

Historical-Clinical Pathways to a Cancer Holistic Perspective

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Abstract

A historical reconstruction of the holistic approach to cancer is presented. A particular attention is given to the United States, since, after reductionism had prevailed in Western world, New York Jungian psychoanalyst Elida Evans published the first modern monograph about the psychology of cancer patients in 1926, proposing a holistic view of cancer again. Evans' theory has largely influenced cancer psychosomatics. Without pretension of completeness, research on cancer is discussed in its epidemiological, social, environmental, behavioural, and psychoanalytical aspects. The results of psychoneuroimmunology and the discoveries of developmental psychobiology are highlighted for their importance in a holistic vision of cancer. Assumption of this paper is that persistent dualism - studying body or mind - is depriving research of fundamental variables involved in human cancer; therefore, integrated multidisciplinary investigation is advocated.

Keywords: Cancer Psychosomatics; Carcinogenesis; Elida Evans; Holistic Medicine; Psychoneuroimmunology; Psycho-Oncology; Type C Behavior.

Introduction

The wholeness of patients was questioned soon in Western medicine, since the division between body and soul carried out by the philosophy of Plato, where soul is the essence of man and his body is only matter. In the 17th century, Descartes replaced Platonic-Christian dualism with *res cogitans* and *res extensa*. From then on, mind-body dualism has been the philosophical reference of medicine, that has developed from anatomical dissection to physico-chemical reductionism, started in 1847 Germany. Osler followed this German trend and his line brought American academic medicine to become an experimental science, on reductionist and exclusively biological positions [1].

The word *Ganzheit* (wholeness, totality) appeared in the German language only in the twentieth century, for the need to define a conceptual counterpart to "specialization" [2]. The concept of holism was introduced by Smuts, in 1926, as a dynamic and synthetic principle linked to the evolutionary process [3]. Regarding cancer, we find holistic observations until the 18th and 19th century, beginning from Galen's theory of a pre disposition to cancer of melancholic women. Some 1800 physicians reported life situations and particular emotions in future cancer patients: the loss or separation of a significant person, but also the frustration of life goals, involved a reaction of despair and hopelessness - negative emotions that were considered "the precursor of the neoplastic state" [4]. In 1844, Walsche's most authoritative cancer treaty of the 19th century included social conditions, temperament and mental affliction among the predisposing causes to cancer [5].

Attention to patients' psychosocial aspects was lost with the rise of reductionist medicine and the successes of cell biology. Further, promising therapeutic results of surgery and radiation contributed to regard cancer as a localized disease: thus, "the neoplasm was more and more considered as a problem of a specific body area, not of the body as a whole" [6].

The Beginning of American Psychosomatics

In the United States, medicine has remained predominantly dualistic and reductionist, intensifying experimental methodologies with increasingly sophisticated technologies [7]. On the side of mind, the turning point for "the somatic style" came from France. William James' Boston School of Psychopathology [8] formed a *Charcot's Axis* (1882-1920) [9] with French, British, and Swiss scholars. Among the latter, Carl Gustav Jung, clinical director in the Burghölzli Psychiatric Hospital of Zurich University, had become famous in America before coming into contact with psychoanalysis [10] because of the results of his experimental researches [11]. In 1909, with Freud and Ferenczi, Jung lectured at Clark University, where they met James, Hall and Putnam [8]. In 1911, the practice of a modified form of Jungian analysis began at the Massachusetts General Hospital in Boston [12]. In 1912, Jung was invited by Smith Ely Jelliffe to lecture at the medical school of Fordham University (they had met in 1907) [13].

Jelliffe was a New York neurologist and Professor, one of the first American psychoanalysts; he is considered the father of American psychosomatics [14] and maintained an exchange of letters with both Freud and Jung, even after their detachment [15]. Regarding the mind-body problem, Jelliffe was a monist as was Adolf Meyer, Professor at Johns Hopkins and the most important American psychiatrist in those years. Meyer - with a term already used by Bernheim in France - defined his holistic conception *psychobiology* and saw the individual as "a psychobiological whole" [16]. Accordingly, Adolf Meyer tried to convince physicians that they should consider both biologic and psychologic influences on illness. He constructed a chart to record the major life events. He included the calendar years of the patient's life-span, important life events, the patient's emotional reactions to those events, and illness experiences through the patient's lifetime [17].

Jelliffe was a convinced representative of the American psychobiological tradition and an innovator who criticized that no psychological methods were added to cancer research [18]. His being an advocate of holistic medicine made him feel very close to Groddeck and Jung, how one can understand from Jelliffe's letters to them [15].

