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Psychosomatic medicine: alive and well in the new century

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Abstract

Psychosomatic medicine provides a comprehensive framework for a holistic (biopsychosocial) consideration of patient care encompassing the role of psychosocial factors in affecting individual vulnerability to all types of diseases; the interaction between psychosocial and biological factors in the course and outcome of disease and the application of psychological therapies to the prevention, treatment and rehabilitation of physical illness.

This framework, modified from the one originally proposed by Lipowski, will serve to highlight the areas where a psychosomatic integration may have important clinical and research implications. The same holistic mentality should also be applicable to the field of psychiatry. In recent years, a new way of integrating pharmacotherapy and psychotherapy in depression has been proposed (i.e. sequential approach), but, not surprisingly, non pharmacological treatment strategies have been swimming against the tide of pharmaceutical propaganda.

Key-words*: Psychosomatic medicine; Mind-body medicine; Psychological well-being; Quality of life; Depressive disorders; Antidepressant drugs; Psychotherapy.*

DEVELOPMENTS IN PSYCHOSOMATICS

About half a century ago, a debate took place in Psychosomatics medicine. The Scottish physician and psychosomatic investigator James Halliday was challenged about the use of the term "psychosomatic affection". Halliday[1] vigorously supported the clinical and heuristic value of the concept of psychosomatic affection, "a bodily disorder whose nature can be appreciated only when emotional disturbances, i.e. psychological happenings, are investigated in addition to physical disturbances, i.e. somatic happenings". The concept, he remarked, "brings together a large number of seemingly unrelated facts. The outlook gained shows that many "localized diseases", the names of which have hitherto been found scat-

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tered through textbooks of medicine under the headings of the various anatomical systems, may now be grouped under a unifying etiological category. The term psychosomatic affection is therefore a valid symbol which provides a new instrument for thinking, for investigation and for direction of action". However, it contained a basic conceptual flow, i.e. consideration of disease as homogeneous entities, while careful appraisal of current medical literature leads in the opposite directions, that is recognition of their multifactorial and heterogeneous components [2].

Kissen, about two decades later, provided a better specification of the term "psychosomatic". "It would appear possible for an illness generally thought of as being 'psychosomatic' to be 'non-psychosomatic' in certain individuals. Likewise an illness not generally thought as 'psychosomatic' may be psychosomatic in some individuals [3]. He thus clarified that the relative weight of psychosocial factors may vary considerably from one individual to another within the same illness and underscored the basic conceptual flaw of considering diseases as homogeneous entities.

This is no different from what Lipowski [4] later wrote: "it is generally agreed now that all diseases, physical and mental, are multifactorial in origin…There is growing evidence that the psychological and social variables are a class of etiologic factors in all diseases. Their relative weight may vary considerably from illness to illness, from individual to individual, and from one episode to another of the same illness in the same person". Lipowski also gave an invaluable contribution in setting the scope, mission and methods of psychosomatic medicine [5]. He identified three interrelated facets: (a) it is a scientific discipline concerned with the study of the relationships of biological, psychological, and social determinants of health and disease; (b) it embodies a holistic approach to the practice of medicine; (c) it encompasses consultation-liaison psychiatry [6].

Engel developed a multifactorial model of illness [7], later subsumed under the rubric of "biopsychosocial" [8]. It allows illness to be viewed as a result of interacting systems at the cellular, tissue, organismic, interpersonal and environmental levels. As a result, the study of every disease must include the individual, his body, and his surrounding environment as essential components of the total system [8]. The various social factors involved may range from the socioeconomic status (e.g., poverty, nutritional deprivation, loss of social support) to toxic environmental exposure [9,10], in what constitutes a truly ecological viewpoint. These components may influence susceptibility to disease by activating a variety of CNS pathways [11]. Disciplines as psychoneuroendocrinology and psychoimmunology, which originally stemmed from psychosomatic research, aim to unraveling the complex balance between emotions and disease [12-14]. Both Engel and Lipowski [15,7] criticized the obsolete notion of psychogenesis (a physi-

cal illness believed to be caused by psychological factors, such as peptic ulcer), since it was incompatible with the doctrine of multicausality, which constitutes a core postulate of current psychosomatic medicine.

Engel, Lipowski, and Kissen deserve credit for setting, in the sixties, the ground for the renaissance of psychosomatic medicine under more appropriate guidelines.

FIGHTING MEDICAL REDUCTIONISM

The term "Psychosomatics" was introduced by Heinroth in 1818, but it is not until the 1930s that modern psychosomatic medicine was founded [15]. It resulted from the confluence of two concepts having an ancient tradition in Western thought and medicine: those of psychogenesis of disease and of holism [15]. The idea of psychogenesis characterized the first phase of development of psychosomatic medicine (1930-1960), and resulted in the concept of psychosomatic disease. Despite early criticism [16], the psychogenic postulate indeed exerted a considerable seduction in view of its explanatory power, particularly in a field then dominated by psychoanalytic investigators. However, these great expectations did not survive the test of scientific evidence.

As psychosomatic medicine in its developing phase was trying to link in a deterministic way a physical illness to a psychological cause, in the field of medicine this type of reductionism was also present and was therefore preventing to perceive diseases under a multifactorial perspective.

In the attempt to overcome the above mentioned conceptual flaws derived from reductionism, psychosomatic medicine provides a comprehensive framework for a holistic (biopsychosocial) consideration of patient care encompassing:

a) The role of psychosocial factors in affecting individual vulnerability to all types of diseases;
b) The interaction between psychosocial and biological factors in the course and outcome of disease;
c) The application of psychological therapies to the prevention, treatment and rehabilitation of physical illness.

This framework, modified from the one originally proposed by Lipowski [15], will serve to highlight the areas where a psychosomatic integration may have important clinical and research implications. The emergence of mind-body medicine and its complex relationships with psychosomatic medicine and behavioral medicine make necessary to redefine the aims and methods of psychosomatic medicine, after Lipowski's reviews in 1977 [6] and 1986 [15].

a) Psychosocial factors affecting individual vulnerability

Developments have occurred in all aspects of psychosomatic medi-

cine. Among factors affecting individual vulnerability to all types of disease, the following have been highlighted by recent research: recent and early life events, chronic stress and allostatic load, personality, psychological well-being, health attitudes and behavior.

Recent life events

The notion that events and situations in a person's life which are meaningful to him or her may be followed by ill health has been a common clinical observation.

Clinical observations, however, have considerable shortcomings: events may be the consequence rather than a cause of illness (due to its insidious development) and patients may not actually experience more events prior to illness, but simply recall more of them, in an'"effort after meaning". The introduction of structured methods of data collection (and particularly semi-structured research interviews with high inter-rater reliability) and control groups has been a turning point in the research in the area [17]. Use of these methods, for instance, has allowed to substantiate the link between life events (discrete changes in the subject's social or personal environment, that should be external and verifiable rather than internal or psychological) and endocrine conditions [18-22]. Stressful life events may affect the regulatory mechanisms of neuroendocrine-immune functions in a number of ways [23-25]. Within a multifactorial frame of reference, stressful life events have been consistently associated with several medical disorders. Table 1 outlines the medical disorders for which controlled studies have pointed to a relationship [14,17-31].

Table 1 - **Medical disorders that have been associated with stressful life events in controlled studies**

– asthma
– diabetes
– Graves' disease
– Cushing's disease
– hypothalamic amenorrhea
– peptic ulcer
– inflammatory bowel disease
– functional gastrointestinal disorders
– myocardial infarction
– functional cardiovascular disorders
– autoimmune disease
– cancer
– infectious disease
– psoriasis, alopecia areata, and urticaria
– headache
– cerebrovascular disease
– sudden death

Chronic stress and allostatic load

Life changes are not the only source of psychological stress. Subtle and long-standing life situations should not too readily be dismissed as minor and negligible [32], since chronic, daily life stresses may be appraised by the individual as taxing or exceeding his or her coping skills. Further, a number of factors may modulate the psychological response to stress [33], such as social support [34] and personality [35] and act by increas-

ing the impact of stressful circumstances or by offering protection against their adverse effects [36].

Mc Ewen and Stellar [27] proposed a formulation of the relationship between stress and the processes leading to disease, based on the concept of allostatic load: the cost of chronic exposure to fluctuating or heightened neural or neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful. It emphasizes the hidden cost of chronic stress to the body over long time periods, which acts as a predisposing factor for the effects of life changes [27]. Four situations are associated with allostatic load: frequent stress, failure to adapt to repeated stressors of the same type, inability to shut off allostatic responses after a stress is terminated, inadequate responses which trigger compensatory increases in other allostatic systems [37]. An important new line of research involves the use of concomitant biological measures of allostatic load, such as glycosylated proteins, coagulation / fibrinolysis markers, and immune markers [38]. The need of combining psychometric and biological measures in laboratory research involved with psychoneuroendocrinology of human disease has therefore emerged [39,40].

Early life events

The role of early developmental factors in susceptibility to disease has been a frequent object of psychosomatic investigation[41]. Due to the difficulties in gathering retrospective information, considerable value has been achieved by psychosomatic studies concerned with animal models [42,43]. Events such as premature separation from the mother have consistently resulted in development of physiological vulnerability [42]. This may reflect increased hypothalamic pituitary adrenal axis (HPA) activation: in fact, deprivation of the infant animal from maternal cure for prolonged periods of time results in increased concentration of immunoreactive CRF in the median eminence and of CRF mRNA expression in the paraventricular nucleus [44]. This has led to the hypothesis that early adverse life events (e.g., separation) or traumatic events in childhood (e.g., sexual abuse) may render the human individual more vulnerable to the effects of stress later in life, by long-lived alteration in CRF-containing neural circuits [45]. This may have important implications in HPA driven disorders such as depression [45] and Cushing's disease [46]. A similar hypothesis has been suggested as to prolactin secretion [47]. The past decade has witnessed an upsurge of interest in the association of childhood physical and sexual abuse with medical disorders [48], pioneered by Engel in the fifties as to chronic pain [49]. Whether sexual abuse results, through neuroendocrine mechanisms, in the development of physiological vulnerability or affects illness behavior [50], or both, is a research question that can only be addressed by proper psychosomatic integration.

