



Between the body and the mind: the involvement of psychological factors in the development of multifactorial diseases

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Abstract

A possible aetiological role for psychological factors has been propounded in particular in relation to diseases of which the causes are only partially known and which are in most cases multifactorial, such as cancer. The long period between a possible first event and the point of no return, gives appeal to the belief that life events other than 'material' causes may play a role in cancer. The evidence that the immune and the nervous system may produce the same substances has opened the way to a new area of research. However, a lack of standardised instruments and the difficulty of conducting systematic and adequate analyses of potential confounding variables have discouraged most qualified scientists from devoting time and effort to investigating the possible role of psychological factors in the aetiology of human diseases. A few studies have reported a positive association between severe life events and breast cancer, but the prevailing view of the medical establishment is that there is no true association between stress and the onset of breast cancer. Although many criticisms of the studies reporting a positive association are definitely based on solid arguments, at least some of the criticisms cling to the requirement for absolute certainty in establishing a cause-effect relationship, which epidemiological studies can rarely, if ever, provide. A challenge for the future of research will be to investigate and better understand the role of subjective factors on the course and outcome of various pathologies, and in modulating the risk of developing a pathology. © 2001 Elsevier Science Ltd. All rights reserved.

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Ultimate mortality is the incurable disease of humans. In defiance of the ineluctability of this condition, humans have proposed various metaphysical theories and metaphorical remedies, such as regeneration, re-incarnation or rebirth. Finally, humans tried to win illness as a form of death by inventing medicine. Recovery from an illness means also an extension in the duration of human life in space and time, in spite of the incontrovertible incurability of human destiny. Medicine, according to Toulmin, "has presented philosophers with a peculiarly rich and close alliance of mind and hand, theory and practice, universal and existential. The art of medicine demonstrates that human reason is practical as well as theoretical, existential as well as universal..." [1].

In ancient times, the value attributed to the agents used for medical purposes amounted to a social truth before being therapeutic truths. They represented,

therefore, social contracts between the therapist and the patient, that is between different social roles. Today, the only competent person in a therapeutic relationship is assumed to be the therapist, and there is no recognition of the competence of others that are not strictly scientific colleagues.

Post-Baconian medicine has declared death as its enemy, and more recently it has been stated that death is a series of preventable diseases, but, as Daniel Callahan puts it, "it is not death that is the enemy, but a painful, impaired and unhealthy life before death" [2]. The paradox of medicine is that while mortality cannot be erased from the horizon of medical research, every effort is made to accomplish this impossible task of overcoming it. Medicine became scientific, first, by detaching itself from the metaphysics of evil and then with the development of morbid anatomy, once death had become the '*a priori*' of medical experience, and the live body became in this way explicable in terms of the dead body [3,4]. Modern medicine has reduced the subject to a number and the body to its various con-

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stituents; this theoretical dismembering is reminiscent of the dissection of a cadaver as the starting point of medical knowledge. Modern hospitals can be seen as a metaphor of the human body as they continue this dissection, as they are divided into departments for the various parts of the body and its functions. A patient entering a hospital is classified according to an organ and/or function, and is thus reduced to that organ.

Medicine has largely rejected the dialogue between patients and physicians in favour of images, and has repressed the awareness of such a rejection. Rather than representing a shared reality between patient and physician, illness thus represents two distinct realities with quite different meanings. "...the phenomenon of illness-as-lived is quite distinct from the phenomenon of the disease state and [...] the two cannot be identified with one another" [4]. Thus, the only way that patients have to acquaint physicians with the inner experiences that let them consider themselves ill [5] has been lost, and, at the same time, the restoring of a patient's integrity as a person has been rendered more difficult. Technology has caused a radical change in the practice of medicine and has redefined the functions of physicians [6]. Together with the progressive expansion of technology, the influence of the pharmaceutical corporations and of the industry of sanitary equipment has also expanded. This may, at least partly, explain why, when considering all that has been gained by increasing the efficiency and the narrowing down the aims of therapeutic devices, very little attention, if any, has been paid to what, at the same time, has been lost.

