

Chapter 2

Let's Talk About Stress

Mind-body medicine- this is the main area where miracles can occur.

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In this chapter we explore:

- Why stress is important including the associations between stress, depression, anxiety and cancer, and the relationships between stress and depression and the endocrine system, immune system and the gut microbiome
- What happens at the cellular level when there is stress, including how it affects the immune system, endocrine system and gut microbiome
- What to do about stress in the Ultimate Consultation including beginning the conversation about stress and techniques for unloading stress and stored emotions.

Introduction

How a person feels is paramount to their health and whether they look after themselves. If a person feels good, they tend to care more for themselves, however when they do not feel good about themselves, they often do things that are counterproductive to good health. This includes not exercising, eating the wrong foods, smoking and drinking excess alcohol. The way the mind influences the body is perhaps the most important area in medicine. Known as mind-body medicine, there is now much science that helps us understand the way we are able to influence our physical selves, by how we behave and what we do.

Hans Seyle (a pioneering Austrian-Canadian endocrinologist) was the one of the first people to recognise the role of stress in the human body, though not the first to use the word [114]. Seyle in 1936 defined stress as ‘the non-specific response of the body to any demand for change’ [114]. He was the first to recognise the role of hypophysis-adrenal cortex axis in the stress response [114].

Stress and pleasure play a crucial role in wellness and disease [118]. Stress describes the effects of psychological and environmental factors on the human's well-being, on a number of levels including physical, emotional and mental. However, even if a person is stressed, if they are feeling good then stress is likely to have fewer negative effects [118]. Stress is also less likely to cause health problems if there is an emotional outlet for it [118].

In This Chapter

In the first part of this chapter, we will explore why stress is important and how it impacts on health and the functioning of the mind and body. In the second part of this chapter, we will look at what can be done about stress in the Ultimate Consultation.

Why Is Stress an Important Factor in Our Health?

Stress affects every system in our body including the immune system, endocrine system and the gut. All these play important roles in physiological homeostasis, and disturbance of functioning is implicated in a range of diseases including cancer. The ancient Chinese knew very clearly that emotions were an aetiological factor in the pathogenesis of disease. Certainly, it is the clinical experience of Professor Sali's that the greater the stress and the worse the personal circumstances are, the greater the likelihood of a cancer with poorer prognosis. A study of breast cancer patients has confirmed this clinical experience [97]. From our Western scientific literature, we see the evidence of a relationship between mind, emotions and the functioning of the body at the level of cells and tissues, as well as at the epidemiological level when we look at patterns of associations between mental illnesses such as depression and cancer. Let's look at some of the evidence.

Storage of Emotions and Its Relationship to Illness

The storage of emotions, at the level of the subconscious mind but also in a more tangible sense, within the physical body, and its relationship to illness is one of the most important concepts that the clinician will need to impart to her/his patient. It is the experience of the authors that many, if not most cancer patients, tend to be sensitive types—that is, they are the ones who pick up and absorb the stress around them. Of course, most people in the Westernised world are exposed to plenty of stresses. However, for some, this is simply 'water off a duck's back', as the saying goes. Those people tend to fare better healthwise. The sensitive person is more

likely to pick up external factors and stressors, storing them internally and adversely affecting immunity and hormones. This can lead to excess worry, anxiety, stress, sleeplessness and other problems. If the sensitive person keeps all these emotions inside rather than ‘unloading’, for example, sharing with a close confidant, then they are at greater risk of illness. Here are some of the reasons why stress is an important factor in our health.

Associations Between Stress, Depression, Anxiety and Cancer

There is evidence that stress is implicated in cancer initiation and progression at an epidemiological level. Although the literature is somewhat divided on whether major life events are associated with increased risk of cancer, some studies indicate that stressful life events can precede cancer [28, 63] and that stress-related psychosocial factors are associated with higher cancer incidence and poorer survival [19]. It is certainly our experience that in many cases, there has either been a history of ongoing stress or in many cases, a traumatic event preceding a diagnosis of cancer.

There is also some evidence of a relationship between coping styles and emotional responses and cancer incidence and survival [19]. For example, a depressive coping style and emotional distress have been found to be associated with poor survival in lung cancer patients [30].

Table 2.1 sets out some evidence from observational studies about the link between stress and cancer.

There is also a link between psychological distress such as anxiety and depression, and cancer. Depression is common in cancer patients, affecting up to 25% [46, 64]. There is evidence to indicate that depression may be associated with an increased risk of cancer and may predict cancer progression [92, 108]: the longer

Table 2.1 Stress and cancer: evidence from some observational studies

<ul style="list-style-type: none">• A review of 165 studies found that stress-related psychosocial factors are associated with higher cancer incidence in initially healthy populations, poorer survival in patients diagnosed with cancer (330 studies), and higher cancer mortality (53 studies) [19]
<ul style="list-style-type: none">• Stress-prone personality, unfavourable coping styles, and negative emotional response were related to higher cancer incidence, poorer cancer survival and higher cancer mortality [19]
<ul style="list-style-type: none">• The Finnish Twin Cohort study found an association between the accumulation of life events during 5 years prior to baseline assessment and increased risk of breast cancer: divorce, separation, death of a husband/close relative/friend were all associated with increased risk of breast cancer [63]
<ul style="list-style-type: none">• Prior stressful experiences in childhood have been linked to decreased cellular immunity and depressive symptoms in breast cancer survivors [28]

the duration of depression, the greater the risk of developing cancer [85]. Risk of developing cancer due to depression is almost doubled, independent of other life-style factors, and this risk is not related to any specific cancer [92]. Depressive symptomatology has been found to be a consistent psychological predictor of decreased survival time [17].

Coexistence of Anxiety and Depression in Cancer

Anxiety and depression often coexist in cancer patients. In a large epidemiological study of women diagnosed with breast cancer, 10.8% had combined anxiety/depression symptoms (CADS), 14.9% had only anxiety symptoms and 2.8% had only depressive symptoms [16]. Another study found that 44.5% of women with breast cancer were diagnosed with CADS, and that higher levels of anxiety with or without sub-syndromal depressive symptoms were associated with higher fears of recurrence and decreased life satisfaction [40]. In addition, both anxiety and depression have also been found to be associated with cancer-related fatigue, a symptom that affects a significant percentage of cancer sufferers [47]. And as Kotsirilos and colleagues point out [56], depression can also influence lifestyle factors that may negatively impact on health including smoking, consuming an excess of alcohol, poor level of physical activity and excess weight [45].