Personality

The notion that personality variables can affect vulnerability to specific diseases was prevalent in the first phase of development of psychosomatic medicine (1930-1960), and was particularly influenced by psychoanalytic investigators, who believed that specific personality profiles underlay specific "psychosomatic diseases". This hypothesis was not supported by subsequent research [15]. Two personality constructs that can potentially affect general vulnerability to disease, however, have attracted considerable attention. One is concerned with the relationship between coronary heart disease and the so-called Type-A behavior pattern. People manifesting this pattern display some or all the following characteristics: "excessive degree of involvement in work and other activities subject to deadlines; sense of time urgency; display of motor-expressive features indicating sense of being under the pressure of time; hostility and cynicism; irritable mood; tendency to speed up physical activities; tendency to speed up mental activities; high intensity of desire for achievement and recognition and high competitiveness [51]. A large number of studies have been conducted in the past three decades on the pathogenetic role of Type-A behavior in coronary heart disease [30,52-54]. Various methods of assessment have been used and the results have been rather controversial; hostility and time urgency appeared to be two key components [52,53]. A substantial problem lies in the fact that the definition of Type-A behavior consists of a mixture of state and trait features, which cannot be ascribed to stable personality aspects [51]. However, the bulk of the literature seems to indicate that there is a pattern of behavior that is associated with coronary heart disease, even though this does not apply to every case and cannot be readily identified [52-54].

The other psychological construct is alexithymia [55]. This concept was introduced by Sifneos to describe an impoverished fantasy life with a resulting utilitarian way of thinking and a characteristic inability to use appropriate words to describe emotions [56]. The characteristic features of alexithymia are the following: inability to use appropriate words to describe emotions; tendency to describe details instead of feelings; lack of a rich fantasy life; thought content associated more with external events rather than fantasy or emotions; unawareness of the common somatic reactions that accompany the experience of a variety of feelings and occasional, but violent and often inappropriate, outbursts of affective behavior[51]. The inhibition of emotional expression and particularly a life-long tendency to suppress anger have been found to involve an increased risk for a variety of health problems, both using the alexithymia [56] or similar [57, 58] psychological constructs. The findings concerned with cancer stemmed from a study finding that women aged under 50 who were subsequently diagnosed as having breast cancer showed significantly higher levels of sup-

pressed anger than those who turned out to have benign tumors [59]. However, despite advances in our understanding of the relationship between the brain and the immune system [12,13], it is premature to conclude that a relationship between suppressed emotion and cancer does exist. Personality traits may be related to the course of cancer, since the cellular mechanisms involved in the progression and metastasis of tumors differ from those that initiate the transformation of cells [60]. In a study [61], it was found that recurrence of breast cancer was significantly less common in women reacting to the disease with denial or a fighting attitude than among those displaying stoic acceptance or feelings of helplessness or hopelessness. Despite more than two decades of research, alexithymia is still a controversial concept, particularly in its assessment [62], psychophysiological correlates [63] and relationships with other affective components [64-68].

Psychological well-being

Positive health is often regarded as the absence of illness, despite the fact that, half a century ago, the World Health Organization defined health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[69]. Ryff and Synger [70] remark that, historically, mental research is dramatically weighted on the side of psychological dysfunction and that health is equated with the absence of illness rather than the presence of wellness. Research on psychological well-being has indicated that it derives from the interaction of several intercorrelated dimensions[70], as described in Table 2. There is substantial evidence [2,71,72] that psychological well-being plays a buffering role in coping with stress, has a favorable impact on disease course, and has important immunological and endocrine connotations. For instance, maintenance of psychological well-being following the onset of breast cancer implies longer survival time [73], whereas impaired well-being tends to shorten survival time [74]. Other examples may be concerned with the role of optimism and coping style in transplantation outcome [75], anxiety and hope in the course of medical disorders [76], the relationship between life satisfaction and cardiological variables [77] and the protective role of well-being in several other medical disorders [78].

Table 2 - **Dimensions of psychological well-being**

– self acceptance (a positive attitude toward self)
– positive relations with others (warm, satisfying, trusting relationships)
– autonomy (self-determination and independence)
– environmental mastery (sense of mastery and competence in managing the environment)
– purpose in life (goals and a sense of directedness)
– personal growth (feeling of continued development)

Health attitudes and behavior

There is growing awareness that certain personality habits, such as smoking cigarettes, drinking alcohol and eating a diet rich in cholesterol and saturated fats, may have a considerable impact on health. Beliefs about risks associated with certain health-damaging behaviors are not necessarily associated with the absence of those health risk behaviors. In a survey of health behaviors in young adults in 8 countries throughout Europe [79], those who engaged more in drinking and smoking were just as much aware of the negative consequences of these health-damaging behaviors as people who did not engage in them. On the other hand, beliefs about the positive effects of health protective behaviors, such as eating a low-fat diet, exercise, safety practices, and participating in health screening exams (e.g., testing for breast or prostate cancer) were strongly associated with their practice[79]. This exemplifies the psychosomatic complexity of both health-damaging and health promoting behaviors [80].

b) Interaction between psychosocial and biological factors in medical disease

The interaction between psychological and biological factors in the course and outcome of disease, the presence of psychiatric as well as subclinical symptoms, illness behavior, and the impact on quality of life, interact in various ways in the course of medical disease and all need to be carefully assessed. The varying influence of those factors determines the unique quality of the experience and attitude of every patient in any given episode of illness[81].

Psychiatric disturbances

The potential relationship between medical disorders and psychiatric symptoms ranges from a purely coincidental occurrence to a direct causal role of organic factors – whether medical illness or drug treatment – in the development of psychiatric disturbance. The latter is often subsumed under the rubric of organic mental disorders whose key feature is the resolution of psychiatric disturbances upon specific treatment of the organic condition [82]. Psychosomatic medicine has pioneered the study of this clinical area (including delirium and dementia), that – up to the eighties – was largely neglected in psychiatry [83]. Major depression has emerged as an extremely important source of comorbidity in medical disorders [84,85]. A depressed mood may in fact influence how a person experiences the pathological process and his or her interaction with others, including medical staff. In particular:

1) the presence of depressive symptoms in association with chronic medical illness was found to affect quality of life and social functioning and lead to increased healthcare utilization [84,85];
2) depression was found to have an impact on compliance.

Many cases of "suicide by default" in the medical population (i.e., the deliberate omission of therapeutic, dietary and other measures necessary to sustain life or prevent the progress of pathology) may mask a major depressive disorder [4]. Examples include diabetic patients who stop taking insulin, those who resume strenuous work after myocardial infarction and those who withdraw from chronic hemodialysis [4];

3) research has suggested that depression may increase susceptibility to medical disease [84,85]. The evidence is particularly impressive in cardiovascular disease [86]. Clinical depression appears to be an independent risk factor for coronary heart disease [87] and to affect mortality rate after myocardial infarction [88]. Depression has been suggested to be also a marker of disease severity. I.e., in pituitary dependent Cushing's disease, the presence of depression was associated with severity of clinical presentation [89] as well as entailed prognostic value (patients were more likely to relapse after a successful pituitary microadenomectomy if they presented with depression at the time of surgery) [90];
4) functional medical symptoms are extremely common in medical practice. Their association with depression has been consistent, regardless of the design of the study [91]. Depressed patients tend to have more somatic symptoms than non-depressed individuals, and somatizers tend to be more depressed than patients with physical disease [91]. The case of depression exemplifies the importance of detecting and treating psychiatric co-morbidity in the setting of medical disease.

Psychological correlates

Current emphasis in psychiatry is on assessment of symptoms resulting in syndromes identified by diagnostic criteria (DSM) [92]. However, there is emerging awareness that subclinical psychiatric symptoms may have a considerable impact on quality of life and entail pathophysiological and therapeutic implications [93-96]. This particularly applies to the setting of medical disease, where most psychological symptoms cannot be assigned a suitable rubric according to psychiatric diagnostic criteria [2]. The case of hostility is particularly indicative. A considerable body of evidence has suggested a pathogenetic role for anger, hostility and irritable mood in physical illness [35,95]. Most of this evidence stemmed from hostility as a risk factor in cardiovascular medicine [97]. For instance, in a prospective study of the progression of carotid atherosclerosis, cynical distrust and anger, in addition to previously established risk factors (i.e., serum low-density lipoprotein cholesterol con-

centration, smoking, etc.) predicted outcome [98]. The association between low serotonin function and hostility and anger [99] may provide a neurobiological framework for these unfavorable effects. Serotonin may in fact affect factors such as macrophage activation, plasminogen activation inhibitor, platelet activation, cytokines, and natural killer cell activity [100]. Similar considerations can be made as to a psychological state characterized by the giving-up complex, helplessness and hopelessness, demoralization [101], which has been found to facilitate the onset of disease to which the individual was predisposed. Such a subsyndromal state cannot be identified with psychiatric categories [102]. Both demoralization and irritability may be part, in association with fatigue, of another psychological state, labeled as vital exhaustion, which was found to be an independent risk factor for myocardial infarction [103]. Unfortunately, several psychosomatic constructs, related to psychological characteristics such as irritability and demoralization, have not resulted in operational tools whereby psychosocial aspects of medical diseases can be differentiated. This has led to the development of a set of Diagnostic Criteria for Psychosomatic Research (DCPR) by an international group of investigators [51]. These criteria aim to identify alexithymia, Type-A behavior, disease phobia, thanatophobia, health anxiety, illness denial, functional somatic symptoms secondary to a psychiatric disorder, persistent somatization, conversion, anniversary reaction, irritable mood and demoralization. In this issue [104], these criteria were found to be more suitable than DSM-IV criteria in identifying psychological distress in a medical population. The conceptual model that underlies the DCPR is devoid of pathogenetic implications (unlike several other psychosomatic constructs) and emphasizes the varieties of associated somatic and mental responses that individuals offer to life situations (psychosomatic syndromes). Psychosomatic investigators have generally attempted to demonstrate that a certain psychological characteristic "x" is more prevalent in the condition "a" compared to the condition "b". Even when they do find a significant difference by reliable statistical and psychometric methods, this does not mean that every patient with "a" also presents with "x" and that a patient with "b" may not present with "x" features. It is their association, not their specificity, which may matter. Bjorntorp [105], for instance, has suggested that an excessive androgen production in women, as occurs in polycystic ovary syndrome, may be associated with physiological and psychological characteristics which are typically found in men. Such psychosomatic combination (the android woman) may pave the way for an increased risk of developing hypertension, non insulin dependent diabetes mellitus and cardiovascular disease, as was found also in epidemiological studies in the general population [105]. Each component of this psychosomatic combina-

tion, taken by itself, would not necessarily lead to the same risky condition. The DCPR are thus aimed to translating psychosocial characteristics observed in various medical diseases in diagnostic criteria, which may entail clinical (prognostic and therapeutic) value, and be studied across disorders.