Actually, Groddeck and Jung (though without having contact with each other) had a very similar conception of totality of man, expressed by their most important notion - Groddeck's *Es* (It) and Jung's *Selbst* (Self) - with a clinical relevance both for psychopathology and for organic diseases.

Groddeck and Jung shared a holistic vision, but also monism and finalism - so with a position opposite of Freud, who was dualist and causalist, and extraneous to the concept of totality [19].

Evans' Theory about Cancer

Considered Jelliffe's openness of mind, it is not surprising that, in 1915, Elida Evans - a lay analyst trained at the "Zurich School" - asked Jelliffe to work with him. Evans became Jelliffe's assistant, then a collaborator: they did research and wrote together two psychosomatic papers, on chronic skin disease [20] and pulmonary tuberculosis [21].

In 1926, Evans published *A Psychological Study of Cancer*, the first modern work with a psychosomatic approach to tumours, based on around one hundred clinical cases [22-23]. Evans interpreted the psychology of cancer patients in the light of Jung's *Psychological Types* [24], published in 1921. Evans knew she was going against the current to study cancer from a psychological point of view, because she was perfectly aware that the "medical profession has been rather reluctant to search for other than physical causes" [22].

Evans collected the detailed personal data of each cancer patient, adding "the emotional history of the individual" [22] to the classic clinical anamnesis, modifying Meyer's aforementioned methodology by a psychoanalytic approach that emphasized the patient's inner experiences. For each patient, Evans gathered carefully a clinical history and a biographical history: *two histories* which have become a model in cancer research, followed by authors like LeShan [25,26] and Chiozza [27]. Evans related to the patient as a psychophysical totality and dwelt on the fact that cancer is mainly a disease of the second part of life - which is of particular importance in Jung's theory of individuation.

Evans connected carcinogenesis to the destructive aspects of the collective unconscious, a very deep psychosomatic level of phylogenetic origin where psychic contents blend with instincts. The collective unconscious is genetically inherited with the brain and is a biological entity that affects both body and mind, physiology and ideas: in 1936, Jung defined its archetypal elements "patterns of instinctual behaviour" [28]. The biological insights of Hediger [29] and Portmann [30] found similar nervous structures in animals for species-specific actions; moreover, ethologist Lorenz [31] studied the open programme of behavioural mechanisms that are phylogenetically inherited, introducing the concepts of innate releasing mechanism and scheme. More recently, the collective unconscious was approached to ethology and Mayr's *open program* [32] by Stevens, who described the archetypes as "phylogenetically acquired, genome-bound units of information which programme the individual to behave in certain specific ways while permitting such behaviour to be adapted appropriately to environmental circumstances" [33].

Obviously, Evans' understanding of the collective unconscious did not include the knowledge of DNA but it was based on Jung's evolutionist approach. For carcinogenesis,

she suggested a regressive energy process to collective unconscious because of traumatic events in individuals who are marked by social conformity for the need to maintain their relationships, relinquishing any form of personal creativity. Evans claimed these patients had an extrovert one-sidedness, a completely turned outward attitude that prevents other psychological adaptations, included those towards internal stimuli. This kind of person does not show negative emotions and instead "gentleness and mildness, the lack of self-assertion" [22], showing an anaclitic behaviour [23]. Consequently, the ego is rigid and fragile, unable to cope with the manifold demands of life. The loss of the object of external dependence, hence, becomes a dramatic fact which pushes the individual to despair - "a renunciation, a giving up of hope", "a total destruction of hope" [22] - until psychobiological collapse: a withdrawal from life without conflict that initiates an unconscious suicidal process.

Evans' "psychosocial approach to cancer" encountered strong resistance from medicine, whose reductionist model does not recognize "that life is based on mutual transactions between two or more living organisms, on field phenomena" [34]. For more than twenty-five years Evans' study had no continuation [35]. Therefore, when even the members of the American Psychosomatic Society did not show interest for cancer, George Engel decided to discuss "Neoplastic disease and psychological process" in the 1954 Society's Meeting. Engel noted that, although "our belief that all diseases are 'psychosomatic', in the sense psychological processes are always involved", this was not true for cancer, which had not publications in the Society's journal nor a concern for its emotional aspects [36]. Engel's position did not produce many results toward cancer psychosomatics in America, and the situation was not very different abroad [34].

In Germany, nevertheless, there has been a line of holistic medicine starting from Groddeck's [37] speculations (also about cancer) [38] to *Gestaltkreistheorie* [39] and beyond. Along this line, Kaelin and Suchantke [40] saw cancer as a disease of the whole organism and created the concept of "cancer psyche" between the 1930s and 1950s. Their results are very similar to Evans' observations and to cancer studies before the twentieth century.