Table 2.2 sets out some of the facts and figures about the relationship between anxiety, depression and cancer.

Table 2.2 Some facts and figures about anxiety, depression and cancer

• Depression affects 15–25% of cancer patients [46, 64], with a higher prevalence in female cancer patients compared with male [22]
• Studies indicate that anxiety and depression can coexist in 10–45% of breast cancer patients [16, 40]
• Chronic and severe depression may be associated with elevated cancer risk and there is evidence that depression predicts more rapid progression of cancer [108]. The longer that depression has existed, the greater risk there is of getting cancer [85]
• Depression [95], stressful life events [19, 43] and social isolation [96] have been found in meta-analyses to be linked with poorer survival in cancer patients.
• Depression prevalence in cancer patients has been found to increase with disease severity and symptoms such as pain and fatigue [108]
• There is some evidence that depression predicts cancer progression and mortality (though this is complicated by several factors including that some cancer symptoms and cancer treatment can mimic depression, and disease progression can have a negative effect on mood) [108]
• Perceived stress, anxiety and pain severity have been found to be significantly associated with greater severity of cancer-related fatigue [47]
• Anxiety and depression has been found to be significantly associated with cancer-related fatigue [86], one of the most prevalent symptoms that cancer patients experience during and after treatment and in disease-free survivors [8]

Key Components of Cancer Pathogenesis

Before we take a look at how the mechanisms of how stress may create changes at the cellular level that may contribute to cancer, we will look briefly at the key components of the microenvironment associated with cancer, or the ‘hallmarks of cancer’. These are the (so far) known pathogenic events that are present in cancer. These include: sustaining proliferative signalling, evasion of growth suppressing signals, resistance to apoptosis (programmed cell death), replicative immortality, ability to induce angiogenesis, ability to invade and metastasise, ability to evade destruction by the immune system and a reprogramming of energy metabolism, underpinned by genome instability and inflammation [44].

Inflammation is a key aspect of the biochemical environment associated with tumors, as it is with other chronic diseases including diabetes and other cardiovascular diseases. Lung, colorectal and breast cancer have all been found to be associated with high levels of C-reactive protein, an inflammatory marker and a stronger association has been found between increased levels of inflammatory markers and risk of cancer death compared with the risk of cancer incidence [49].

Sex hormones have also been implicated in the pathogenesis of some cancers such as breast and prostate cancer, though for prostate cancer, there is mixed evidence for the role of testosterone in carcinogenesis [75].

Insulin and IGF, and oxidative stress are also involved. In cancer, oxidative stress and the production of free radicals occur at a much higher rate in cancer cells than normal cells [9]. Increased insulin can stimulate tumor development and progression, including cancer cell proliferation and migration in cancer cell lines [26] and has been found to have mitogenic and anti-apoptotic effects in endometrial cancer [119]. Oxidative stress can increase mutagenesis and DNA mutation rate and upregulate angiogenesis, disrupt mitochondrial functioning (causing fatigue) and accelerate tumor sculpting [9].

What is happening at the cellular level is obviously very complex. The reader is referred to other sources for detail on the cancer pathogenesis.

The Cellular Level: Stress, Endocrine and Immune Systems and Cancer

Stress and depression influence the body through the brain: psychoneuroimmunology (PNI) is the study of how the mind influences the immune system (to be normal, abnormal or hyperactive), and psychoneuroendocrinology (PNE) describes how the mind influences the body’s endocrine system [103]. Inflammation, a key process in cancer and other chronic diseases, is modulated via bidirectional communication between the neuroendocrine system, immune system and the brain [118], with increasing evidence of the role of the gut microbiome (more later).

Stress is able to activate the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis and thereby alter the tumor microenvironment. When stress activates the HPA axis, corticotrophin-releasing hormone (main regulator of HPA axis) is secreted and this induces the release of adrenocorticotrophic hormone into the systemic circulation, where it stimulates the adrenal cortex to produce glucocorticoids. Glucocorticoids (e.g. cortisol) along with catecholamines (noradrenaline and adrenaline) from activation of the autonomic nervous system are released into the bloodstream as part of the stress response, as are inflammatory cytokines [23, 68]. These can all affect the tumor microenvironment. Glucocorticoids can also directly mediate processes that promote tumor growth, activate survival genes in cancer cells, down-regulate repair genes and inhibit the cellular immune response [68]. Stress has also been shown to influence many parts of the steps involved in metastatic spread of cancer [68].

Stress and the Immune System

Chronic stress, via activation of the HPA axis, results in the release of various mediators that can suppress some of the non-specific and specific parts of the immune response including NK-cell activity, phagocytosis, production of inflammatory cytokines (e.g. IL-2, interferon, TNF by Th1 cells) and activity of cytotoxic T cells, all of which are important components of the cancer surveillance and the immune response against cancer [68, 99]. Psychological stress also reduces the ability of cells to initiate genetically programmed cancer cell death [116].

Chemical messengers secreted by nerve cells, endocrine organs or immune cells mediate the communication between the central nervous system (CNS) and the immune system, and psychological stress can down-regulate various parts of the cellular immune response, disrupting these communication networks between the CNS and immune system [99]. Bio-behavioural oncology research has found that stress can not only down-regulate the cellular immune response (mediated largely by adrenergic and glucocorticoid signalling) but that it can also affect tumor angiogenesis, invasion and anoikis, stromal cells in the tumor microenvironment and inflammation, all pathways involved in cancer [68].

Interventions that reduce psychological distress have been found to create changes at the cellular level, for example, significantly increasing the percentage of large granular lymphocytes and increasing NK cytotoxic activity in patients with malignant melanoma [31].

Stress and Chronic Inflammation

There is strong evidence that chronic inflammation precedes tumorigenesis [59] and that the stress response and inflammation play an important role in the pathogenesis

of cancer metastasis [68, 91]. Chronic stress can lead to inflammation through the production of cytokines, including interleukins [68, 99]. People with major depression have been found to have increased production of pro-inflammatory cytokines interleukin 1, interleukin 6, soluble interleukin 2 and interleukin 6 receptors, suggesting that concentrations of pro-inflammatory cytokines correlate with HPA activity and disease severity [99]. Stress increases the level of cytokines such as Vascular Endothelial Growth Factor (VEGF), a cytokine which mediates angiogenesis and cancer patients with high levels of VEGF have a poorer prognosis [45]. Cytokines can also stimulate tumor growth [45].