Illness behavior

Lipowski remarks that once the symptoms of a somatic disease are perceived by a person, "or he has been told by a doctor that he is ill even if symptoms are absent, then this disease related information gives rise to psychological responses which influence the patient's experience and behavior as well as the course, therapeutic response and outcome of a given illness episode" [4]. The study of illness behavior, defined as the ways in which individuals experience, perceive, evaluate and respond to their own health status [106], has yielded important information in medical patients [107]. It was translated clinically by Pilowsky's concept of abnormal illness behavior, defined as the persistence of a maladaptive mode of perceiving, experiencing, evaluating, and responding to one's health status, despite the fact that a doctor has provided a lucid and accurate appraisal of the situation and management to be followed if any, with opportunities for discussion, negotiation and clarification, based on adequate assessment of all relevant biological, psychological, social and cultural factors [108]. The two main forms of abnormal illness behavior (illness affirming and illness denying) have several common clinical expressions in clinical practice. They range from hypochondriasis and disease phobia [107] to illness denial [109,110] and lack of compliance [111,112]. In recent years, there has been increasing interest in assessing patients' perceptions of the impact of illness [113,114]. The integration of measurements of psychopathology of illness behavior, such as those provided by Kellner's Illness Attitudes Scales [107] and Pilowsky's Illness Behavior Questionnaire [108], with those concerned with patients' perceptions appear to be an important task of current psychosomatic research.

Quality of life

Quality of life, particularly in chronic diseases, has became the focus of an increasing number of publications. While there is neither a precise nor agreed definition of quality of life, research in this area seeks essentially two kinds of information, the functional status of the individual and the patient's appraisal of health [115]. The concept stems from the fact that the measures of disease status alone are insufficient to describe the burden of illness and that the subjective health status (e.g., well-being, demoralization, difficulties fulfilling personal and family responsibilities, etc.) is as valid as that of the clinician when it comes to evaluating outcomes [115-118]. The concept of quality of life is substantially based on the classic psychosomatic concept of disease: "How a person experiences the pathologi-

cal process, what it means to him, and how this meaning influences his behavior and his interaction with others are all integral components of disease viewed as a total human response" [119]. Unfortunately, investigators dealing with quality of life seem to discard psychosomatic research failing to incorporate the methodological insights acquired by this discipline in the past decades [120]. Not surprisingly, the quality of quality of life measurements is often rather poor [121].

c) Applications of Psychological Therapies to physical illness

Psychological interventions in the medically ill encompass the use of psychotherapeutic strategies, psychopharmacological interventions, and preventive strategies. They may be performed by a variety of health professionals (psychiatrists, psychologists, nurses, primary care physicians, etc.). The importance of the interaction of psychiatric, psychosomatic or behavioral medicine services with primary care has progressively increased [122]. Another valuable source of collaboration has been identified in medical-psychiatric units for the treatment of patients who require acute hospital care and cannot be managed adequately either in a standard psychiatric ward or in medical-surgical wards of the general hospital [123].

Psychosomatic prevention

In a multifactorial frame of reference, consideration of the role of stressful life events, allostatic load, and health damaging behavior, lends itself to important preventive efforts. Two important causes of allostatic load appear to be isolation and lack of control in the work environment [37]. Theorell [124] has illustrated the effectiveness of programs for improving the ability to cope with difficult life situations, particularly involving the work environment, and to counteracting loneliness among pensioners. A number of psychological treatments have been shown to be effective in health-damaging behaviors, such as smoking [125].

Treatment of psychiatric morbidity

There is evidence [84,85,126,127] that psychiatric disorders, and particularly major depression, are frequently unrecognized and untreated in medical settings, with widespread harmful consequences for the individual and the society. Treatment of psychiatric comorbidity such as depression, whether pharmacological or psychotherapeutic, was found to favorably affect outcome and compliance [84, 85]. Psychiatric disorders in the medically ill may, however, require treatment strategies that are different from those endorsed in clinical psychiatry. Use of psychotherapeutic strategies (cognitive-behavioral therapy, stress management procedures, brief dynamic therapy) in controlled investigations has yielded a substantial improvement either in quality of life, and / or in coping, and / or in the course of disease in a number of medical disor-

ders, as listed in Table 3 [125,128-131]. Examples of these strategies are concerned with interventions that increase social support and enhance coping strategies in patients. At times interventions can be as simple as writing about stressful experiences, as in asthma and rheumatoid arthritis.

Research on psychotherapy has disclosed some common therapeutic ingredients that most of the psychotherapeutic techniques share, and that are outlined in Table 4 [133,134]. These ingredients may also apply to routine medical practice. In a pioneer study [135], a small amount of individual attention and education (what to expect during the post-surgical period) by the anesthetist resulted in a significantly lower requirement of post-surgery analgesia and in a shorter hospital stay compared to a control group submitted to routine post-surgical care as usual. The non-specific therapeutic ingredients of Table 4 can thus be used with specific effects and do not require highly specialized training.

Table 3 - **Medical conditions in which short-term psychotherapies have been found to be effective in randomized controlled trials**

– chronic pain
– chronic fatigue syndrome
– coronary heart disease
– hypertension
– tension headaches
– diabetes
– cancer
– asthma
– epilepsy
– obesity
– peptic ulcer
– irritable bowel syndrome
– inflammatory bowel disease
– HIV infection and AIDS
– arthritis
– preparation to medical procedures

Table 4. **Non specific therapeutic ingredients that are shared by most forms of psychotherapy**

Ingredients	***Characteristics***
1. Attention	The therapist's full availability for specific times
2. Disclosure	The patient's opportunity to ventilate thoughts and feelings
3. High arousal	An emotionally charged, confiding relationship with a helping person
4. Interpretation	A plausible explanation of the symptoms
5. Rituals	A ritual or procedure that requires the active participation of both patient and therapist and that is believed by both to be the means of restoring the patient's health

Awareness of non-specific ingredients should not lead, however, to the conclusion that all psychotherapeutic interventions yield similar results in the medically ill. For instance, the effects of relaxation were found to be superior to attention and education in preparation for surgery[136]. Marks[137] has outlined how specific cognitive behavioral strategies may yield, by different methods, a common therapeutic change (increase in sense of control), that is of paramount importance in mood and anxiety disorders. Astin[138] has reviewed the implications of the construct of control for health care. Since illness frequently results in feelings of loss of control, gaining a sense of mastery can help patients to cope with illness. Several studies, however, suggest that it is important to match control strategies to patient styles and preferences [138]. As a result, different psychotherapeutic techniques, which are aimed to enhancing control, should be available in the setting of medical disease.

Improvement of psychological well-being by means of a specific psychotherapeutic strategy defined as well-being therapy [139,140] is another area of interest, in view of the protective effects of well-being as to life adversities[74]. It is conceivable, even though yet to be tested, that well-being therapy may be particularly valuable in patients whose disease has determined a loss. In this context loss refers not just to body parts and functions actually lost, but also to deprivations of personally significant needs and values, such as self-esteem, security and satisfaction[119].

Lipowski[81] outlined six stages of illness: symptom perception, decision making, medical contact, acute illness, convalescence and rehabilitation, and chronic illness or disability. It is conceivable that application of psychotherapeutic techniques may follow these stages and be specifically geared for them[141].

Treatment of abnormal illness behavior

For many years abnormal illness behavior has been viewed mainly as an expression of personality predispositions and considered to be refractory to treatment by psychotherapeutic methods. There is now evidence, both of psychotherapeutic and pharmacotherapeutic nature, to challenge such pessimistic stance [91,142,143]. For instance, several controlled studies on psychotherapy [144-148] indicate that hypochondriasis is a treatable condition. Providing accurate information and the use of simple cognitive strategies, such as clarification of both previous faulty communications with physicians and common psychophysiological reactions (patients may in fact be unable to attribute somatic symptoms to anxiety) underlie treatment of hypochondriacal patients [91]. The application of these simple suggestions has yielded significant improvements in controlled studies concerned with functional medical disorders [91]. The correlation between abnormal illness behavior and health habits may have implications in preventive efforts. Indeed, individuals

with hypochondriacal fears and beliefs were found to take worse care of their health than control subjects in several studies [149]. They may be so distressed by their belief of having an undiagnosed or neglected disease that behaviors that may yield benefits in the distant future appear to be irrelevant to them.

The use of psychotropic drugs in the medically ill

Aside from the use of psychotropic drugs for treating psychiatric comorbidity in medical disease (e.g., the use of antidepressant drugs in patients with major depression), there is evidence from a number of double blind placebo controlled studies that psychotropic drugs may favorably affect the course and outcome of several medical conditions [150-152], such as peptic ulcer and chronic pain. Psychosomatic studies such as the ones concerned with the relationship between neurotransmitters and functional medical disorders [153] may shed some light on the underlying mechanisms. In view of the increasing awareness of the pathogenetic role of stressful life situations (resulting in disregulation of the HPA axis), a novel pharmacological strategies could be offered by the recent availability of CRH receptor antagonists [154]. Whether these agents may provide a decrease in psychophysiological activation that is superior to that entailed by benzodiazepines in functional medical disorders [150] is certainly an issue worthy of investigation.