Among the various internists and specialists of all kinds that a patient may encounter, the 'true physician' remains the person who takes the patient's history [1]. Taking the patient's history means establishing particularly privileged relationships through which the physician may learn intimate details of an individual's life, including his or her feelings concerning cause attribution and also, if a physician is keen, what a patient tries not to say or to hide. To understand a patient is to understand what his past life has made of him, his "... history, who he is and how he now perceives himself to be". A physician's experience grows in relation to his increasing capacity of evaluating correctly individual facts and events, to help in his understanding of individual histories. A right balance would seem to blend the general understanding provided by science with the particular understanding provided by history [1].

In modern medicine, the practical value of a remedy is intemporal: it is not designed for a particular person or to a single specific event, but rather for an entire class of events. This lack of individualised attention may be deeply resented by the patient and could explain why up to 60% of people may turn to non-conventional therapies or have a positive attitude towards alternative medicines [7,8]. Modern technology has made it possible

to narrow the aims and therefore to reach targets that have been well-defined, and this is clearly an advantage, but depersonalised. In such an atmosphere, death may not appear as the ultimate tragedy of life: "The ultimate tragedy is depersonalization—dying in an alien and sterile area" [9]. In the 1930s, over 80% of people died in their homes, while presently over 80% die in an institution. Dying at home is a family experience, but dying in a hospital is too often a dreadful experience associated with a total loss of control and the denial of grief and emotions [10].

Physicians must learn that they cannot exclusively objectivise illness, with the purpose of its elimination. Illness cannot be considered separately from the person, as something on its own that must be faced and overcome [11]. Physicians should be aware that they may be confronted not only with a sick body, but with a personality that may be deeply troubled by a physical illness. They must therefore adapt their behaviour to the complexity represented by the encounter with an ill subjectivity.

A good start would be understanding that the physician and the patient do not just play two roles, but are two people. The relationship would be improved if physicians thought not in the exclusively biomedical paradigm, but in a bio-psycho-social paradigm, in which not only is illness understood in a biological sense, but there is room for the ill human being and his or her environment. It is essential to understand the difference between scientific medicine and true medical art, which is in fact the difference between general knowledge and the concrete application of such knowledge to a single case [11].

Approximately 80% of the encounters between the physician and patient are related to situations of discomfort or generic suffering which must be recognised as illness, but are not identifiable as a true disease. They rather represent a reaction to various personal problems that any individual may have at home as well as at work or at school. These encounters could be an occasion for deepening the relationships between patient and physician and should, in most instances, end without the prescription of laboratory analyses or drugs. There is evidence instead that in the majority of cases they end with the prescription of analyses and/or drugs at the expense of listening, counselling and reassurance [12].

The possible aetiological role of psychological factors has been propounded in particular in relation to diseases of which the causes are only partially known and which are in most cases multifactorial, such as cancer. This has favoured, for instance, the widespread belief that cancer is related to the repression of violent feelings. Sontag mentions the case of Norman Mailer who justified the stabbing of his wife by saying that had he not done it he would have developed cancer [13]. The long period between a possible first event and the point

of no return, gives appeal to the belief that life events other than ‘material’ causes may play a role in cancer. Any disease “that is treated as a mystery and acutely enough feared will be felt to be morally, if not literally, contagious” [13]. Nowadays, much has changed about the way cancer is considered by society compared with the 1970s when Sontag wrote her essay. Nevertheless, it is still much easier that the truth about prognosis is hidden to cancer patients than to patients with a disease equally lethal, such as certain heart diseases. There still seems to be the perception that cancer is something to be ashamed of, while such a perception does not exist for people with heart disease.

Furthermore, the uncertainty or the lack of knowledge about the causes of a serious illness may favour the developing of a sense of guilt. A person who develops cancer may ask: Why me? What did I do to deserve it? [10]. A serious illness, such as cancer, is said to be easier to deal with if its causes are known. While the causes of many cancers are unknown, the aetiology of certain types is fairly well documented. This is true in particular for occupational cancers, such as cancer of urinary bladder in workers of dye factories or mesotheliomas in workers exposed to asbestos. Knowledge of the cause of their tumours certainly did not help the individuals to overcome the disease, and to recover from it, although it may have had an indirect psychological boost from the recognition of the occupational origin of the disease and their consequent right to compensation. Awareness of the cause may increase the feelings of blame in the case of certain cancers, e.g. cervical cancer which is attributable to a sexually-related disease, or lung cancer which is largely attributable to the personal habit of smoking. There is, however, little sense in trying to convince people that they became sick because they unconsciously wanted to, and consequently that they could also contribute substantially to their recovery by utilising all their energies and will. Such an attitude tends to put the blame for the disease on the patient who becomes himself the cause of it and may be pushed to recognise that he or she has deserved the disease [14].

In most industrialised countries, we think we are at least a few generations away from superstition and magic, but phenomena such as placebo effects, for instance, are today widely accepted, even if they cannot be satisfactorily explained [5]. The placebo effect is an inseparable, although variable, component of a regimen of pharmacotherapy and unless a patient is unconscious, a drug cannot be administered without an element of conditioning [15]. While the specific mechanisms of action of placebos are not understood, their efficacy has been amply demonstrated [5,16]. For instance, physicians happily prescribed aspirin as an analgesic long before they understood the mechanism by which it relieves pain. Similarly, milk was recommended to relieve ulcer’s pain, but in the 1970s it was

shown that milk raises gastric secretion, and immediately the use of milk was dropped, in spite of the proven comfort it provided. More recently, it was shown that milk stimulates endomorphins and epidermal growth factor production. It might now be asked whether milk acted as a placebo or an antacid or both [5]. For quite a long time, and to a certain extent still today, physicians were unable to distinguish among the plethora of drugs of which the mechanism of action was unknown, between those that acted for their intrinsic efficacy, and those that were just simple placebos, although there is clearly a substantial difference between the two.

Placebos are particularly relevant in the treatment of pain and the possibility of relieving it, but the dominant medical model of pain has prevented a deepening of the understanding on how placebos may act by focusing all its attention on the action of nerves and neurotransmitters and excluding the role of the mind and for culture [16]. “Placebos work not just because the nervous system has provided humans with their own endogenous pain-killing neuropeptides, but because, in effect, belief proves especially effective in helping to unravel what belief has helped to construct” [16]. The activation of the neurobiological circuits is necessary for placebo effects to take place “through the subtle and diffuse experience of living within the inescapably meaning-rich domain of culture” [16].

When the human body is confronted with environmental stimuli that have a negative impact, it reacts with a series of responses aimed at reducing or opposing the consequences. The responses mainly rely on two different systems, the nervous and the immune systems, through which we succeed in modulating appropriate responses, comprised of both behaviour and the production of substances for facing an emergency. The two systems were thought to be completely separate: on the one side the nervous system which produces appropriate behaviours, reactions for escape or attack, the mobilisation of energy, and stimulating the production of hormones from the adrenals; on the other side, the immune system with its capacity to mobilise leucocytes and to produce antibodies and other substances to destroy infectious agents or neoplastic cells. This separation has been questioned, as the two systems have been shown to produce the same substances and influence each other [17].

The response to stress was for a long time considered to depend on the sympathetic nervous system, resulting mainly in the stimulation of the adrenal medulla. The adrenergic system is known to have immunomodulatory effects. However, the corticotropin (ACTH) secreted by the hypophysis also stimulates the adrenal cortex, and under stress not only corticotropin, but also other substances such as endomorphins are secreted. Moreover, in the brain, both the sympathetic system and the parasympathetic or cholinergic system, formed by neurones

that use acetylcholine as a neurotransmitter, are involved. Increased cholinergic activity, with overproduction of acetylcholine, together with gamma-aminobutyric acid (GABA) and certain peptides, may alter the immune response and result in a decreased reaction to infectious agents or also to neoplastic processes that normally are blocked by the immune system. In support of this, it is often observed that grief depresses the reaction of lymphocytes to mitogenic agents and makes natural killer cells (NK) less efficient against tumour cells. Depression is reported to be associated with a decreased secretion of the immunostimulants prolactin and growth hormone [18]. Both acute and chronic stress may have long-term consequences. The adaptive or allostatic (allostasis has been defined as “the ability to achieve stability through change” [19]) response, implies the activation of defence systems and their inactivation after the stress is terminated. Inactivation, however, can be insufficient for a variety of reasons, resulting in adverse effects (allostatic load) [19].

The issue of the role of the mind in disease is further complicated by the fact that, perhaps more than in other fields of biology, cause-effect relationships are very hard to prove, as there are no ‘laws’ for ascertaining beyond doubt that a stressful event is *per se* responsible for the occurrence of a particular disease. Each individual responds in a different way to similar situations, and there is still great uncertainty about the extent to which the mind can mobilise the body’s defences to prevent and/or fight illness.

The difficulty of conducting systematic and adequate analyses of potential confounding variables have perhaps discouraged qualified scientists from devoting time and effort in investigating the possible role of psychological factors in the aetiology of human disease. This may have resulted to a certain extent in a negative selection with, as a consequence the production of poor papers and undue amplification of undependable results, which may have further discredited a field of research that is particularly arduous [20].

The respected scientist Rene’ Dubos strongly supported the view that the mechanisms of humoral and cellular immunity are affected by the mental state. He pointed out, for instance, that the vascular manifestation of the Mantoux test, which consists of intradermal injection of tuberculin in order to evaluate the body’s response to TB infection, can be obliterated by hypnosis. The Mantoux reaction represents cell-mediated immunity, which plays an important role in resistance to numerous diseases, including perhaps cancer. There is good reason to believe, therefore, according to Dubos, that “the patient’s state of mind can affect the course of all pathological processes that involve immunological reactions” [21]. In addition, it is well recognised that 10–30% of patients in general hospitals are suffering from medical and psychiatric comorbidity. If

they are inadequately treated for the psychiatric component, the evolution and outcome of their medical condition is worse and mortality higher [22].

Among those who support the aetiological role of psychological factors, the most supported hypothesis is that stressful events may cause transient impairment of immune functions, which predispose the individual to the initiation and progression of various pathologies, including infections, allergies and cancer. Opponents to this view may go a long way in denying such a role, claiming, for instance, that the human organism is highly adaptable even to extreme psychological stress which has always been a fundamental part of life [23]. As an example, a rather careful study suggesting an almost 2-fold increase in cancer risk in depressed elderly individuals [18], has been criticised on methodological grounds [24]. Although a share of the criticisms of the studies reporting a positive association are definitely based on solid ground, at least some of the criticisms seem to cling to the requirement for absolute certainty in the cause-effect relationship data that epidemiological study can not provide [25]. The breast has been a preferred site for studies aimed at verifying the possible role of stressful events on the risk of cancer. While a study has reported a positive association between severe life events and breast cancer [26], the prevailing view is that there is no ‘true’ association between stress and the onset of breast cancer [27,28]. The difficulties in establishing the onset of the carcinogenesis process clearly represent an almost insuperable obstacle for establishing such a definite casual association. There is a consistent fraction of the medical establishment that want clinical medicine to become an impersonal technology. But “if one does not wish to accept some real psychic involvement with sick people and is not really willing to involve one’s whole personality in that interaction... then... why be a physician at all?” [1].

Lately psychotherapists, as well as several practicing physicians, are more inclined to recognise the comorbidity of psychological and physical disorders [29]. Furthermore, results from a variety of investigations have provided evidence that the ability to construe a meaning for an adverse circumstance, a belief in personal control and optimism help people to adapt more successfully to stressful events and actually protect health [29]. Such an effect was shown in a study on HIV-infected individuals. In contrast to other chronic diseases, HIV-infected individuals can be followed for rather a long period before the clinical disease manifests itself and the level of a biological marker, like the number of CD4 cells, can be monitored. Only those individuals who did engage in cognitive processing and were able to find a meaning in a bereavement experience, did not show a decline in CD4 helper cells during a 2 to 3-year period, and had a lower rate of AIDS-related mortality [30]. On a quite different level, psychological

stress is considered to play an important role in the deterioration of health and the consequent shortening of life expectancy in Eastern Europe [31].

We are still mainly wrapped up in the philosophical thinking of Descartes who has successfully imposed a sharp partition between mind and matter. Descartes' *cogito ergo sum* implies that thinking and the awareness (consciousness) of thinking are the true constituents of the being, but, at the beginning of life on this planet, at the dawn of humanity there was the being, and only later the thinking. Similarly, all of us entering this world begin by being and only later do we start thinking, since thinking is caused by the structures and activities of the being (A. Damasio, cited in Ref. [32]).

A challenge for the future of research will be to investigate and better understand the role of subjective factors on the course and outcome of various pathologies. It will also be to investigate the role of subjective factors in modulating the risk of developing a pathology, which will mean tackling the problem of the aetiology of chronic diseases and the complexity of their multifactorial origin. Much more attention will have to be focused on both the psychological consequences of a clinical disease, the so-called 'true diseases', and on the somatic effects of the psychological conflicts. While the possible role of psychological troubles is receiving increasing attention, there are few, if any, studies on the circumstances and the extent that these events may be of relevance.

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