Stress and the Endocrine System

Stress and depression can alter the functioning of the endocrine system, leading to increased insulin secretion from the pancreas, increased cortisol, growth hormone and prolactin, which can contribute to increased tumor growth [56]. Neuroendocrine stress hormones, released via the brain, sympathetic nervous system and/or HPA axis, in the tumor microenvironment assert a systemic influence on tumor growth [68]. High cortisol levels (and a tendency towards flatter diurnal cortisol rhythms) have been found to be associated with greater disease severity in women with metastatic breast cancer [1]. Other research in women with early metastatic breast cancer found that women who repressed emotions and those who were highly anxious had a significantly flatter diurnal cortisol slope than self-assured and non-extreme groups, though there was no difference in mean cortisol levels [36].

In patients with depression, cortisol was found to be increased in those who were chronically stressed, suggesting that depression is associated with sensitisation of the HPA axis to chronic stress [110]. As previously stated, depression affects a significant proportion of cancer patients [22, 46 and 64].

Corticotropin-releasing factor (CRF) is a hypothalamic neuropeptide that is involved in the control of the stress response. It is also expressed in organs and peripheral tissues [6]. In the tumor microenvironment, it may be produced by innervating sympathetic neurons, immune cells and endothelial cells [5, 6]. CRF has been found in breast cancer cells and tissue and can affect breast cancer cells in an autocrine or paracrine manner [5]. Research has found that CRF stimulates cell motility and invasiveness of breast cancer cells, and that the likely mechanism is via induction of Focal Adhesion Kinase (FAK) phosphorylation and the reorganisation of actin filaments and the production of prostaglandins: CRF induces the production of prostaglandins and expression of Cox-1 in breast cancer cells, which are factors that can promote invasiveness and metastasis [5]. In vitro, research has found that CRF can induce the expression of genes involved in breast cancer proliferation and metastases. In vivo, research has also demonstrated that peripheral CRF at least partly mediates the tumor-promoting effects of stress (including neoangiogenesis and tumor growth) [6].

Stress and Genetic Damage

Stress can lead to DNA damage, accumulation of somatic mutations, impaired genetic mutation repair and inhibition of apoptosis [39, 50, 99]. In human studies, perceived psychological stress and perception of inability to alleviate stress have both been found to be associated with increased levels of 8-hydroxydeoxyguanosine (8-OH-dG), a biomarker of cancer-related oxidative DNA damage, in females but interestingly not in males [50]. In healthy workers, the levels of 8-OH-dG were higher in females with poor stress-coping behaviours and in males with a self-blame coping strategy [51].

At the Cellular Level: Stress, Depression, Anxiety and the Gut

The gut microbiome is assuming a much greater importance than previously given credit for in the stress response. The interaction between stress, the HPA axis and immune system is well established, and it is now believed that the gut microbiota mediates this response [23].

The newborn child is exposed to the maternal vaginal microbiota during childbirth, providing the main source for normal gut colonisation, host immune maturation and metabolism [52]. Microorganisms within the gut form part of a complex and multidirectional communication network with the brain, the microbiome-gut-brain axis [106]. The gut contains as many neurons as the spinal cord and there are many hormonal connections [42]. The microbiota and host, the human, have co-evolved into a complex 'super-organism' which has been beneficial to the host, but it can also create problems when the microbiota becomes dysregulated or disturbed. Each organ has a microbiome; however, 99% of the microbial mass is in the gastrointestinal tract [105].

The Gut and the Immune System

The gut microbiome is now understood to play a critical role in the functioning of the immune system, thereby influencing inflammation, as well as the nervous system [93]. The gut microbiome plays a key role in regulating intestinal permeability and maintaining the intestinal barrier function and deficits in intestinal permeability may be a causal factor in the chronic low-grade inflammation observed in depression [54]. A U.S. study found that major depression is accompanied by activation of the inflammatory response system and that pro-inflammatory cytokines and lipopolysaccharide (LPS) may induce depressive symptoms—a significant increase in level of antibodies against LPS in the blood was found in those with

major depression [71]. LPS, the major component of the outer membrane of certain bacteria, is able to enter the bloodstream only if the normally tight junctions in the cells lining the intestine are compromised and the intestine lining becomes permeable or ‘leaky’ [93]. It can then fuel inflammation. Inflammation is a key component of many chronic diseases including cancer.

Regulation of Moods by the Microbiome-Gut-Brain Axis

The gut microbiome has been found to affect neural, immunological and endocrine systems, with the microbiome-gut-brain axis modulating emotions and moods. Stress is able to modulate the microbiota and the microbiota is able to alter the set point for stress sensitivity [106]. The gut microbiota generates several neurotransmitters including gamma-aminobutyric acid (GABA), acetylcholine, dopamine, norepinephrine and serotonin [42]. Neurotransmitter imbalances or deficiencies are known to cause psychiatric problems such as depression [42]; altered GABA receptor expression is implicated in the pathogenesis of anxiety and depression (both of which are associated with functional bowel problems) [15]. Depression has been found to be associated with dysregulation of the gut microbiota composition [106].

Animal research demonstrates clear links between the gut microbiome and stress/anxiety/depression as well as changes in the brain. This includes findings that

Table 2.3 Pre-clinical (animal research): gut microbiome, stress, anxiety and depression

• Germ-free mice have an exaggerated HPA axis response to restraint stress which was reversed by monocolonisation with <i>Bifidobacterium infantis</i> [113]
• Female mice stressed during pregnancy pass on lowered levels of gut bacterium to their pups [52]
• Increased stress was found to be associated with decreased microbial diversity in the gut of wild red squirrels [111]
• Absence of the gut microbiota in rats exacerbated behavioural responses to acute stress and was associated with an altered neurotransmitter turnover rate in areas of the brain known to regulate reactivity to stress and anxiety-like behaviour [20]
• Short-term colonization of germ-free adult mice was found to reduce anxiety-like behaviours [84]
• Research has demonstrated that normal gut microbiota is critical for normal social development in mice [24]. Treatment of mice with probiotics can reduce early life stress-induced immune changes [25], depressive-related behaviours [15, 25] and anxiety-like behaviours [69, 87]
• Lack of normal gut microbiota in mice is associated with decreased expression of BDNF in the hippocampus, a key protein involved in neuronal plasticity and cognition [72, 73]
• Treatment of mice with <i>Lactobacillus rhamnosus</i> (JB-1)-induced changes in GABA mRNA expression in areas of the brain and reduced stress-related corticosterone and anxiety and depression-related behaviour, with the Vagus Nerve implicated as the major modulatory pathway between the gut and the brain [15]
• Germ-free adult mice exposed to faecal microbiota from pathogen-free donors had decreased blood-brain barrier permeability and increased expression of tight junction proteins [14]

the gut microbiota can modulate the blood-brain barrier [54]. How translatable such findings are to humans in understanding brain-gut relationships and disorders is not yet known [72, 73]. Some key findings from pre-clinical (animal) research are set out in Table 2.3.