CURRENT DEVELOPMENTS IN PSYCHOSOMATIC MEDICINE

Critical appraisal of current developments in clinical medicine is likely to underscore several areas which can potentially benefit from a psychosomatic approach. They include:

a) *Somatization*. The tendency to experience and communicate psychological distress in the form of physical symptoms and to seek medical help for them [15] is a widespread clinical phenomenon that may involve up to 30 to 40% of medical patients. It may well be the most costly comorbidity [155]. Fourteen common physical symptoms are responsible for almost half of all primary care visits [156], but only 10% to 15% are found to be caused by an organic illness over a 1-year period.

b) *Mysterious symptoms.* A significant proportion of problems presenting to a primary care physician cannot be assigned a suitable diagnostic rubric [157]. And when this latter takes the form of a functional medical disorder, it does not seem to prevent excess health care use and therapeutic frustration [91]. The need of new approaches to ambulatory care, encompassing the biological, psychological and social aspects of human disease, has emerged [158]. Not surprisingly, the past decade has witnessed an upsurge of

use of alternative medicine and its underlying models [159-165].

c) *Quality of life*. The need to include consideration of function in daily life, productivity, performance of social roles, intellectual capacity, emotional stability and well-being, has emerged as a crucial part of clinical investigation and patient care [115-121]. This has become particularly important in chronic diseases where cure cannot take place and also extends over family caregivers of chronically patients, whose emotional burden has become more and more manifest [166,167] and health providers [168,169] .Patients have become more and more aware of these issues. Their difficulties in coping with medical illness and its psychological consequences have indeed led to the development of several patients' associations.

There is also increasing emphasis on health promotion rather than simple disease prevention [170].

In the past 60 years, psychosomatic medicine has addressed some fundamental questions about health and disease. Many of these questions were addressed well ahead of the current prevailing medical orientation. Disciplines such as psychoneuroendocrinology, psychoimmunology, consultation-liaison psychiatry, behavioral medicine, health psychology, as well as quality of life research, stemmed from the psychosomatic field. Even though they may now claim full autonomy, their psychosomatic linkages are crucial for their balanced developments. As Wittkower suggested, to accomplish its goals psychosomatic medicine should be fully incorporated in the practice of medicine, and therefore be dedicated to its own "dissolution" [171]. We are still very far from accomplishing it [172].

FIGHTING PSYCHIATRIC REDUCTIONISM

The holistic (biopsychosocial) approach adopted in psychosomatic medicine implies a multidimentional understanding of psychiatric diseases and the combination of different types of intervention (psychotherapy, pharmacotherapy) to prevent and treat psychiatric morbidity.

In recent years, a new way of integrating pharmacotherapy and psychotherapy in depression has been proposed (i.e. sequential approach) [141], but, not surprisingly, non pharmacological treatment strategies have been swimming against the tide of pharmaceutical propaganda.

In the medical field, the term 'propaganda' generally refers to open and direct pharmaceutical operations (e.g. advertisements, talks by sales representatives and presents). It also has, however, a more subtle and pervasive connotation, related to media control. Noam Chomsky has been instrumental in disclosing such a link. Chomsky [173] analyzed the mechanisms whereby propaganda may un-

fold its potential: filtering information (selective perception), engineering opinion, using the public relations industry and marginalizing dissident cultures.

In his latest essay, Chomsky [174] describes how these mechanisms are operational in the world events following the September 11 tragedy (the Afghanistan war).

In the past 2 decades, clinical medicine has witnessed the emergence of special interest groups [175]. Corporate interests have fused with academic medicine to create an unhealthy alliance that works against objective reporting of clinical research (selective perception), sets up meetings and symposia with the specific purpose of selling the participants to the sponsors (engineering opinions), gets its prodigal experts into leading roles in journals, medical associations and nonprofit research organizations (public relations industry) and provides the appropriate degree of rejection of outliers (marginalization of dissident cultures).

Current trends in prescribing antidepressant drugs provide an excellent example of the risk which clinical medicine faces.

The starting point of this discussion is an issue which became very apparent in the 1990s, i.e. the high rate of relapse following discontinuation of antidepressant drugs in unipolar depression [94]. On the basis of a few controlled trials, long-term use of antidepresssant drugs to avoid relapse was advocated and became a common clinical practice [176]. This led to both extension of the duration of antidepressant drug therapy to the longest possible time for treating the acute episode of depression and suggestion of an indefinite (lifelong) pharmacological prevention of depression. At about the same time, the effectiveness of antidepressant drugs in the short-term treatment of anxiety disorders and the chronicity of many forms of anxiety disturbances paved the way for justification of years of ongoing drug treatment [177].

The availability of antidepressant drugs which are far more tolerable than traditional tricyclics has also led to an extension of their use to forms of depression which do not reach the severity threshold of major depressive disorders and can be subsumed under the rubrics of minor depression and demoralization, despite lack of evidence for their efficacy in these situations [178]. Leading journal articles, symposia and practice guidelines push clinicians toward prescribing antidepressant drugs more and more. This propaganda, with respect to which the taint of conflict of interests has been highlighted recently in a consumer magazine [179], makes the clinician who would retain a cautious and balanced attitude feel like the person whom Chomsky [173] depicts as sitting alone in front of the TV, thinking that he must be crazy or outdated for not buying what comes out of the tube.

a) Long term treatment of depression: research findings neglected by propaganda

The Duration of Drug Treatment Does Not Seem to Affect Long-Term Prognosis once the Drug is Discontinued

There is evidence that casts doubt on the ability of antidepressant drugs to favorably affect the course of depressive illness, despite their recognized ability to treat the depressive episode and to prevent relapse while the patient is taking the drug. Viguera et al [180] analyzed 27 studies with variable lengths of antidepressant treatment which reported follow-up of drug discontinuation. The duration of drug treatment did not seem to affect the long-term prognosis once the drug was discontinued. Whether you treat a depressed patient for 3 months or 3 years, it does not matter when you stop the drug (it does matter, of course, whether patients are on drugs or placebo). Indeed, there was a nonsignificant trend which suggested that the longer the drug treatment, the higher the likelihood of relapse[180]. An observational study of 236 patients with unipolar depression who had received antidepressants during recovery and were followed for an affective recurrence for up to 5 years showed that the rate of recurrence for patients with fewer than five previous episodes was not affected by medication after the initial 8 months[181].

These issues are amplified in the setting of anxiety disorders, where relapse after discontinuation of antidepressant drugs is even more common [182] and joint use of psychotherapy and antidepressants has been found to yield a worse prognosis than psychotherapy alone [183-186].

The Efficacy of Antidepressant Drugs Has Been Overemphasized

A recent analysis of 186 randomized controlled trials comparing amitriptyline with other antidepressant drugs (including selective serotonin reuptake inhibitors; SSRIs) disclosed the clear superiority of amitriptyline in terms of recovery rates [187]. Since amitriptyline is one of the oldest antidepressants, this means that while considerable progress has been made in terms of side effects profile, little (if any) has been made in terms of efficacy. Not surprisingly, the presence of residual symptomatology upon pharmacological treatment has been substantiated in the majority of successfully treated patients [94]. Residual symptoms are among the most powerful predictors of relapse [94], and their abatement by means of cognitive behavioral strategies has been found to improve long-term outcome [188-190]. The findings on residual symptoms of successfully treated depressed patients are reinforced by the very high percentage of patients who do not respond to drug treatment (up to 50%) [191]. The conclusion that can be drawn is that pharmacological treatment of depression does not provide the solution for a substantial proportion of depressive episodes and is likely to leave residual symptomatology.

Loss of Efficacy Occurs during Maintenance Treatment of Depression

The return of depressive symptoms during maintenance antidepressant treatment – which has been found to occur in 9-57% of patients in published trials [192] – is a common, vexing problem. Relapse of depression has also been found to occur during the follow-up of patients receiving tricyclic antidepressants for panic disorder[193]. Some studies point to dispositional (pharmacokinetic) tolerance, which reduces the concentration of a drug or its duration of action[194]. Other studies, however, suggest the likelihood that pharmacodynamic processes change sensitivity to the drug[195]. In particular, the oppositional model of tolerance (continued drug treatment may recruit processes that oppose the initial acute effect of a drug or its receptor modifications) seems to entail a considerable explanatory power[194,196]. In clinical terms, increasing the dosage of the antidepressant drug does not always help, and, when it does, it may yield only temporary relief. Since this is a very touchy area for the pharmaceutical industry, there is insufficient research on these crucial clinical issues.

The Full Meaning of Withdrawal Reactions from Antidepressant Drugs Is Not Appreciated

Withdrawal symptoms following discontinuation of antidepressants were recognized soon after the introduction of these drugs [197]. They have been described with all types of antidepressant drugs, but particularly with SSRIs [198-201]. From a randomized controlled trial [202], we know that not all SSRIs induce a 'discontinuation' syndrome (as the propaganda of special interest groups redefined withdrawal reactions) to the same degree; fluoxetine is less prone to do so than paroxetine or sertraline. What we do not know is what all this really means. Are withdrawal phenomena simply bothersome and self-limiting reactions or are they a sign of something else? As Grahame-Smith [203] has aptly stated: 'Chronic drug therapy may induce a sleeping tiger, which awakens when the drug therapy is stopped and results in rebound withdrawal effects with serious consequences, as with many drug addictions' [p. 227]. But what is this 'sleeping tiger'? The inverse relationship between the duration of maintenance antidepressant treatment and the time to recurrence off treatment [180] raises concern about the induction of a vicious circle. It in fact suggests the possibility of an addiction model whose most immediate clinical manifestations are withdrawal symptoms [200]. According to a sensitization hypothesis [194], antidepressant drugs may facilitate relapse once they are discontinued and worsen illness outcome. The possibility that antidepressant drugs may induce acceleration of episodes has not been adequately studied in unipolar depression, but it is widely recognized in bipolar disorder [194]. Goodwin [204] has illustrated how this could occur. If both depressive and manic episodes tend naturally to evolve toward remission (either into a euthy-

mic phase or into an episode of opposite polarity), and if antidepressant drugs accelerate this natural tendency, drug treatment may accelerate the next sequence in the natural course (i.e. the onset of a manic episode instead of euthymia). Goodwin [204] stated it thus: 'If the natural sequence of recurrent unipolar illness goes from depression to recovery and then eventually to the next episode, treatments that accelerate recovery of the index depression could also accelerate the onset of the next episode' [p. 43].

These clinical phenomena (withdrawal and sensitization) may also apply to the long-term use of antidepressant drugs in anxiety disorders [182,205].

Nonpharmacological Prevention Strategies Are Neglected

It is ironic that while psychiatrists view prevention of relapse of depression purely in pharmacological terms as if it were a disease such as diabetes [176], diabetologists emphasize the importance of nonpharmacological strategies (lifestyle modification) in the prevention of type 2 diabetes mellitus [206]. This is a perfect exemplification of a phenomenon described by Lipowski [207] in the late 1980s: '… after a period marked by one-sided emphasis on psychodynamics and social issues, or what could be called "brainless" psychiatry on account of its relative neglect of cerebral processes, we are witnessing an opposite trend towards extreme biologism or "mindless" psychiatry' [p. 244].

Yet, there is now extensive evidence for the role of cognitive behavioral psychotherapy in the prevention of relapse in unipolar depression [188-190,208-211].

Ryff and Singer [70] remark that mental health research is dramatically weighted on the side of psychological dysfunction and that health is equated to the absence of illness rather than to the presence of wellness. They suggest that the absence of well-being creates conditions of vulnerability to possible future adversities and that the route to recovery does not lie exclusively in alleviating the negative, but also in engendering the positive. In depression research, little attention is paid to the balance between positive and negative affects [212] and to the promotion of psychological well-being [188]. Similarly, lifestyle modification, which is widely practiced for the prevention of relapse in myocardial infarction [213], is not even considered in clinical psychiatry, despite the fact that depressed patients are often unaware of the long-term consequences of a maladaptive lifestyle which does not take chronic stress, interpersonal friction and excessive and inadequate rest into consideration [188].

THE GREAT ACHIEVEMENTS OF PROPAGANDA

Antidepressant drugs were developed and found to be effective in the treatment of the major depressive episode [214]. In recent years, however,

their use has been prolonged and extended to maintenance and prevention, with apparently reassuring results in comparison with placebo [215]. However, treatments that are effective in the acute phase of illness are not necessarily the most suitable for postacute and residual phases or maintenance [71].

If we are able to remove the conceptual obstacles that obstruct our view [216] and silence the sound of propaganda, we may then become aware of a different scenario.

We are stretching the original indications (major depressive episodes) of drugs of modest efficacy to include prevention of relapse, anxiety disorders and demoralization. Patients do not suddenly become well, but tend to gradually lose their depressive symptoms over the months following treatment [217]. Stassen et al. [218] found that the time course of improvement among responders to amitriptyline, oxaprotiline and placebo was independent of the treatment modality and thus identical in the three groups. Once triggered, the time course of recovery from illness became identical to the spontaneous remission under placebo. Antidepressant drugs, therefore, may not change the pattern of the natural course of recovery from depressive illness, but simply speed the recovery and change the boundary between 'responders' and 'nonresponders' [218]. When we prolong treatment over 6-9 months, we may thus recruit different phenomena, such as tolerance, episode acceleration, sensitization and paradoxical effects[194]. Antidepressant drugs may still be superior to placebo, but their hidden costs may far outweigh their apparent gains.

A series of excellent studies by a research group in Seattle is illustrative of this unfair trade. Three hundred and eighty-six patients with recurrent major depression or dysthymia who had recovered after 8 weeks of antidepressant treatment prescribed by their primary care physicians were randomized to a relapse prevention program (based on pharmacological treatment) or standard primary care [219]. There were no significant differences in episodes of relapse. However, patients in the intervention group were significantly more likely to refill medication prescriptions over the 12-month follow-up. In another study [220], there were no substantial differences between depressive patients treated by psychiatrists and those treated by primary care physicians. A third investigation [221] disclosed significant differences between an intervention arm (based on the use of paroxetine) and a standard – care arm in panic disorder, particularly in the first 6 months. We wonder, however, what would happen subsequently, if patients tried to discontinue paroxetine. Even if they were treated with an approach entailing enduring effects (cognitive behavioral therapy), their course would be less favorable than if paroxetine had not been used at all [183-186].

Carroll [222] anticipated the effects of inappropriate trends in the pre-

scribing of antidepressant drugs 2 decades ago, in the following statement: '... we strongly suspect that many patients who are simply unhappy or dysphoric receive these drugs, with predictable consequences in terms of mortality from overdose, economic waste and irrational, unproductive clinical management'.

AN ALTERNATIVE APPROACH

In recent years, a new way of integrating pharmacotherapy and psychotherapy in depression has been proposed, i.e. the sequential approach [141]. According to this model, which has been validated in randomized controlled trials in unipolar depression [188-190, 209] and in a pilot investigation in bipolar disorder [223], pharmacotherapy is used in the acute phase of depression and cognitive behavioral psychotherapy in the residual phase. Its preventive effects appeared to be related to the abatement of residual symptoms and / or an increase in psychological well-being and coping skills.

The practical steps for implementing this approach are described in Table 5 and detailed elsewhere [224]. It may include discontinuation of antidepressant drug treatment, as outlined here, or its maintenance. It may offer the advantage of yielding enduring effects while limiting the exposure to drug therapy.

As to anxiety disorders, effective cognitive behavioral strategies have been developed which are likely to entail long-lasting effects [182-186]. These therapies challenge the routine use of antidepressant drugs, unless specific clinical situations occur, such as depression comorbidity.

Not surprisingly, advocates of nonpharmacological treatment strategies are swimming against the tide of pharmaceutical propaganda. Those who are involved in mental health (both as care providers and consumers), however, should be aware that life after antidepressant drugs does exist and that it may be far more gratifying for both. Psychiatrists, in particular, may rediscover the spectacular achievements of competent treatment and the joy of intellectual freedom.

Table 5 - **Steps for implementing the sequential approach in recurrent depression**

1. Careful assessment of patient 3 months after antidepressant drug treatment, with both observer-rated instruments (with special reference to anxiety and irritability) and self-observation (diary)
2. Cognitive behavioral treatment of residual symptoms (cognitive restructuring and / or homework exposure), if present
3. Tapering of antidepressant drug treatment at the slowest possible pace (such as 25mg of tricyclic every other week)
4. Well-being enhancing therapy (well--being therapy) and lifestyle modification
5. Antidepressant drugs discontinuation
6. Careful assessment of patient 1 month after drug discontinuation

CONCLUSIONS

These considerations make psychosomatic medicine alive and well in at the beginning of the new century. Its role is as important in psychiatric as it is in clinical medicine.

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BIBLIOGRAPHY

1. Halliday JL. The significance of the concept of a psychosomatic affection. *Psychosom Med* 1945; 7: 240-245.
2. Fava GA. The concept of psychosomatic disorder. *Psychother Psychosom* 1992; 58: 1-12.
3. Kissen DM. The significance of syndrome shift and late syndrome association in psychosomatic medicine. *J Nerv ment Dis* 1963; 136: 34-42.
4. Lipowski ZJ. Physical illness and psychopathology. *Int J Psychiat Med* 1974; 5: 483-497.
5. Fava GA. Lipowski's legacy: the psychosomatic spirit. *Psychother Psychosom* 1999; 68: 1-2.
6. Lipowski ZJ. Psychosomatic medicine in the seventies: an overview. *Am J Psychiatry* 1977; 134: 233-244.
7. Engel GL. The concept of psychosomatic disorder. *J Psychosom Res* 1967; 11: 3-9.
8. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science* 1977; 196: 129-136.
9. Anderson NB, Armstead CA. Toward understanding the association of socioeconomic status and health. *Psychosom Med* 1995; 57: 213-225.
10. Landrigan PJ. Environmental disease: a preventable epidemic. *Am J Public Health* 1992; 82: 941-943.
11. Sternberg EM. Emotions and disease: from balance of humors to balance of molecules. *Nature Medicine* 1997; 3: 264-267.
12. Solomon GF. Whither psychoneuroimmunology? A new era of immunology, of psychosomatic medicine, and of neuroscience. *Brain Behav Immunity* 1993; 7: 352-366.
13. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet* 1995; 354: 99-103.
14. Sonino N, Fava GA. Psychological aspects of endocrine disease. *Clin Endocrinol* 1998; 49: 1-7.
15. Lipowski ZJ. Psychosomatic medicine: past and present. *Can J Psychiatry* 1986; 31:2-21.
16. Halliday JL. *Psychosocial medicine. A study of the sick society*. London; Heinemann, 1948.
17. Paykel ES. *Methodology of life events research.* In Fava GA, Wise TN, eds. Research paradigms in psychosomatic medicine. Basel: Karger, 1987: 13-29.
18. Winsa B, Adami HO, Bergstrom R, Gamstedt A, Dahlberg PA, Adamson U, Jansson R, Kalsson A. Stressful life events and Graves' disease. *Lancet* 1991; 338: 1475-1479.
19. Sonino N, Girelli ME, Boscaro M, Fallo F, Busnardo B, Fava GA. Life events in the pathogenesis of Graves' disease. A controlled study. *Acta Endocrinol* 1993; 128: 293-296.
20. Kung AWC. Life events, daily stresses and coping in patients with Graves' disease. *Clin Endocrinol* 1995; 42: 303--308.

21. Radosavljevic VR, Jakovic SM, Marinkovic JM. Stressful life events in the pathogenesis of Graves' disease. *Eur J Endocrinology* 1996; 134: 699-701.
22. Sonino N, Fava GA, Boscaro M. A role for life events in the pathogenesis of Cushing's disease. *Clin Endocrinol* 1993; 38: 261-264.
23. Chrousos GP, Gold PW. The concept of stress and stress system disorders . *JAMA* 1992; 267: 1244-1252.
24. Reichlin S. Neuroendocrine-immune interactions. *N Engl J Med* 1993; 329: 1246-1253.
25. Schmidt-Ott G, Jacobs R, Jager B, Klages S, Wolf J, Werfel T, Kapp A, Schurmeyer T, Lamprecht F, Schmidt RE, Schedlowski M. Stress-induced endocrine and immunological changes in psoriasis patients and healthy controls. *Psychother Psychosom* 1998; 67: 37-42.
26. Biondi M. Zannino LG. Psychological stress, neuroimmunomodulation, and susceptibility to infectious diseases in animals and man. *Psychother Psychosom* 1997; 66: 3-26.
27. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* 1993; 153: 2093-2101.
28. Hubbard JR, Workman EA (eds). *Handbook of stress medicine*. Boca Raton: CRC Press, 1998.
29. Sonino N, Fava GA, Boscaro M, Fallo F. Life events and neurocirculatory asthenia. A controlled study. *J Intern Med* 1998; 244: 523-528.
30. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 99: 2192-2217.
31. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma. *Thorax* 1998; 53: 1066-1074.
32. Wagner BM. Major and daily stress and psychopathology. *Stress Med* 1990; 6: 217-226.
33. De Jong GM, Van Sonderen E, Emmelkamp PMG. A comprehensive model of stress. *Psychother Psychosom* 1999; 68: 290-298.
34. Berckman LF. The role of social relations in health promotion. *Psychosom Med* 1995; 57: 245-254.
35. Scheier MF, Bridges MW. Person variables and health. *Psychosom Med* 1995; 57: 255-268.
36. Cassel J. The contribution of the social environment to host resistance. *Am J Epidemiol* 1976; 104: 107-123.
37. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998; 338: 171-179.
38. Kelly S, Hertzman C, Daniels M: Searching for the biological pathways between stress and health. *Annu Rev Public Health* 1997; 18: 437-462.
39. Biondi M, Picardi A: Psychosocial stress and neuroendocrine function in humans: the last two decades of research. *Psychother Psychosom* 1999; 68: 114-150.
40. Jonsson BH, Theorell T: Low plasma prolactin levels in patients with functional dyspepsia. *Psychother Psychosom* 1999; 68: 151-156.
41. Christodoulou GN, Dragonas TG. *Role of early development factors in susceptibility to disease*. In Fava GA, Freyberger H, eds. Handbook of psychosomatic medicine. Madison, CT: International Universities Press, 1998: 191-203.
42. Hofer M. Animal models in the understanding of human disease. *Psychiat Clin N Am* 1979; 2: 211-226.
43. Williams RB: The role of psychosocial factors in human disease: lessons from animal models. *Acta Physiol Scand* 1997; Suppl. 640: 100-102.
44. Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factors (CRF)

in RNA, median eminence CRF content and stress-induced release in adult rats. *Mol Brain Res* 1993; 18: 195-200.

45. Heim C, Owens MJ, Plotsky PM, Nemeroff CB. Persistent changes in corticotropin-releasing factor systems due to early life stress. *Psychopharmacol Bull* 1997; 33: 185-192
46. Sonino N, Fava GA. Psychosomatic aspects of Cushing's disease. *Psychother Psychosom* 1998; 67: 140-146.
47. Sobrinho L. Emotional aspects of hyperprolactinemia. *Psychother Psychosom* 1998; 67: 133-139.
48. McCauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, De Chant HK, Ryden J, Derogatis LR, Bass EB. Clinical characteristics of women with a history of childhood abuse. *JAMA* 1997; 277: 1362-1368.
49. Engel GL. Psychogenic pain and the pain prone patient. *Am J Med* 1959; 26: 899-918.
50. Salmon P, Calderbank S. The relationship of childhood physical and sexual abuse to adult illness behavior. *J Psychosom Res* 1996; 40: 329-336.
51. Fava GA, Freyberger HJ, Bech P, Christodoulou G, Sensky T, Theorell T, Wise TN. Diagnostic criteria for use in psychosomatic research. *Psychother Psychosom* 1995; 63:1-8.
52. Littman AB. Review of psychosomatic aspects of cardiovascular disease. *Psychother Psychosom* 1993; 60: 148-167.
53. Coelho R, Ramos E, Prata J, Barros H. Psychosocial indexes and cardiovascular risk factors in a community sample. *Psychother Psychosom* 2000; 69: 261-274.
54. Hemingway H, Marmot M: Psychosocial factors in the etiology and prognosis of coronary heart disease. *BMJ* 1999; 318: 1460-1467.
55. Taylor GJ, Bagby RM, Parker JDA. *Disorders of affect regulation*. Cambridge: Cambridge University Press, 1997.
56. Sifneos PE. The prevalence of alexithymic characteristics in psychosomatic patients. *Psychother Psychosom* 1973; 22: 255-262.
57. Greer J. Cancer and the mind. *Br J Psychiatry* 1983; 143: 535-543.
58. Berry DS, Pennabaker JW. *Non verbal and emotional expression and health.* In Fava GA, Freyberger H, eds. Handbook of psychosomatic medicine. Madison, CT: International Universities Press, 1998: 69-84.
59. Greer S, Morris T. Psychological attributes of women who develop breast cancer. A controlled study. *J Psychosom Res* 1975; 19: 147-153.
60. Weiner H. Specificity and specification: two continuing problems in psychosomatic research. *Psychosom Med* 1992; 54: 567-587.
61. Pettingale KW. Coping and cancer prognosis. *J Psychosom Res* 1984; 28: 363-364.
62. Bernard B, Vorst HCM, Vingerhoets AJJM, Gerritsen W: The Amsterdam alexithymia scale. *Psychother Psychosom* 1999; 68: 241-251.
63. Naatanen P, Ryynanen A, Keltikangas-Jarvinen L. The influence of alexithymic characteristics on the self-perception and facial expression of a physiological stress state. *Psychother Psychosom* 1999; 68: 252-262.
64. Honkolampi K, Saarinen P, Hintikka J, Virtanene V, Viinamaki H: Factors associated with alexithymia in patients suffering from depression. *Psychother Psychosom* 1999; 68: 270-275.
65. Iancu I, Horesh N, Offer D, Dannon PN, Lepkifker E, Kotler M: Alexithymia, affect intensity and emotional range in suicidal patients. *Psychother Psychosom* 1999; 68: 276-280.
66. Berenbaum H, Davis R, McGrew J. Alexithymia and the interpretation of hostile-provoking situations. *Psychother Psychosom* 1999; 67: 254-258, 1998.
67. Verissimo R, Mota Cardoso R, Taylor

G. Relationships between alexithymia, emotional control, and quality in life in patients with inflammatory bowel disease. *Psychother Psychosom* 1998; 67: 75-80.

68. Kooiman CG, Spinhoven P, Trujsburg RW, Roojmans HGM. Perceived parental attitude, alexithymia and defense style in psychiatric outpatients. *Psychother Psychosom* 1998; 67: 81-87.
69. World Health Organization. *World Health Organization constitution*. Geneva: World Health Organization, 1948: 28.
70. Ryff CD, Singer B. Psychological well--being. *Psychother Psychosom* 1996; 65: 14-23.
71. Fava GA. The concept of recovery in affective disorders. *Psychother Psychosom* 1996; 65: 2-13.
72. Ryff CD, Singer B. The contours of positive human health. *Psychol Inquiry* 1998; 9: 1-28.
73. Spiegel D, Kraemen HC, Bloom T, Gottheil E. Effect of a psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989; ii: 888-891.
74. Ramirez AJ, Craig TKJ, Watson JP, Fentiman IS, North WR, Rubens RD. Stress and relapse of breast cancer. *BMJ* 1989; 298: 291-294.
75. Stilley CS, Miller DJ, Manzetti JD, Marino IR, Keenan RJ. Optimism and coping styles. *Psychother Psychosom* 1999; 68: 299-303.
76. Heszen-Niejodek I, Gottschalk LA, Januszek M: Anxiety and hope during the course of three different medical illnesses. *Psychother Psychosom* 1999; 68: 304-312.
77. Majani G, Pierobon A, Giardini A, Callegari S, Opasich C, Cobelli F, Tavazzi L. Relationship between psychological profile and cardiological variables in chronic heart failure. *Eur Heart J* 1999; 20: 1579-1586.
78. Ryff CD, Singer BH. Biopsychosocial challenges of the new millenium. *Psychother Psychosom* 2000; 69: 170-177.
79. Steptoe A, Wardle J. Cognitive predictors of health behavior in contrasting regions of Europe. *Br J Clin Psychol* 1992; 31: 485-502.
80. Jenkins CD. New horizons in psychosomatic medicine. *Psychosom Med* 1985; 47: 3-25.
81. Lipowski ZJ. *Physical illness, the patient and his environment*. In Reiser MF, ed. American Handbook of Psychiatry, vol 4. New York: Basic Books, 1975: 3-42.
82. Lishman WA. *Organic Psychiatry. The psychological consequences of cerebral disorders*. Oxford: Blackwell, 1998.
83. Lipowski ZJ. A new look at organic brain syndromes. *Am J Psychiatry* 1980; 137: 674-678.
84. Fava GA, Sonino N. Depression associated with medical illness. *CNS Drugs* 1996; 5: 175-189.
85. Robertson MM, Katona CLE, eds. *Depression and physical illness*. Chichester; Wiley, 1997.
86. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease. *Arch Gen Psychiatry* 1998; 55: 580-592.
87. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is a risk factor for coronary artery disease in men. *Arch Intern Med* 1998; 158: 1422-1426.
88. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction. *Psychosom Med* 1996; 58: 99-110.
89. Sonino N, Fava GA, Raffi AR, Boscaro M, Fallo F. Clinical correlates of major depression in Cushing's disease. *Psychopathology* 1998; 31: 302-306.
90. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M. Risk factors and long-term outcome in pituitary-dependent Cushing's disease. *J Clin Endo-crinol Metab* 1996; 81: 2647-2652

91. Kellner R. Psychosomatic syndromes, somatization and somatoform disorders. *Psychother Psychosom* 1994; 61: 4-24.
92. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-IV)*. Washington, DC: American Psychiatric Association, 1994.
93. Judd LL. Subsyndromal symptomatic depression. *CNS Drugs* 1994; 1: 399-404.
94. Fava GA. Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. *Psychol Med* 1999; 29: 47-61.
95. Fava GA. Irritable mood and physical illness. *Stress Med* 1987; 3: 293-299.
96. Fava GA, Mangelli L: Subclinical symptoms of panic disorder. *Psychother Psychosom* 1999; 68: 281-289.
97. Manuck SB, Marsland Al, Kaplan JR, Williams JK. The pathogenicity of behavior and its neuroendocrine mediation: an example from coronary heart disease. *Psychosom Med* 1995; 57: 275-283.
98. Jalkanen J, Salonen R, Kaplan GA, Chesney MA, Salonen JT. Hostility and the progression of carotid atherosclerosis. *Psychosom Med* 1994; 56: 519-525.
99. Fava M, Rosenbaum JF, McCarthy M, Pava J, Steingard R, Bless E. Anger attacks in depressed outpatients and their response to fluoxetine. *Psychopharmacol Bull* 1991; 27: 275-279.
100. Williams RB. Neurobiology, cellular and molecular biology, and psychosomatic medicine. *Psychosom Med* 1994; 56: 308-315.
101. Schmale AH. *Giving up as a final common pathway in changes in health*. In Lipowski ZJ, ed. Psychosocial aspects of physical illness. Basel: Karger 1972; 20-40.
102. Bech P. Measurement of psychological distress and well-being. *Psychother Psychosom* 1990; 54: 77-89.
103. Appels A. Mental precursors of myocardial infarction. *Br J Psychiatry* 1990; 156: 465-471.
104. Porcelli P, De Carne M, Fava GA: Assessing somatization in functional gastrointestinal disorders. Integration of different criteria. *Psychother Psychosom* 2000; 69: 198-204.
105. Bjorntorp P. The android woman. A risky condition. *J Intern Med* 1996; 239: 105-110.
106. Mechanic D, Volkart EH. Illness behavior and medical diagnosis. *J Health Hum Behav* 1980; 1: 86-94.
107. Kellner R. *Somatization and hypochondriasis*. New York: Praeger, 1986.
108. Pilowsky I. *Abnormal illness behavior*. Chichester: Wiley, 1997.
109. Goldbeck R: Denial in physical ill-ness. *J Psychosom Res* 1997; 43: 575-593.
110. Muskin PR, Feldhammer T, Golfand JL, Strauss DH: Maladaptive denial of physical illness: a useful new dia-gnosis. *Int J Psychiat Med* 1998; 20: 463-477.
111. Blackwell B. Compliance. In Fava GA, Freyberger H, eds. *Handbook of psychosomatic medicine*. Madison, CT: International Universities Press, 1998: 625-638.
112. Emdad R, Belkic K, Theorell T, Cizinsky S. What prevents professional drivers from following physicians' cardiologic advice? *Psychother Psychosom* 1998; 67: 226-240.
113. Buchi S, Sensky T, Sharpe L, Timberlake N. Graphic representation of illnes: a novel method of measuring patients' perceptions of the impact of illness. *Psychother Psychosom* 1998; 67: 222-225.
114. Schnyder U, Buchi S, Morgeli H, Sensky T, Klaghofer R. Sense of coherence. A mediator between disability and handicap? *Psychother Psychosom* 1999; 68: 102-110.
115. Muldoon MF, Barger SD, Flory JD, Manuck SB. What are quality of life

measurements measuring? *BMJ* 1998; 316: 542-545.
116. Leplege A, Hunt S. The problem of quality of life in medicine. *JAMA* 1997; 278: 47-50.
117. Viemero V, Krause C. Quality of life in individuals with physical disabilities. *Psychother Psychosom* 1998; 67: 317-322.
118. Burman P, Deijen JB. Quality of life and cognitive function in patients with pituitary insufficiency. *Psychother Psychosom* 1998; 67: 154-167.
119. Lipowski ZJ. Psychosocial aspects of disease. *Ann Intern Med* 1969; 71: 1197-1296.
120. Fava GA. Methodological and conceptual issues in research on quality of life. *Psychother Psychosom* 1990; 54: 70-76.
121. Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. *JAMA* 1994; 272: 619-626.
122. Shore JH. Psychiatry at a crossroad: our role in primary care. *Am J Psychiatry* 1996; 11: 1398-1403.
123. Fava GA. Medical-psychiatric service. *Psychother Psychosom* 1987; 48: 96-100.
124. Theorell T. Critical life changes. *Psychother Psychosom* 1992; 57: 108-117.
125. Compas BE, Haagon DA, Keefe FJ, Leitenberg H, Williams DA. Sampling of empirically supported psychological treatments from health psychology: smoking, chronic pain, cancer, and bulimia nervosa. *J Consult Clin Psychol* 1998; 66: 89-112.
126. Mayou R, Smith EOP. Hospital doctors' management of psychological problems. *Br J Psychiatry* 1986; 148: 194-197.
127. O'Malley PG, Jackson JL, Kroenke K, Yoon IK, Hornstein E, Dennis GJ. The value of screening for psychiatric disorders in rheumatology referrals. *Arch Intern Med* 1998; 158: 2357-2362.
128. Emmelkamp PMG, Van Oppen P. Cognitive interventions in behavio-ral medicine. *Psychother Psychosom* 1993; 59: 116-130.
129. Cottraux J. Behavioral psychotherapy applications in the medically ill. *Psychother Psychosom* 1993; 60: 116-128.
130. Covino NA, Frankel FH. Hypnosis and relaxation in the medically ill. *Psychother Psychosom* 1993; 60: 75-90.
131. Blanchard EB. *Behavioral medicine and health psychology*. In Bergin AE, Garfield JL, eds. Handbook of psychotherapy and behavior change. New York: Wiley, 1994: 701-733.
132. Smyth JM, Stone AA, Hurewitz A, Kaell A. Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis. *JAMA* 1999; 281: 1304-1309.
133. Frank JD, Frank B. *Persuasion and healing*. Baltimore: The Johns Hopkins University Press, 1991.
134. Fava GA. *Cognitive-behavioral therapy*. In Fink M, ed. Encyclopedia of stress. San Diego: Academic Press (in press).
135. Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patients. *N Engl J Med* 1964; 270: 825-827.
136. Mirò J, Raich RM. Preoperative preparation for surgery: an analysis of the effects of relaxation and information provision. *Clin Psychol Psychother* 1999; 6: 202-209.
137. Marks I. Is a paradigm shift occurring in brief psychological treatments? *Psychother Psychosom* 1999; 68: 169-170.
138. Astin JA, Shapiro SL, Lee RA, Shapiro DH. The construct of control in mind--body medicine: implications for health care. *Altern Ther Health Med* 1999; 5: 42-47.
139. Fava GA, Rafanelli C, Cazzaro M, Conti S, Grandi S. Well-being therapy. *Psychol Med* 1998; 28: 475-480.
140. Fava GA. Well-being therapy. Conceptual and technical issues. *Psychother*

Psychosom 1999; 68: 171-179.
141. Fava GA. Sequential treatment: A new way of integrating pharmachotherapy and psychotherapy. *Psychother Psychosom* 1999; 68: 227-229.
142. Fava GA. The definition, diagnosis and clinical relevance of somatoform disorders. *Rev Contemp Pharmacother* 1996; 7: 269-277.
143. Kroenke K, Swindle R: Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. *Psychother Psychosom* 2000; 69: 205-215.
144. Warwick HM, Clark DM, Cobb AM, Salkovskis PM. A controlled trial of cognitive-behavioral treatment of hypochondriasis. *Br J Psychiatry* 1996; 169: 189-195.
145. Avia MD, Ruiz MA, Olivares ME, Crespo M, Guisado AB, Sanchez A, Varela A. The meaning of psychological symptoms. *Behav Res Ther* 1996; 34: 23-31.
146. Bouman TK, Visser S. Cognitive and behavioral treatment of hypochondriasis. *Psychother Psychosom* 1998; 67: 214-221.
147. Clark DM, Salkovskis PM, Hackmann A, Wells A, Fennel M, Ludgate J, Ahmad S, Richards HC, Gelder M. Two psychological treatments for hypochondriasis. *Br J Psychiatry* 1998; 173: 218-225.
148. Fava GA, Grandi S, Rafanelli C, Fabbri S, Cazzaro M. Explanatory therapy of hypochondriasis. *J Clin Psychiatry* 2000; 61: 317-322.
149. Fava GA, Grandi S. Differential diagnosis of hypochondriacal fears and beliefs. *Psychother Psychosom* 1991; 55:114-119.
150. Shader RI, Weinberger DR, Greenblatt DJ. *Psychopharmacological approaches to the medically ill patient*. In Karasu TB, Steinmuller RI, eds. Psychotherapeutics in medicine. New York: Grune and Stratton, 1978: 117-155.
151. Silver PA, ed. *Psychotropic drug use in the medically ill*. Basel: Karger, 1994.
152. Ananth J. *Psychopharmacological agents in physical disorders*. In Fava GA, Freyberger H, eds. Handbook of psychosomatic medicine. Madison, CT: International Universities Press, 1998: 593-624.
153. Lechin F, van der Dijs B, Lechin ME. Plasma neurotransmitters and functional illness. *Psychother Psychosom* 1997; 65: 293-318.
154. Holsboer F. The rationale for corticotropin-releasing-hormone receptor (CRH-R) antagonists to treat depression and anxiety. *J Psychiat Res* 1999; 33: 181-214.
155. Kellner R. *Somatization: the most costly comorbidity?* In Maser JD, Cloninger CR, eds. Comorbidity of mood and anxiety disorders. American Psychiatric Press, 1990: 239-252.
156. Katon WJ, Walker EA: Medically unexplained symptoms in primary care. *J Clin Psychiatry* 1998; 59 (suppl. 20): 15-21.
157. Kroenke K, Mangelsdorff D. Common symptoms in ambulatory care. *Am J Med* 1989; 86: 262-268.
158. Randall JL. Evolution of the new paradigm. *Primary Care* 1996; 23: 183-198.
159. Pert CB, Drehert HE, Ruff MR. The psychosomatic network: foundations of mind-body medicine. *Alternat Ther Health Med* 1998; 4: 30-41.
160. Dossey L. A journal and a journey. *Alternat Ther Health Med* 1995; 1: 6-9.
161. Galland L. *The four pillars of healing*. New York: Random House, 1997.
162. Gordon JS. *Manifesto for a new medicine*. Reading, MA: Addison-Wesley, 1996.
163. Weil A. *Spontaneous healing*. New York, Fawcett-Columbine, 1995.
164. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kesler RC. Trends in alternative me-

dicine use in the United States, 1990--1997. *JAMA* 1998; 280: 1569-1575.
165. Astin JA, Marie A, Pelletier KR, Hansen U, Haskell WL. A review of the incorporation of complementary and alternative medicine by mainstream physicians. *Arch Intern Med* 1998; 158: 2303-2310.
166. Given BA, Given CW. Health promotion for family caregivers of chronically ill elders. *Annu Rev Nursing Res* 1998; 16: 197-217.
167. Weitzner MA, Knutzen R. The impact of pituitary disease on the family caregivers and the overall family functioning. *Psychother Psychosom* 1998; 67: 181-188.
168. Lopez Castillo J, Gurpegni M, Ayuso--Mateos JL, Lunn JD, Catalan J. Emotional distress and occupational burnout in health care professionals serving HIV-infected patients. *Psychother Psychosom* 1999; 68: 248-256
169. Thomsen S, Soares J, Nolan P, Dallender J, Arnetz B. Feelings of professional fulfillment and exhaustion in mental health personnel. *Psychother Psychosom* 1999; 68: 157-164.
170. Breslow L. From disease prevention to health promotion. *JAMA* 1999; 281: 1030-1033.
171. Wittkower ED. Historical perspective of contemporary psychosomatic medicine. *Int J Psychiat Med* 1974; 5: 309-319.
172. Engel GL. How much longer must medicine's science be bound by a seventeenth century world view? *Psychother Psychosom* 1992; 57: 3-16.
173. Chomsky N. *Media Control: The Spectacular Achievements of Propaganda*. New York, Seven Stories, 1997
174. Chomsky N. 9-11. New York, Seven Stories, 2001.
175. Fava GA. Conflict of interest and special interest groups. The making of a counter culture. *Psychother Psychosom* 2001; 70: 1-5.
176. Andrews G. Should depression be managed as a chronic disease? *BMJ* 2001; 322: 419-421.
177. Practice guideline for the treatment of patients with panic disorder. Work Group on Panic Disorder. American Psychiatric Association. *Am J Psychiatry* 1998; 155 (5 suppl): 1-34.
178. Meek C. Fraud and misconduct in medical research. *Health Which*, December 2001; 21-24.
179. Paykel ES, Hollyman JA, Freeling P, Sedgwick P. Predictors of therapeutic benefit from amitriptyline in mild depression: A general practice placebo-controlled trial. *J Affect Disord* 1988; 14: 83-95
180. Viguera AC, Baldessarini RJ, Friedberg J. Discontinuing antidepressant treatment in major depression. *Harv Rev Psychiatry* 1998; 5: 293-306.
181. Dawson R, Lavori PW, Coryell WH, Endicott J, Keller MB: Maintenance strategies for unipolar depression: An observational study of levels of treatment and recurrence. *J Affect Disord* 1998; 49: 31-44.
182. Marks IM. Behavioural and drug treatments of phobic and obsessive--compulsive disorders. *Psychother Psychosom* 1986; 46: 35-44.
183. Brown TA, Barlow DH. Long-term outcome in cognitive-behavioral treatment of panic disorder: Clinical predictors and alternative strategies for assessment. *J Consult Clin Psychol* 1995; 63: 754-765.
184. Otto MW, Pollack MH, Sabatino SA. Maintenance of remission following cognitive behavior therapy for panic disorder. *Behav Ther* 1996; 27: 473-482.
185. Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. *JAMA* 2000; 283: 2529-2536

186. Fava GA, Rafanelli C, Grandi S, Conti S, Ruini C, Mangelli L, Belluardo P. Long-term outcome of panic disorder with agoraphobia treated by exposure. *Psychol Med* 2001; 31: 891-898.
187. Barbui C, Hotopf M. Amitriptyline v. the rest: Still the leading antidepressant after 40 years of randomised controlled trials. *Br J Psychiatry* 2001; 178: 129-144.
188. Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P. Prevention of recurrent depression with cognitive behavioral therapy: Preliminary findings. *Arch Gen Psychiatry* 1998; 55: 816-820.
189. Fava GA, Rafanelli C, Grandi S, Canestrari R, Morphy MA. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry* 1998; 155: 1443-1445.
190. Paykel ES, Scott J, Teasdale JD, Johnson AL, Garlan A, Moore R, Jenaway A, Cornwall PL, Hayhurst H, Abbot R, Pope M: Prevention of relapse in residual depression by cognitive therapy. *Arch Gen Psychiatry* 1999; 56: 829-835.
191. Fava M, Kendler KS. Major depressive disorder. *Neuron* 2000; 28: 335-341.
192. Byrne SE, Rothschild AJ. Loss of antidepressant efficacy during maintenance therapy: Possible mechanisms and treatments. *J Clin Psychiatry* 1998; 59: 279-288.
193. Noyes R Jr, Garvey MJ, Cook BL. Follow-up study of patients with panic disorder and agoraphobia with panic attacks treated with tricyclic antidepressants. *J Affect Disord* 1989; 16: 249-257.
194. Fava GA. Potential sensitising effects of antidepressant drugs on depression. *CNS Drugs* 1999; 12: 247-256.
195. Baldessarini RJ. Risks and implications of interrupting maintenance psychotropic drug therapy. *Psychother Psychosom* 1995; 63: 137-141.
196. Sonino N, Fava GA. CNS drugs in Cushing's disease. Pathophysiological and therapeutic implications for mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry*, in press.
197. Kramer JC, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. *Am J Psychiatry* 1961; 118: 549-550.
198. Oliver JS, Burrows GD, Norman TR. Discontinuation syndromes with selective serotonine reuptake inhibitors. *CNS Drugs* 1999; 12: 171-177.
199. Medawar C. The antidepressant web. *Int J Risk Saf Med* 1997; 10: 75-126.
200. Fava GA, Tomba E. The use of antidepressant drugs: Some reasons for concern. *Int J Risk Saf Med* 1998; 11: 271-275.
201. Shoenberger D. Discontinuing paroxetine: A personal account. *Psychother Psychosom* 2002; 71: 237-238.
202. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. *Biol Psychiatry* 1998; 44: 77-87.
203. Grahame-Smith DG. The Lilly Prize Lecture. 1996. 'Keep on taking the tablets': Pharmacological adaptation during long-term drug therapy. *Br J Clin Pharmacol* 1997; 44: 227-238.
204. Goodwin FK. The biology of recurrence: New directions for the pharmacologic bridge. *J Clin Psychiatry* 1989; 50 (suppl 4): 40-47.
205. Ruini C, Fava GA. Panic and depression. *Am J Psychiatry* 2002; 159: 681.
206. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. Finnish Dia-

betes Prevention Study Group. *N Engl J Med* 2001;344:1343-1350.
207. Lipowski ZJ. Psychiatry: Mindless or brainless, both or neither? *Can J Psychiatry* 1989;34:249-254.
208. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out--patients with recurrent depression. *Br J Psychiatry* 1997;171:328-334.
209. Teasdale JD, Segal ZV, Williams JMG, Ridgeway VA, Soulsby JM, Lan MA. Prevention of relapse / recurrence in major depression by mindfulness--based cognitive therapy. *J Consult Clin Psychol* 2000; 68: 615-623
210. Jarrett RB, Kraft D, Doyle J, Foster BM, Eaves GG, Silver PC. Preventing recurrent depression using cognitive therapy with and without a continuation phase: A randomized clinical trial. *Arch Gen Psychiatry* 2001; 58: 381-388.
211. Jarrett RB, Kraft D, Schaffer M, Witt-Browder A, Risser R, Atkins DH, Doyle J. Reducing relapse in depressed outpatients with atypical features: A pilot study. *Psychother Psychosom* 2000; 69: 232-239.
212. Rafanelli C, Park SK, Ruini C, Ottolini F, Cazzaro M, Fava GA. Rating well--being and distress. *Stress Med* 2000; 16: 55-61.
213. Bankier B, Littman AB. Psychiatric disorders and coronary heart disease in women – a still neglected topic: Review of the literature from 1971 to 2000. *Psychother Psychosom* 2002; 71: 133-140.
214. Bech P. *Pharmacological treatment of depressive disorders: A review*; in Maj M, Sartorius N (eds): Depressive Disorders. Chichester, Wiley, 1999, pp 89-127.
215. Kupfer DJ. Maintenance treatment in recurrent depression: Current and future directions. The first William Sargant Lecture. *Br J Psychiatry* 1992; 161: 309-316.
216. Fava GA. Conceptual obstacles to research progress in affective disorders. *Psychother Psychosom* 1997; 66: 283-285.
217. Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RMA, Shea T. Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry* 1992; 49: 809-816.
218. Stassen HH, Delini-Stula A, Angst J. Time course of improvement under antidepressant treatment: A survival--analytical approach. *Eur Neuropsychopharmacol* 1993; 3: 127-135.
219. Katon W, Rutter C, Ludman EJ, Von Korff M, Lin E, Simon G, Bush T, Walker E, Unutzer J. A randomized trial of relapse prevention of depression in primary care. *Arch Gen Psychiatry* 2001; 58: 241-247.
220. Simon GE, Von Korff M, Rutter CM, Peterson DA. Treatment process and outcomes for managed care patients receiving new antidepressant prescriptions from psychiatrists and primary care physicians. *Arch Gen Psychiatry* 2001; 58: 395-401.
221. Roy-Byrne PP, Katon W, Cowley DS, Russo J. A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry* 2001; 58: 869-876.
222. Carroll BJ. *Neurobiologic dimensions of depression and mania*; in Angst J (ed): The Origins of Depression. Berlin, Springer, 1983, pp 163-186.
223. Fava GA, Bartolucci G, Rafanelli C, Mangelli L. Cognitive-behavioral management of patients with bipolar disorder who relapsed while on lithium prophylaxis. *J Clin Psychiatry* 2001; 62: 556-559.
224. Fava GA, Ruini C. *Psychotherapy of residual symptoms*; in Alpert J, Fava M (eds): Handbook of Chronic Depression. New York, Dekker, in press.