Research at the University of Rochester and Psychoneuroimmunology

Psychoanalysis "was the only dynamic language of inner experience allowed entry into the ultra positivistic scientific era" of 20th century United States [9,41]. Engel was a Freudian psychoanalyst at Rochester school of medicine, who created a holistic theory to overcome an exclusively biologic and mechanistic vision [42]. He began to develop his *biopsychosocial model* in the 1950s [43], realizing that the prevailing biomedical model - reductionistic, physicalistic and dualistic - needed to be supplemented by psychological, environmental and social factors to better understand and restore the patient's health.

Engel's approach to "the psychobiological unity of man" concerned medicine in general [44], and saw every disease as conditioned by psychosocial factors [45], including cancer but also mental diseases [46]. He expanded the role of depressive emotions: the affective states of helplessness and hopelessness became part of a non-specific condition called "giving up-given up complex", seen as a contributing factor to the emergence or aggravation of diseases [47]. This complex occurs when the mind is unable to cope and the "conservation-withdrawal" biological pattern come into operation through the parasympathetic nervous system, altering body homeostasis with anabolic processes and so facilitating disease to develop [48]. Therefore, Engel suggested a second innate reaction pattern, in addition to "fight or flight" [49] (caused by anxiety and anger), which instead activates the sympathetic system with catabolic processes.

Engel's team predicted cancer in biologically predisposed women on the criteria of hopelessness prone personality or recent feelings of hopelessness [50,51]. However, non-specificity of the giving up-given up complex left unresolved the reason for the onset of cancer instead of another disease. Nevertheless, Engel's biopsychosocial model constituted the theoretical framework [52] for *psychoneuroimmunology* (PNI), a holistic discipline started in 1975 [53] - that is also the year of the formal beginning of American psycho-oncology [54].

In 1981, Robert Ader - he too at Rochester - edited the first results of PNI research on the interactions between psychosocial factors and the nervous, endocrine, and immune systems, providing evidence of continuous information exchange among these systems through neurotransmitters, peptides and hormones [55]. A large body of research documented the presence of neuropeptides and their receptors throughout the body, with "nodal points" in the CNS: the limbic system, the dorsal horn of the spinal cord and the peri aqueductal gray region of the brain stem; but also in the entire gastrointestinal tract, glands and mobile cells of the immune system - thus configuring an extended physiological basis of emotions [56]. It was also discovered that the immune system can produce neuroendocrine peptide hormones and nerve cells produce immune-associated cytokines, proving the total integration of the immune and neuroendocrine systems which control each other in a bidirectional regulatory circuit [57,58]. The holistic concept of a *unified psychosomatic network* on the basis of PNI has therefore been affirmed [59]. Besides, studies have been performed to show psychological or behavioural influences on immune system, contributing to cancer incidence or progression through alterations of NK cell activity and in DNA repair [60,61].

Interestingly, *psychoimmunology* is a term used by Solomon since the early 1960s (about twenty years before Engel and Ader) at Stanford University [62,63]. U.S. Department of Health officially admitted immunotherapy as a cancer cure from 1992 and published the results of research on neuro-endocrine-immune-behaviour interactions [64]. In 1994, a book about the psychoimmunology of cancer was published and its 2002 second edition [65] provided a growing

supportive evidence of the biologic mechanisms underlying the relationship between psychological factors and the immune system in cancer onset and progression.

Psychoanalytical and Behavioural Research on Cancer

In 1953, a symposium was held about psychological variables in cancer: the role of emotional factors on organic defences was discussed and Cutler expressed the idea of cancer "as a form of passive suicide" [66]. Later, there were three international conferences – 1963 conference in Cambridge, England [67]; 1965 and 1968 conferences in New York [68,69] - where important contributions were made. Lawrence LeShan, Claus Bahnson and Marjorie Brooks Bahnson intervened at all three conferences.

LeShan - a New York clinical psychologist - is considered a founder of American psycho-oncology, on which he has worked since the 1950s also studying the historical precedents of the subject [6,70]. We can see LeShan as the prosecutor of Evans' work on cancer; in fact, he cited her book and also referred to Jung's ideas. From his psychotherapeutic sessions, LeShan [71] learned that cancer patients have had a weak "will to live" even before becoming ill. He attributed this deficiency to an excess of adaptation: future patients live "other-directed", namely they are more concerned of others' opinions rather than the needs of their own self. Thus, LeShan resumed Evans' line and linked cancer to the neglect of that "inner development" which is Jungian individuation. LeShan followed Evans also regarding future cancer patients' loss of one intense emotional involvement (situation or relationship) as a crucial moment of existential crisis that deprives them of life's meaningfulness [26]. This is the theoretical basis of LeShan's psychotherapeutic techniques (*crisis therapy*), addressed to increase the will to live in cancer patients but also as a preventive method "to help those persons whose personality patterns and life history might make them especially vulnerable to cancer" [26]. Actually, LeShan's research led him to hypothesize an emotional life-history pattern associated with neoplastic disease [72], a vision very similar to that of Evans; but LeShan, unlike Evans, has backdated the presence of feelings of isolation and despair since patients' childhood, a position that makes him close to Baltrusch [73,74] and is confirmed by further research [75].