The relationship between the gut microbiome and emotions and stress is an important and complex one. However, there is increasing evidence that the gut microbiome and brain, immune and endocrine systems are all in constant communication, and the gut microbiome is a key player in the stress response. And the storage of emotions and stress is closely linked to the pathogenesis of cancer.

The Gut Microbiome and Cancer

There is increasing evidence that the bacterial microbiota plays a key role in carcinogenesis [105]. Whilst particular cancers are triggered by specific bacteria (e.g. gastric cancer and *Helicobacter pylori*), other cancers such as colorectal cancer appear to be triggered by tumor-promoting effects of microbiota (e.g. liver cancer may be promoted by pro-inflammatory micro-organism associated metabolic patterns (MAMPs) and bacterial metabolites from the intestine, via the portal vein) [105]. Colorectal cancer (CRC) has been found to be associated with decreased overall microbial community diversity and relative depletion of the Clostridia class of Firmicutes bacteria. Increased risk of CRC was found with increased carriage of *Atopobium*, *Fusobacterium* and *Porphyromonas* bacteria [3].

Use of antibiotics, known to disturb the gut microbiome, has been shown to be linked to an increased risk of breast cancer and of fatal breast cancer: a U.S. study demonstrated that there was a significant correlation between antibiotic use and terminal breast cancer [117].

Disturbances in Anatomical Barriers

Disturbances of the anatomical barriers between the host and microbes can also promote inflammation and diseases including cancer. The relationship is bidirectional: barrier failure can trigger inflammation, and inflammation and carcinogenesis can promote barrier failure [105]. These are but a few of the potential pathways of involvement of the microbiota; the mechanisms involved in carcinogenesis are complex. The reader is referred to other sources for a more complete explanation.

Obesity and Microbial Dysbiosis

Obesity, a major modifiable risk factor for the development of many types of cancer, is associated with microbial dysbiosis which may result in several

physiological changes that could contribute to the link between obesity and cancer. These include altered microbial metabolism that can contribute to the generation of pro-carcinogenic toxic metabolites, induction of subclinical inflammation that could initiate tumor formation, and/or increased extraction of energy and nutrient availability causing metabolic dysregulation, thereby contributing to tumor growth [101].

The Gut Microbiome During Chemotherapy

The gut microbiome, of course, undergoes quite a beating during chemotherapy, with a severe compositional and functional imbalance in the gut microbiome associated with chemotherapy-induced mucositis [77]. Research has established that over the course of chemotherapy, there is a significant decrease in oral and intestinal microbial diversity and an increase in specific microorganisms known to cause infection [4]. A patient's microbial diversity, even *prior to cancer treatment*, can be linked to increased risk of infection during induction chemotherapy. Thus researchers have suggested that microbiome sampling could be used to predict the chance of infections during chemotherapy, and that monitoring a patient's microbiome during induction chemotherapy could be used to predict risk of microbial-related illness during subsequent treatments [4]. A depleted gut microbiome following chemotherapy leaves the patient with a greater risk of future illness.

Suffice to say, the gut microbiome is an important player in the pathogenesis of cancer. Given its role in influencing the immune, nervous and endocrine systems, including its role in depression which often coexists in cancer sufferers, addressing any imbalance in the gut will be important.

Social Support and Cancer

There is evidence of the impact of lack of social support in those with cancer. Tumors from high risk ovarian cancer patients (high levels of depression and low levels of social support) were compared with tumors from low risk patients (low levels of depression, high levels of social support)—it was found that tumors from high risk individuals showed more than 200 upregulated gene transcripts, many of which were involved in tumor progression. In addition, high risk patients had increased intra-tumor norepinephrine [67]. The association between storage of emotions and cancer is demonstrated in the findings of a systematic review that found that depression and constraint of emotions were associated with decreased survival in breast cancer patients [29].

Loneliness has been found to be related to higher levels of tumor vascular endothelial growth factor (VEGF) in patients with colon cancer [82]. In breast cancer patients, women with low levels of emotional expression and perceived

emotional support were found to have poorer survival than women reporting high levels of both, and use of emotion-focused coping strategies was significantly associated with better survival [100]. A study of 9247 women with breast cancer found that women who were socially isolated women (small networks) were 1.43 times more likely to have a breast cancer recurrence, 1.64 times more likely to die from breast cancer and 1.69 more likely to die of any cause than socially integrated women [57]. Another study of people with cancer found that being unmarried carried a 27% and 19% higher risk of death in men and women, respectively, compared with their married counterparts [41].

Good News

The good news is that research indicates that social support can positively influence cancer survival, discussed in the later sections of this chapter.

What to Do About Stress in the Ultimate Consultation

In the Ultimate Consultation, the clinician's role is to help the patient with cancer understand the link between the mind, stress and those processes in the body that contribute to poor health, and to harness the power of their mind to positively impact their health. The clinician can then guide the patient to several techniques that can help alleviate stress and in particular, unload the storage of stress and emotions.

The clinician will need to allow plenty of time for the consultation, in the order of 1–2 h. The benefit of taking this time will be tremendous, for both patient and clinician. Patients invariably are very appreciative of the opportunity to talk, in detail, with their clinician, and in many ways, this is part of the unloading of stored stresses and emotions itself. Importantly, this is an opportunity for both patient and clinician to understand what factors may have led to the patient becoming out of balance, and for the clinician to empower the patient to be proactive in not only changing those factors that can be changed, but also adopting other strategies to improve their well-being. Remember, the Ultimate Result (whatever that is for the patient, but ideally at the very least an improvement in health and well-being) really depends on the Ultimate Patient, one who is empowered and pro-active. The Ultimate Consultation is fundamentally about enabling and facilitating that empowerment.

Key Point

Allow plenty of time for the consultation, in the order of 1–2 h.

Beginning the Conversation About Stress

Mind Your Language

The language the clinician uses is most important. At the very outset, it is important to remember this is a person *with* cancer you are talking to, and the cancer is part of them, it originated due to imbalance within them, and it is a reflection of what is happening within them as a person. The cancer is *not* a separate, external entity and therefore ‘it’ cannot be ‘aggressive’ (as compared with an external infectious organism which could be described as aggressive). In the world of oncology, cancer is treated almost like a separate, external entity to be removed, poisoned or irradiated. This type of thinking may have evolved from the world of infectious diseases where microbes were the infectious agent, the enemy to be gotten rid of. The language that has evolved around this still positions cancer as something separate and unfortunately, the focus of many oncologists is on the disease, the tumor, the cells and not the human being.

Opening up the Conversation About the Patient’s Life Stresses

To open up the conversation about stresses in the patient’s life, Professor Sali typically begins with handing the patient a diagram such as the one in Fig. 2.1 that sets out in diagram form the relationship between the mind/stress/depression and the immune system, the endocrine system and the gut microbiome. He explains the different components involved in the stress response, including the link between the mind and storage of emotions and stress and the link between the mind/depression/nervous system and the immune system, endocrine system and the gut. Professor Sali elaborates on the concept of storage of emotions and stress, and how one can, by relieving some of the stresses in one’s life, positively influence health (via those afore-mentioned interdependent systems).

Talking through this diagram can be an ice-breaker—a means of opening up a discussion with the patient about *their* life stresses. It is most important that patients with cancer understand how stress negatively impacts on them, and come to identify what stresses might be present in their own lives. If the patient can understand what stresses may have contributed to their deviation from wellness, they may be in a better position to make the necessary changes to alleviate their stresses that will then contribute to positive changes in terms of the various bodily systems involved. As there is some evidence of traumatic events preceding a diagnosis of cancer, it is worthwhile talking with the patient about whether there have been any major events such as a death of a loved one.

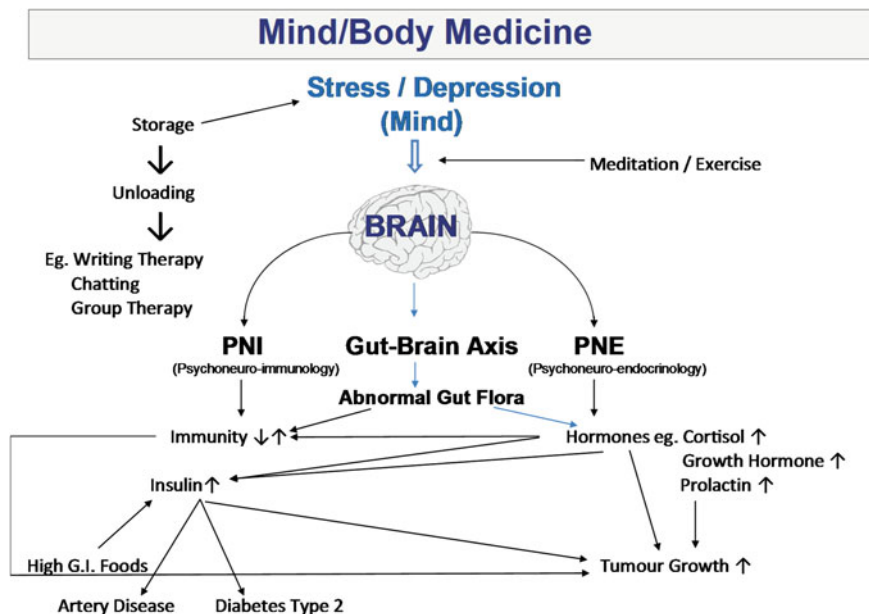


Fig. 2.1 Mind/body medicine

Listening to the Patient's Story

At this point, the clinician needs to sit back and listen, and simply prompt the patient to consider and talk about what difficulties they might be facing. This part of the consultation is critical, and in many ways facilitates a feeling, by the patient, of being heard and understood. Therefore, do not rush this part of the consultation—there is plenty of time for you to impart your knowledge. Listen carefully and you will be able to pick up important clues.

In discussing the link between mind/emotions and the body, it is important that the patient is not left feeling in some way guilty or anxious that they have somehow brought the cancer on themselves or 'drawn' cancer to them, for example, through negative thinking or actions. This is simply neither the case nor helpful to the patient. The power of the mind to positively impact on various pathophysiological pathways should be emphasised, as should how they can be proactive in changing the status quo—this is about empowering positive change through the power of the mind.

The discussion on storage of stress and emotions then leads onto a discussion on how the patient can help themselves by decreasing the storage of stress and emotions: by 'unloading storage'.

Probing About Social Support

Unloading of stress and emotions is important in the prevention of illness, including cancer, and as part of a therapeutic approach. Social support and its role in unloading are extremely important. The disadvantages of poor social support have been discussed in the previous section. Therefore, the clinician should probe whether the cancer patient has social avenues for unloading in their personal life. If not, then there are professional options including working with a psychologist, cancer support groups, and other therapists. And there are other ways to unload stress and emotions, discussed later in this chapter.

Things to Look Out for

The conversation about stress is not a one-off conversation. It should be an ongoing dialogue over subsequent conversations, and an opportunity to check in with how the patient is doing.

Some things to look out for in consultations include symptoms and signs of:

- Anxiety
- Depression
- Cancer-Related Fatigue.

During the initial and subsequent consultations, the clinician will need to be sensitive to the level of anxiety that the patient is likely to be experiencing, particularly on initial diagnosis but also at other time points. For example, following surgery, chemotherapy or radiation therapy, a patient will likely be extremely anxious about follow-up pathology results. Where results are not positive, or where the symptoms and signs associated with the cancer or cancer treatment are impacting physically on the patient, anxiety and depression can compound an already extremely difficult experience.

As we learned earlier, depression can also influence lifestyle factors that may negatively impact on health including smoking, consuming an excess of alcohol, lack of physical activity and excess weight [45]. So it is good to question the patient about their smoking status/habits, alcohol consumption and other lifestyle factors and gently probe to see if they are leaning on any of these as a crutch; lack of or a decrease in physical activity and increase in weight gain in someone who has previously indicated they were active may give some clues as to their current state of mind.

Assist the Patient to Explore Treatment Options for Anxiety and Depression

An integrative medicine approach will encourage the patient to explore various treatment options to help them with their anxiety and depression. For example, a timely referral to a psychologist or counsellor or a cancer support group may assist the patient work through and cope with anxiety and/or depression. At the very least, how the experience of cancer is impacting on the patient emotionally should be discussed with the patient at each consultation. The emotional aspects of what the patient with cancer and their loved ones are facing are critical to address, as the patient has much to gain if they can use their mind positively to impact their health. There is enough research to demonstrate how anxiety and depression can negatively impact on the body, creating in some ways a negative spiral.

Key Points

- Be vigilant at all consultations for symptoms and signs of anxiety, depression and cancer-related fatigue
- Refer the patient to an appropriate professional or support group for help to address the anxiety and depression.

Talking of Happiness

As humans, we have many things in common. One is that most humans seek happiness. It is an important goal to pursue. The fourteenth Dalai Lama says:

Whether one believes in religion or not, whether one believes in this religion or that religion, the very purpose of our life is happiness, the very motion of our life is toward happiness (His Holiness the Dalai Lama and Cutler [21]).

In healing from cancer and other serious diseases, it is useful to help the patient tap into what brings them happiness. Some people are so caught up in their anxiety, stress and emotional pain that they have lost sight of what brings them joy. If the patient can engage in activities and with people that bring them a sense of happiness, this can have enormous emotional, spiritual and physical healing benefits. When someone is truly happy, stress very often just wilts into the background. In the end, it is our response to external stresses or internally created ones, that determines whether an event is stressful or not.

Techniques for Unloading Stored Stress

There are several techniques that the clinician may suggest to the patient to assist with unloading of stored stress and emotions. Development of a routine is extremely important and should be emphasised, whatever activities they decide to try. Techniques for unloading include the following:

- Stress management through social therapy
- Pet therapy
- Art therapy
- Writing therapy
- Color therapy
- Gardening
- Meditation
- Spirituality and religion
- Multimodality programmes
- Tai chi and qi gong
- Others, including exercise.

It is crucial that the clinician is in no way judgemental or disapproving of the patient's interest or exploration of forms of complementary medicine, as many may be quite interested or may already have experienced other forms of medicine and therapies. What follows are some examples of activities that may assist the patient with unloading of storage and emotions. However, within reason, any technique or activity that takes the patient's mind off their cancer and focusses it on something else is likely to have value.

Stress Management Through Social Therapy

The value of close, social connections and unloading of stress cannot be understated. A prospective longitudinal study of elderly Australians living in community care or residential care carried out over 10 years found that greater networks of friends were protective in terms of decreasing mortality [37]. Research points to the positive value of social support in people with cancer, indicating that it may affect cancer survival favourably ([32, 70, 109]. Having at least one confidant has been found to reduce 7-year mortality by 39% in women with breast cancer, for example [70]. Women who have a strong social network are more likely to survive breast cancer compared with women who are isolated [57]. Some of the key research into social support in cancer is included in Table 2.4.

Going to movies and concerts can be a great escape for a few hours and provide an important circuit breaker from stress and worry in many cases. Group therapy such as cancer support groups may also provide the patient with a sense of not being alone in their experience.

Table 2.4 Research into social support in cancer

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- A 6 week structured psychiatric intervention in malignant melanoma patients found significantly reduced levels of psychological distress, greater use of coping methods, and significant increases in % large granular lymphocytes and natural killer (NK) cells with indications of increased NK cytotoxic activity at 6 months [31]. At 5–6 year follow-up, those in the intervention group had a significantly lower rate of death and a trend toward lower recurrence rate compared with the control group. Higher levels of baseline distress and coping, and enhancement of active-behavioural coping over time were predictive of lower rates of recurrence and death [32]. At 10 year follow-up, participation was still significantly predictive of survival [33]
-
- Research in women with breast cancer has demonstrated a 39% reduction in relative mortality after seven years in those who used at least one confidant in the three months after surgery, and a 46% reduction in relative mortality when they utilised two confidant categories [70]
 - An investigation of group support in women with advanced metastatic breast cancer found that the average survival time in those in the group support intervention group (which included improving their ability to express their emotions and learning simple relaxation and self-hypnosis techniques) almost doubled from 18.9 to 36.6 months in comparison to the control group after 20 months of the programme [109]
-
- A systematic review found that social support and marriage were associated with better breast cancer prognosis [29]
 - A study of 9267 breast cancer survivors found that those with small networks (socially isolated) had significantly higher risk of cancer recurrence (hazard ratio 1.43, meaning a 1.43 times greater risk), breast cancer mortality (hazard ratio 1.67) and total mortality (hazard ratio 1.67) than women who were socially integrated. The associations were stronger in women with Stage I and II cancer. In older white women but not other women, lack of a partner and community ties was associated significantly with higher breast cancer-specific mortality. Lack of relatives and lack of friendship ties were both significantly associated with higher breast cancer mortality in non-white women (only) [57]
-
- Social support in women with ovarian cancer has been found to be associated with greater NK-cell activity in peripheral blood and in tumor-infiltrating lymphocytes [65], and lower levels of vascular endothelial growth factor (an angiogenesis promoter) in tumor tissue and serum [66]
-

In the Age of Technology and socially networking, research has shown that Facebook users with more friends and more requests to connect live longer [48, 55]. Online social behaviour that indicates face-to-face activity such as posting photos was associated with reduced mortality, however online-only behaviours such as sending messages had a non-linear relationship with moderate use being associated with the lowest mortality [48]. Use of technology, of course needs to be balanced with some of the potential harmful effects of exposure to electromagnetic frequencies (discussed in Chap. 7). The point here is that these positive effects flow on from connecting with other people: that's what is truly beneficial.

Professor Sali tells the story of a Greek gentleman whose family migrated from the Greek island of Icaria to the United States. At the age of 64 he was told that he had cancer and to put his affairs in order. The gentleman sold up his business, and moved back to Icaria, where he proceeded to live a life tending his vegetable garden

and meeting his friends for coffee every morning. This was his informal social therapy where no doubt he unloaded storage of stress and emotions in a supportive atmosphere. Twenty-one years later, he was still going strong, no cancer, tending his veggie patch. Professor Sali, himself once a boy from a tomato-growing town in rural Victoria called Shepparton, refers to this as *Veggie Patch Therapy*.

The key point here is that having someone to share troubles with, and unload stored stress and emotions, is very valuable in patients suffering from cancer and something that the clinician can suggest.

Pet Therapy

Pet Therapy is another form of social therapy, except with a furry friend. Numerous studies have demonstrated the value to health of owning a pet. For example, a study in patients with head and neck cancer undergoing combined radiation and chemotherapy found that assisted pet therapy was associated with significant improvements in social and emotional well-being despite the high symptom burden and expected decreases in physical and functional well-being associated with radiation-chemotherapy treatment [35]. Animal-assisted therapy (using dogs) during chemotherapy has been found to significantly reduce depression of patients and increase their arterial oxygen saturation [88].

Art Therapy

Art therapy encompasses a broad range of therapies including music therapy, dance/movement and various types of art such as painting. It is interesting to note the sudden worldwide popularity of coloring books for adults, which are designed specifically for mind stress reduction. Several studies in cancer patients have demonstrated that art therapy can improve well-being [112]. Research also indicates that art therapy may be effective in decreasing anxiety as well as depression and pain in patients with cancer, and decreasing anxiety in those receiving cancer therapy [7, 60, 80, 112, 115]. Art therapy can be beneficial as a means of expressing emotions when a patient cannot articulate or voice them. Art therapy can be useful for children with cancer who may not be easily able to articulate their feelings.

Meta-analyses indicate that music therapy may have several benefits for people living with cancer, including reduction of anxiety, pain and fatigue and improved mood and quality of life [11, 12].

Table 2.5 sets out some of the evidence of the usefulness of art therapy in patients with cancer.

Table 2.5 Evidence of usefulness of art therapy in cancer

<ul style="list-style-type: none">• A meta-analysis of 13 trials found that art therapy (inclusive of music therapy interventions, various types of art therapy and dance/movement therapies) positively affects cancer patient’s anxiety, though it did not find a significant effect on depression or quality of life [10]
<ul style="list-style-type: none">• Music therapy has been found to decrease anxiety in cancer patients in two systematic reviews [11, 83] (though meta-analysis of one study failed to show a positive effect which may be due to small sample size) [83] and moderately reduce pain in one of these [11]. A later meta-analysis of 22 studies concluded that music interventions may have benefits in reducing anxiety, pain, fatigue and improving quality of life in cancer patients [12]
<ul style="list-style-type: none">• Group music therapy of listening to music has been found to improve well-being, relaxation and energy levels, reduce cortisol levels and increase salivary Immunoglobulin A levels [18]
<ul style="list-style-type: none">• Mindfulness-based art therapy during treatment in women with cancer has been found to significantly decrease symptoms of physical and emotional distress and significantly increase aspects of health-related quality of life [78]

Recommendation for Art Therapy

Adult coloring books have enjoyed great popularity in the past few years. Coloring in allows the mind to switch off and focus on the now, and may allow negative thoughts to be replaced with positive ones [27]. No special artistic skill is needed. Book and pencils essential!

Writing Therapy

Unloading of stresses including family, work and school problems through writing about them can be very beneficial. Research indicates that writing therapy is associated with improved quality of life in cancer patients and changes in thoughts about their cancer [79].

Studies show that writing for 20 min on each of three days about life stresses produced an improvement in asthma patients within two weeks, and an improvement in joint pain in patients with rheumatoid arthritis at four months in comparison with a group who did not write about life stresses (they received no improvement) [107].

Recommendation for Writing Therapy

It is suggested that patients write in a journal for three consecutive days, then after the first week, once a week for 15–20 min (more often if he or she likes to do so).

Color Therapy

Some people react quite strongly to various colors in their environment. In Ayurvedic Medicine, different colors are associated with the different chakras-energy vortices running along the midline of the body. The color purple or violet is associated with the seventh chakra or crown chakra and has traditionally been associated with healing. In contrast, the color red is more stimulatory in its effect and is associated with the first (base) chakra and is somewhat less calming. In terms of relaxation, wearing colors or having colors within the environment that are calming to the patient can aid in relaxation. Placing a purple colored amethyst stone in the home environment or in a quiet meditation area in the home can also bring a calming quality to the space. The association of colors with chakras comes from the Ayurvedic tradition, though there is much research on the impact of colors on emotions and moods.

Color Therapy Exercise

The color mauve or purple can be very relaxing. A short color therapy relaxation exercise involves drawing a small circle with a yellow highlighter on a piece of yellow paper. After looking at the yellow circle for about 30 s, a violet/mauve halo begins to appear around the circle. The patient should practise this for about two minutes over the next 4 days, then after 4 days, try closing their eyes and retaining the mauve color for 30 or more seconds. The goal is to see if they can do this five times in the one session. This exercise may be done one to three times daily (three sessions per day). Over time, the patient will be able to retain the violet/mauve color for up to half an hour.

Gardening

A systematic review of 22 articles that investigated the potential benefits of gardening for community-living and institutionalised older people found that gardening can promote overall health, quality of life, physical strength, fitness and flexibility, cognitive ability and socialisation [120]. A small qualitative study of ten people with chronic mental illness who engaged in a 6-week group-based gardening activity found that horticulture had an immediate and positive effect on life satisfaction, well-being and self-concept (all components of quality of life) [94].

Meditation

There is a wide body of research supporting the many health benefits of meditation. This includes the benefits of meditation in people with cancer. Dr. Ainslie Meares was one of the pioneers in the meditation field who found that intensive meditation was associated with cancer regression [74]. For example, a study on Transcendental Meditation over eight years found a 49% decrease in the rate of mortality from cancer [104]. Another earlier study of 2000 meditators compared with 600,000 non-meditators found a 55% reduction in tumors. A follow-up over 11 years found 3.3 times fewer admissions for cancer in meditators compared to non-meditators [89].

Benefits of Meditation

Meditation has a number of purposes, including promoting the relaxation response and achieving a greater state of self-awareness. The relaxation response helps undo many of the harmful effects of stress, and incorporates a deeply relaxed physical state with a focused, clear mental state [45]. Some of the physiological benefits of the relaxation response include reduction in blood pressure and heart rate, improved immune regulation and function, reduced platelet adhesiveness, reduced inflammatory and stress hormones, better digestion (increased blood flow, gut motility), changes in brain activity including greater electroencephalogram coherence, increased alpha and theta waves (associated with rest and focus), increased serotonin, reduced reactivity to pain, neural plasticity and neurogenesis, decreased anxiety and depression, increased optimism, and improved coping abilities and resilience [45].

Forms of Meditation

There are a number of different forms of meditation, however essentially they are mental disciplines aimed at regulating the attention [45]. Mindfulness is a term that has gained in use in recent times, typically in relation to meditation, i.e. mindfulness meditation. According to Australian mindfulness meditation expert and medical practitioner and academic Dr. Craig Hassed, mindfulness is simply about awareness [45].

Some forms of meditation utilise a mantra, a word or phrase that is repeated over and over, as a point of focus whilst other techniques focus the attention on the breath. When thoughts arise, the meditator is encouraged to simply observe the thoughts coming and going, like an external observer, bringing the attention back to the breath. In the Progressive Muscle Relaxation (PMR) technique, the idea is to practise letting go of muscle tension in the body [45].

Instructing Patients to Meditate

The clinician may choose to learn some simple meditation techniques themselves, and to practise them in order to gain the benefits of stress reduction themselves, and be able to talk about the benefits to their patients from first-hand experience. The clinician might also feel confident enough to instruct the patient in a simple meditation technique, for example, the PMR technique. This is a simple introduction into meditation and the relaxation response.

Since meditation is often quite new and unusual to many patients and also to their significant others, it often helps to instruct the patient along with their partner or parent or support person, so that this exercise is not foreign to them either. This has a several purposes—the significant other might share in the exercise at home, providing a level of support in sharing the experience, or at the very least not make the patient feel awkward about practising at home. Efforts that the patient makes towards reducing stress, unfortunately, are sometimes not always supported by an often-frightened partner to whom the exploration of experiences such as meditation can be foreign and challenging.

Referring to Meditation Teachers

It is very useful to have a handy reference list of good meditation teachers on hand to give to the patient. Meditation is often easier in a group situation, at least in the early stages of learning, where the meditator can ask questions of the teacher as necessary.

Spirituality and Religion

The benefits of spirituality and religion to people with cancer have been established. Studies of people with cancer have found spirituality and religion to be significantly associated with improvements in subjective well-being and quality of life [13, 38, 58, 102], hope and positive mood states [34, 76], adjustment to cancer [81], management of symptoms [122] and reduced anger-hostility, despair and social isolation [2]. Spiritual well-being has been also found to be associated with lower levels of anxiety in persons with cancer [53]. The challenge of a cancer diagnosis can often be a catalyst for a search for meaning in life and for some, provides the impetus to make changes to their life.

Multimodality Programmes

Lifestyle interventions can improve immunity and health and assist those with cancer. Australian research has been conducted into a lifestyle programme (conducted by the Gawler Foundation, a support centre for people with cancer) which

incorporates meditation, social support, positive thinking and a vegetarian diet in a cohort of predominantly women with cancer. The study found beneficial effects of the programme, conducted over 3 months, on mood, coping and quality of life (QOL). Spiritual well-being was, in particular, linked with improvement in QOL. The finding that programme was particularly beneficial in those with low QOL and emotional well-being may be largely due to the effects of meditation in reducing anxiety and increasing spiritual well-being [98].

The Ornish lifestyle programme was trialled in 80 men with prostate cancer who had chosen to wait and watch rather than undergo treatment. The lifestyle programme incorporated dietary recommendations (including dietary supplements of fish oil, Vitamin E, Vitamin C and selenium, plus a diet low in fats [in particular saturated fats and animal fats], and that included vegetables/fruits/wholegrains, legumes and soy products), exercise (30 min walking, six times per week), stress management (yoga, meditation, breathing and PMR) and attendance at a support group one hour per week. Forty men were in the treatment group and 40 in the comparison group (usual lifestyle). A year later, six of the 40 men in the usual lifestyle group developed aggressive cancer whereas none in the Ornish lifestyle programme did. In addition, the mean PSA level in the Ornish programme group decreased 4% in comparison to the control group (usual lifestyle) which increased an average of 6% [90].

Tai Chi and Qi Gong

Variously described as meditation in movement, the Chinese art/exercise forms of tai chi (also referred to as tai chi chuan or taijiquan) and qi gong incorporate slow, controlled movements with breathing to help still the mind and circulate the qi, or energy, around the body. Originally based on observations of movements of animals, tai qi movements are essentially martial arts movements, though in practise the martial arts applications of the various movements are not always taught. There is evidence that regular tai chi is can cause changes in the Th1 and Th2 immune responses which are associated with immune modulation of Natural Killer T-cells and Dendritic Cells and their reciprocal interactions [62]. Other reported benefits include increased strength and flexibility, improved sleep, reduced pain and anxiety, reduced depression, improved general stress management, improved self-efficacy and exercise self-efficacy, better balance and less falls, and increased cardiopulmonary function [61, 121]. A meta-analysis demonstrated that tai chi had a significant effect on reducing depression [121]. In cancer patients, a systematic review and meta-analysis of nine randomised controlled trials found that qi gong and tai chi had positive effects on cancer-specific quality of life, as well as fatigue, anxiety, immune function and cortisol levels [123].

Others

There are several other activities or therapies which may be useful in reduction of stress an unloading. These include hypnosis, cognitive behavioural therapy, breath work and exercise (see Chap. 6 on exercise). The reader is referred to other sources for a description of these.

Conclusion

The science behind the impact of stress on the human is becoming well elucidated. There is compelling evidence that storage of stress plays a part in the pathogenesis of cancer, and that the immune system, endocrine system, nervous system and the gut are all involved. In the Ultimate Consultation, by explaining at a basic level how storage of stress and emotions impacts on the various systems of the body, the patient may come to understand how stresses in their life may have contributed, along with other factors, to imbalance in their body that has manifested as cancer. If they can understand this, then they are in a better position to also see how they can make changes that can affect these body systems in a positive way, leading them back to better health. A healthy patient will always do better than an unhealthy one, no matter what the illness.

By discussing various options with the patient about how they might reduce stress (as part of a holistic approach that considers other factors including diet and exercise), the clinician can open up a different way of being to the patient that they may not have considered before. The goal is empowerment of the patient to become the Ultimate Patient, one who is proactive in taking charge of their health. The Ultimate Result really does depend on the Ultimate Patient.

Summary: Key Points About Storage of Emotions and Stress

1. There is clear evidence of an association between stress, depression, anxiety and cancer and that stress is implicated in cancer initiation and progression.
2. Depression, stressful life events, social isolation and lack of social support have been linked with poorer outcomes in cancer patients.
3. Constraint of emotions and low levels of emotional expression are associated with poorer survival in those with cancer.
4. Stress not only involves the HPA axis and the immune system—research indicates the gut microbiome plays a major part in the stress response, and there is increasing evidence that the bacterial microbiota plays a key role in carcinogenesis.

5. Stress reduction and social support have been shown to improve physiological functioning in the body and improve outcomes in patients with cancer.
6. Any technique or activity that takes the patient's mind off their cancer and focusses it on something else is likely to have value.

Summary: Key Techniques for Unloading Stress

Unloading of stored stress can be done in many ways including the following:

- Stress management through social therapy
- Pet therapy
- Art therapy
- Writing therapy
- Color therapy
- Gardening
- