the world was new achievements in modern physics. The philosophical consequences of quantum mechanics teach us that we cannot separate the observer from the observed. The knower is connected to any topic to be known in the world and any boundary between the subject and object is arbitrary. Bateson and other pioneers of second- order cybernetics like Heinz von Foerster explored this view (Pörksen 2003). To put it in a medical context, the relationship of the observer and the act of observing can be applied to the therapist-patient relationship in the clinical encounter. Placing any border between these two here is also arbitrary. There are ongoing feedback loops present that regulate the encounter; and the feelings,

emotions, beliefs and intentions of both are influential in the outcome of the process. Biomedicine does not provide such a view. Instead the general picture is a patient, a broken machine to be repaired and the doctor, the person who knows what is wrong and tries to repair it by prescribing drugs or manipulating surgically.

Applying these views is the aim of Cybersemiotic medicine (Rafieian 2010); a framework in which different disciplines dealing with mankind, from physiology and anatomy to psychology and sociology, are equally important and relevant. The so-called "soft data" coming from the phenomenological experience of the patient exploring the psychosocial context of the emergence of the problem are as important as the "hard data" coming from physical examination, laboratory data, etc. The importance of the concept of information is well appreciated in the modern world, with different theories about the nature of the information. As Brier explains (2008), materialistic views of information consider it as a real entity in the world which is transferred from one place to the other. In contrast, the semiotic view of information takes an interpretative view and considers the semiosis as a translator of the message coming from one level to the other. He also considers the point that the materialistic view of information is more applicable in micro levels of physical and chemical interactions. Considering the example of a neurotransmitter or a hormone as a sign, the interpretation of the message is a semiotic process although the interaction between the ligand and receptor happens in the material world. In macro levels of interpersonal and social interactions, the semiotic view is more prominent although these interactions are ultimately based on the processes occurring at the molecular level.

Last but not least is the concept of culture-specific disorders, which are the health problems specific to a certain culture. Culture is developed in a network of semiotic interactions and sometimes health problems emerge out of that which is meaningful only in that context. These problems cannot then be generalized with those of other cultures. These health issues also could be explored in a cybersemiotic framework, as there are other issues such as medical ethics, health semiotics, and lifestyle modification that could be dealt with in this context (Rafieian 2010). These however remain open for more exploration and further research.

1.8 Applying the Biosemiotic Perspective: Towards an Integrative Medicine

The signs of dissatisfaction of the modern mainstream medicine have become evident in recent decades both in the public sphere and among health care professionals. Doctors who have been trained in modern conventional medicine are irritated by the rigid framework of biomedicine and are interested in alternatives. In a reactive manner to preserve its authority, the current paradigm has developed the new movement called Evidence Based Medicine (EBM). As Roberti di Sarsina and Iseppato (2011) explain, the pillars of this movement have been defined as: "1) medical

knowledge and clinical skill, 2) (scientific) evidence through clinical investigations, and 3) patient preferences" (p. 5). But these aspects contradict themselves because the evidence that has come from biomedical research could not take the patients' preferences into consideration. Practically, patients' preferences are based on their beliefs, thoughts, and desire, and therefore cannot be categorized by the available methods of scientific research.

On the other hand, overemphasis on the anatomical and physiological aspects of human beings resulted in the focus of research and intervention production in these levels, and every day medicine is becoming increasingly drug and technology-based (Webster 2002; Conrad and Leiter 2004). The commercial benefits of the companies that produce these drugs and technologies have resulted in support of this trend and the development of a concept called medicalization. With medicalization, the medical system tries to define ordinary personal and social problems like shyness or baldness as medical problems and, instead of solving these problems in the context of life or simply accepting them as normal occurrences, tries to invent new drugs, technologies, or interventions to manipulate them (Conrad 2008; Rafieian 2010). As a result, the health care system is more and more becoming disease-centered with increased emphasis on new terms for new pathologies and developing new specialties instead of being saloutogenic, exploring prevention, and considering the person as a whole.

In fact, ordinary people noticed before professionals that there is something wrong with this approach. Re -emergence of pluralism in medicine and the interests of people in complementary alternative medicine (CAM) show that they do not trust the mainstream medicine as they did before. Studies have shown that roughly half of the population in industrialized countries and as high as eighty percent in developing countries use CAM (Bodeker and Kronenberg 2002). There are some alternative methods like acupuncture, the efficacy of which has been corroborated by the research methodology of biomedicine, but the rigidity of this paradigm does not allow them to be incorporated into the main body of health care systems and they have generally a marginal place and are applied as adjuvant methods. Accordingly, there is a need for innovation in designing research in this field (Pritzker and Hui 2012).

The reason behind these deficiencies is that medicine has applied a framework which has a much too narrow perspective and is unable to explain the seemingly anomalous phenomena like placebo responses and so-called alternative methods of treatment like energy medicine (Foss 1994). Because of the narrowness of this view, even when medical professionals try to search for the mechanisms underlying these phenomena or assess the validity of these methods, problems arise because of the paucity of available methodologies.

As discussed, biosemiotics provides a broader view that enables us to explain phenomena like placebo and to think creatively about healing and health in the semiosphere. The aim of this book is to explore different aspects of the placebo response from this perspective. The explosive rise in the research about placebo in different fields from philosophy and psychology to psychoneuroimmunology and neuroscience provides us with the raw material that could be incorporated in the framework of biosemiotics.

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