Bahnson and Bahnson criticized the delay of medicine for a holistic view of disease [76] and suggested a monistic approach [77] such as Grinker's [78,79]. The Bahnsons introduced a *global psychobiological approach* which admitted neither physiological reductionism nor psychologism. Accordingly, they rejected Cartesian dualism, looking at physiological and psychological phenomena as complementary representations and developing "a social-psychological-somatic theory [...] encompassing both behavioral and somatic processes within one framework" [80].

The Bahnsons interpreted the depressive behaviour in future cancer patients as a "syndrome of barrenness" due to strong and persistent defences of repression and denial in

individuals with psychological aspects of extroversion and lack of inner resources. These persons' childhood is characterized by dependency and they become rigid and constricted adults with an impersonal reality orientation. To the Bahnsons, future cancer patients develop two selves completely distinct and strangers to each other: "The conscious self is socially adequate, but empty and meaningless. The unconscious self is explosive, tragic, and tormented" [81]. The Bahnsons assumed that cancer patients make use of projective defences less than normal individuals do and see their environment too positively due to a strong repression [82,83]. The Bahnsons referred to psychoanalytical ego-psychology for their *model of psychophysiological complementarity*, which is holistic: each disease is seen as the mere manifestation of "a total psychobiological process" with *isomorphism* between psychological and biological processes.

Starting from the 1950s, American Internal Medicine "moved in a biochemical and generally reductionist direction, separated itself from organismic physiology, and disconnected from psychiatry." Thereby, even the diseases once considered "classical" psychosomatic were treated in a reductionist way, until the "molecular revolution" arrived in the 1970s [1]. A "neo-somatic style" imposed itself and the psychoanalytic model in psychosomatic medicine was questioned as a clinical methodology often without scientifically verifiable procedures [84].

Also the notion of psychosomatic cancer was criticized, so research and clinical practice shifted from the etiological role of emotions to the emotional consequences of being sick and anti cancer therapies, with the aim of improving patients' lives. The new sub specialty of psycho-oncology developed instruments to study subjective symptoms of pain, anxiety, nausea, depression, delirium. Moreover, consultation-liaison psychiatry spread, exploring comorbid mental disorders for their treatment [54].

Placing psychoanalysis in the background, "clinical-anamnestic methods" were abandoned for the benefit of laboratory and psychometric testing [1]. Along with psychoanalysis, interest in the inner experience was put aside. Thus, social aspects predisposing to diseases were studied and patterns of behaviour were sought, bringing in the 1970s a renewed impetus on the psychosocial aspects of cancer with Behavioral Medicine, based on the biopsychosocial model [85]. And with a behavioral approach a *Type A* behaviour was discovered in competitive, tense, anxious, hostile, self-centred people, who were predisposed to cardiovascular diseases. *Type B* was instead called the behaviour of uncompetitive and relaxed individuals who were not prone to heart problems [86].

Lydia Temoshok - a psycho-oncologist in Behavioral Medicine - had long studied melanoma patients [87] when she began a research on cardiovascular patients (*Type A*) realizing that their behaviours were the opposite of each other [88]. Therefore, she worked to define the characteristics of a specific pattern of behaviour for cancer patients [89] and called it *Type C* [90]. In the same years, this pattern was

developed independently by London psychiatrist Steven Greer [91,92]. Interestingly, the evolutionary approach to social behaviour has provided a possible explanation for selfish assertiveness and altruistic cooperation - referable to Type A and Type C - as selected forms of adaptation to the environment in individuals defined respectively proselves and prosocials [93].

Temoshok explained that Type C is not a personality but a behaviour pattern, a coping style: contrary to Type A, this behaviour is cooperative, appeasing, self-sacrificing, unassertive and free of negative feelings. It is a product of adaptation started in childhood, a condition devoid of depressive symptoms but characterized by "non expression of emotions", that may be more or less rigid. To Temoshok [90], a total control over emotions leads to not knowing one's needs and to induce an unconscious suffering, until a "sort of quiet desperation - a form of hopelessness - [which] has been shown to damage the immune system". She called it a "hidden hopelessness" and claimed that a life long Type C behaviour "can cause a generalized deficiency in the cancer defense system."

According to Temoshok, there is not a causal relationship between Type C and cancer, but this behaviour is a "risk factor" that can play a more or less significant role within the theoretical contest of Engel's biopsychosocial model. Her research was conducted with a rigorous methodology, finding evidence that non expression of emotions is the toxic core of Type C [90], associated to reduction of lymphocytes and faster cell multiplication in the tumour site. It has been proved that "Type C coping - non-expression of emotions, stoicism, and a passive coping style - is a risk factor for disease progression or less favorable survival outcomes among cancer patients" [94].

Temoshok's theory is composed by the results of previous studies combined with her findings: features of Temoshok's behaviour pattern can be traced back to the traits identified by Evans. Temoshok did not cite Evans, who is however present in a historical article by LeShan [6] quoted in Temoshok's book [90], but Evans' priority in several aspects of Temoshok's theory is evident. Moreover, referring to the work of LeShan and the Simontons, Temoshok indirectly adopted Jungian concepts such as "inner guide" [95] (the Self) [96], "guided imagery" (active imagination) [97], and "creative expression." Evans, following the Jungian notion of instinctive creativity, described cancer as a pathological manifestation of "creative urge" to be balanced [22]. In 1936, at Harvard University, Jung would state: "Creation is as much destruction as construction" [98].

Social Factors

Since Evans' book, an interpersonal dimension - alien to the biomedical model - has been introduced in modern cancer research. A sociological expression was used for cancer patients [90]: they live "other-directed" by social norms or the central people in their lives. However, Riesman [99] considered the other-directed type to be a character of contemporary

Western humanity, and of Americans in particular: this widespread dependence is progressively internalized since childhood, leading to "an exceptional sensitivity to the actions and wishes of others" and to "a close behavioral conformity". This existential attitude proposed by Riesman corresponds to what Evans called one-sided extroversion. Evans herself had highlighted the increasing risks to move away from a natural life and called cancer "a disease of civilization", followed by others claiming that cancer is "a symptom of a losing existential encounter between the world and a person predominantly identified with the spirit of the industrial age" [34] and that "cancer goes together with mass society" [100].

This social vision of cancer must be included in the more general criticism of contemporary Western lifestyle, what Jung [101] did with an evolutionary approach. Suchlike remarks also came from Neumann [102], Lorenz [103], and Stevens [33]; while Fromm [104] described automaton conformity as the most important mechanism of escape for normal people in modern society. To Fromm, *automaton conformity* can be assimilated to animal mimicry, a form of extreme social adaptation that makes an individual identical to others for eliminating anxiety, at the price of depriving him of his original self. Fromm's pseudoself corresponds to the Jungian concept of *pseudoego*, a rigid and fragile ego where only an external orientation is possible, so what happens inside (in the body, too) is not recorded [105]. Pseudoself and pseudoego are linked to overadaptation to the outside world, a status already called into question by Evans and later by Ammon for psychosomatic patients [106].

It is worth noting a convergence between psychological and sociological studies, which leads to a continuity between pathological inner experiences and adaptation mechanisms in industrial societies, so much to hypothesize that certain characteristics of contemporary society are carcinogenic.

Epidemiology

Cancer is more widespread in industrial societies than in rural areas, but this fact has not a single explanation. In the United States, the need to carry out a survey on lifestyle and environmental factors led to 1981 Doll and Peto's national study [107]. In their assessment of the known risks of cancer, Doll and Peto had expressed percentages that proved substantially similar in the reviews carried out 35 years later [108]: tobacco smoking is the most important avoidable cause with 30%. Doll and Peto had assumed between 10% and 70% the estimate related to diet and their average risk of 35% was questioned [109], bringing the percentage to 20% despite the correlations recently demonstrated for lack of physical activity and obesity, red meat intake, and *Helicobacter pylori* infection. This lower estimate was, however, criticized because it did not include the effects of early-life over nutrition - *in utero* and during growth - on adult cancer risk [110].

In 1982, a specific research program about the role of diet in carcinogenesis was indicated [111], highlighting two aspects: the abundant use of fat and meat in Western diets is correlated with colon and breast cancer [112]; migrants take

the cancer risks of the country where they go and eat, thus minimizing the role of genetics in carcinogenesis [113,114]. Therefore, it became important to investigate cancer incidence in different countries [115] and to compare the effect on health of a diet low in fat and high in vegetable, common in non-industrialized areas.

A member of 1982 Committee, T. Colin Campbell, became the project director of the China-Cornell-Oxford Project on nutrition, environment and health, a long research carried out through two surveys (1983 and 1989) in rural China [116]. The China Project's results [117] and further studies have led to evidence that correct dietary practices may reduce cancer risks [118], "diet does play an important role in the cause and prevention of cancers" [119] and "nutrition and life-style factors may be determinants of up to 80% of large bowel, breast and prostate cancer cases and of one third of all cancer cases" [120].

The data on the role of diet in carcinogenesis with greater convergence can be summarized as follows [121,122]: a modern Western nutrition - characterized by high intakes of meat, dairy products, sugar and refined carbohydrates, and by micronutrients deficiency - may be a major determinant of risk, especially associated to an excessive caloric value resulting in over-weight or obesity. The latter are the most important avoidable causes of cancer, after tobacco. In particular, high consumption of animal fats and preserved or red meat is strongly connected with colorectal cancer. Alcoholic beverages, salt preserved food, and some chemical substances are also considered important risk factors. In reverse, physical activity along with a high intake of fruit and vegetables (at least 400 g per day) besides dietary fibres and micronutrients (such as vitamins and trace minerals) are believed to decrease the risk of cancer.

These findings have been substantially confirmed to date by the 2007 WCRF/AICR review [123] and its 2018 updating [124], that interestingly passes from the identification of specific dietary factors in causing or protecting against cancer to a "more holistic focus on the determinants of resilience to external and endogenous challenge". From this new perspective, it is the metabolic state of *an integrated pattern of behaviours* (consisting of diet, physical activity, and many other variables) which determines the conditions that may lead to cancerous changes. Therefore, the 2018 WCRF/AICR's approach examines the individual "way of life" overall (and no longer just specific foods or nutrients), going in a holistic direction.

Environmental Influences on Health

In 1935, Jelliffe [18] defined *ecology* as the study of "adaptation of man as a whole to the whole of the cosmos" and proposed medicine to be a branch of ecology: to him, chemical, biological and psychological levels together can explain the whole individual. Jelliffe deemed the application of the ecological principle as the best approach for future medicine, in order to understand diseases in individuals who must continually adapt to their environment.

Jelliffe's extraordinary foresight is taking shape in the recent turn of immunology, which has added an ecological perspective to its classic defensive function. As regards the latter, the specific immune dysfunction in cancer was defined as an "underactive" immune system [125]. Further, a mutation theory of cancer has been formulated, in which the pathogenic mutation is caused by environmental carcinogens or viruses, but also by error proneness in replication and repair of DNA, especially in aging when a progressive reduction of the immune system efficiency occurs [126].

Taking the holistic approach of systems biology, ecological immunology [127] has expanded its investigation from individuals to their environment. Since the immune system receives and processes molecular information from both organism and environment, it has been assimilated to cognitive functions [128,129]. The immune system was, therefore, called *mobile brain* [130] and, for its integration with the psycho-neuro-endocrine system, forms an extremely complex cognitive system. Therefore, eco-immunology can also be included among environmental sciences [131].

Mother is the first environment in human life [132]. Her antibodies prime child's immune system since intrauterine life, so mother's immune experience conditions early immune development [129]. However, research has showed that relationships regulate other biological processes in early childhood. After Spitz's study on anaclitic depression [133,134], and Harlow [135,136] and Bowlby's [137] ethological research on maternal separation and loss, Hofer conceived animal and human attachment as a regulatory process "by which the mother serves as an external regulator of the infant's behavior, its physiological state, and even the neurochemistry of its maturing brain" [138]. Therefore, Hofer has hypothesized that effect of an early separation may be an emotional and physiological vulnerability to diseases in adulthood over the life span, caused by an altered course of development [139,140]. Actually, infant separation causes alterations in metabolism, sleep, and in cardiovascular physiology, but also reduced secretion of growth hormone and decreased T-cell activity [141-142]. Thus, Hofer argued that the normal mother-infant interaction contains *hidden biologic maternal regulators*, to be added to the more known psychological aspects. Field [143,144] claimed that a behavioural and biological dysregulation occurs both for the caregiver's physical or emotional unavailability: thus also hostility, rejection, neglect and abuse against the child [145] should be included among the causes of psychophysiological disorganization.

Moreover, Hofer [141] noted that the "infant responses to maternal separation closely resemble adult responses to bereavement" and that homeostatic regulatory systems remain under environmental influence in adulthood; accordingly, attachment relationships represent a strong environmental regulator throughout life, whose cessation causes a biobehavioural dysregulation. There is also supportive evidence that the death of a partner is associated with an alteration of endocrine and immune functions, and

greater vulnerability to diseases [146,147]. Schore has recently claimed that the most potent environmental events are "emotional transactions" [148].

The modern practice of "depersonalized nursing" was considered an important environmental factor accounting for the rise of cancer in industrial societies [34], and family emotional climate has been associated to cancer [149,150]. Further, an integration between attachment theory and Type C behaviour was proposed to examine relational processes in cancer [151].

Theoretical Discussion

In 1986, the PNI realization of a communications network through neuropeptides induced Pert to question dualism, because mind and body "are best understood as an integrated entity" [152]. Twenty years before, von Bertalanffy [153] had argued that the Cartesian dualism between matter and consciousness was no longer adequate to scientific knowledge, and the concept itself of the unconscious did not find a place in this dualism. von Bertalanffy was referring to an unconscious inside a brain-mind, instead it has become necessary to take into consideration a widespread somatic unconscious and cognitive functions extended to the immune and endocrine systems, so that a new configuration of the human organism emerges where is not possible to establish an actual boundary between mind and body.

Before current experimental confirmations, Jung had a monistic and holistic conception based on his clinical method and studies on medicine and psychology in Western and Eastern culture. Jungian *dual-aspect monism* developed with the collaboration between Jung and the Nobel laureate in physics Wolfgang Pauli. This version of monism is based on quantum theory [154] and its main notion is complementarity (introduced by William James into psychology in 1890 and imported into physics by Niels Bohr in 1927 [155]): mind and body are conceived as complementary aspects of a same reality: the totality of the individual. Jung hypothesized a specific interconnection between matter and psyche - acausal and meaningful - which he called *synchronicity* [156]: this principle is able to explain "the co-ordination of psychic and physical processes in a living organism" better than a cause-effect relationship [157]. The importance of psychobiological synchronicity for cancer was discussed by Booth [34].

In dual-aspect monism, the individual is considered a *psychophysically neutral domain* - neither mental nor material. The Bahnsons' aforementioned model presents similarities with Jung's conception, since it sees physiological and psychological phenomena as complementary representations of a process taking place "synchronously, not conceptualized within a Cartesian parallelism, but within a monistic and 'total' configuration" [77]. Moreover, their notion of interpersonal and intrapersonal functions is close to Jungian extraversion and introversion.

Having detected these theoretical affinities, Balenci [23,158] integrated the Bahnsons' model with Jungian

attitude-types into an *integrated model* of diseases, which connects one-sided introversion to the Bahnsons' psychological axis, and extroversive one-sidedness to their somatic axis. Balenci started from Evans' emphasis on one-sided extroversion as an energetic imbalance from psychophysical homeostasis and interprets cancer as a psychosis in the body, an isomorphic view shared with Goldberg [159].

Jungian attitude-types were checked by some scholars [160] and experimentally validated by Eysenck [161], inserting them in his psychometric scales that proved a higher extraversion score in cancer patients since the 1960s research of Kissen and Eysenck [162], Coppen and Metcalfe [163], and Hagnell [164]. Eysenck developed a research - first with Kissen and then with Grossarth-Maticcek [165] - on the connections between personality and cancer, predicting cause of death based on psychosocial data 14 years ahead [166].

In the literature on cancer, however, a much more debated concept is *stress*. Since Selye's description in 1936 [167,168], the general adaptation syndrome has been widely used to explain effects on immune function facilitating the onset of infections and diseases, including cancer. Actually, acute stress has salubrious adaptive effects, while, on the contrary, chronic stress can disturb or suppress immune function [169]. There is also evidence, both in animals and in humans, that stress at an early age (since the neonatal period) affects the baseline characteristics of the stressor-induced responsiveness of the brain [170,171]. Consequently, research has been undertaken to understand the effects of childhood trauma on behaviour and health in adulthood. The Adverse Childhood Experiences (ACE) study has provided an enormous amount of data proving the link between early stressful experiences and chronic diseases as adults, like depression, heart disease and cancer [172,173]. In particular, ACEs have been associated with the risk of lung cancer, depending on an increased smoking behaviour, but it has been assessed that additional mechanisms may exist [174]. Accordingly, a review of numerous studies on longitudinal associations between stress and cancer demonstrated that "stressful life experiences are related to poorer cancer survival and higher mortality but not to an increased incidence. Stress-prone personality or unfavourable coping styles and negative emotional responses or poor quality of life were related to higher cancer incidence, poorer cancer survival and higher cancer mortality" [175].

Therefore, we must argue that cancer onset is not dependent on stress alone but requires other factors. This is also Garssen's conclusion, suggesting to consider interaction with social support and coping style [176]. Thus, "Stress per se is not a critical factor" [91]: it can play a role in increasing the risk of infections, allergies, autoimmune and cardiovascular diseases, but a direct link between stress and cancer is not proven [177]. Cunningham expressed a shareable point of view: "While 'stress' is a useful catch-all to describe the stereotyped response to a variety of threatening stimuli, it is too broad to account fully for many of the changes that underly *specific* psychosomatic pathways" [178].

Conclusions

A holistic approach to cancer requires a holistic model of medicine [179], which is more suitable than the biomedical model to address the whole patient. Scholars such as Bahnson [80], de la Peña [180], Pert [181], LeShan [182], Solomon [63], have embraced this orientation. Greer and Watson [183] suggested that the failure of "an integrated psychobiological control system" permits cancer growth and spread; this kind of models shift cancer from a local phenomenon to a *systemic disease* - a holistic perspective justified by the aforementioned interdependence of organism systems and the hypothesis of an organizing centre [128,129] or an inner guide [19].

Organisms - as open and active systems [184] - present features of organization, regulative capacities, increasing differentiation and tendency to self-organize. The human organism is a system in exchange of matter and communication with its environment, presenting the specificity of symbolic activities: in humans, the flow of incoming and outgoing information is conditioned by an individual attribution of meaning. Such uniqueness greatly complicates patients' assessment, even for the same disease. Since every kind of information - coming from inside or outside the body, material or relational - is processed by a single integrated system, it follows the inability to determine cause-effect of one input within the cybernetic apparatus of that organism.

For cancer development, therefore, it is necessary to consider a summation of heterogeneous inputs that potentially represent risk factors. As seen above, some genetic hypotheses have been replaced by environmental evidence, but genetic factors are likely implicated in forms of cancer with familiarity. Conceptually - excluding extreme cases, such as acute radiation exposure, where it is convincing to consider only one genesis - cancer should be considered of *multifactorial origin*, as others authors claimed. Garssen [176] suggested the need to study the interactive effects of psychological, demographic and biomedical risk factors, concluding that the most important studies are still to be done. Holistic research would require probabilistic reasoning, suitable for mathematical models [185], which are increasingly used in medicine to optimize therapies but also for diagnosis and prognosis. There are almost 7000 computational models of cancer online currently, but they consider biological data only. Thus, a probabilistic model for multifactorial risk factors does not exist yet; but a holistic integrated model for the evaluation of cancer healing has been proposed, taking in consideration sociocultural, psychological, behavioural, and biomedical variables - also using informatics [186].

Thorough investigations can highlight chronic hopelessness [90] and long-term individual psychotherapy often leads to consciousness feelings of deep despair dating back to a long time before cancer [182]. Fundamental task of medicine is prevention more than therapy of overt disease. "Primary prevention of cancer depends on changing behaviors and lifestyle" [54] - a commitment that goes beyond the limits of biomedical science to enter into the understanding of incorrect habits with serious effects on health. Even when cancer occurs, "*Physical therapy alone is an emergency measure*" [187].

This not only because of the psychosocial needs that are beginning to be recognized as important for the care of the whole patient (although they are still "often ignored or not defined as part of health care") [188]. Indeed Booth [34], referring to Elida Evans, connected cancer with a real or psychological loss, and conditioned the prognosis to the circumstance that the patient would find a satisfactory substitute. Lack of hope and dire need for relationships may be present together in cancer patients, who run the risk to be isolated by the technical equipment and mentality of a hospital, while they should be emotionally supported to prevent a definitive renunciation of life. Guidelines for an *optimal healing environment* have been prepared [189], where modifications of diet, lifestyle and psychosocial factors are joined to staff training for empathic listening and communication. The application of these recent guidelines is providing positive results and an increase in survival times.

In 1973, the process of replacing the lost relationship was called *rehabilitation* by Booth, who related spontaneous regressions of cancer to "a favorable change in the psychosocial situation of the patient" [190]. After the Simontons [191,192], Spiegel [193], and Fawzy's [194] studies, there is evidence that psychological supportive-expressive group therapy for cancer patients is associated with a survival increase of about two-fold among participants compared to statistical expectations. This research has been continued by Cunningham [195-197], who has shown the importance of participants involvement on survival. Despite their positive results, these psycho-oncological interventions (carried out in a few research centres) have not spread, above all because of mutual mistrust between clinicians of body and mind.

Persistent dualism - studying body or mind - is depriving research of fundamental variables involved in human cancer. A monistic-holistic perspective allows us to consider the whole individual; however, higher and lower levels of investigation are not incompatible. On the contrary, holism and reductionism should constitute co-operating and mutually dependent research programmes [198] in order to achieve a better prevention and therapy of cancer. Therefore, the implementation of integrated multidisciplinary research can provide the best answers.

Competing Interests

The author declares that he has no competing interest.

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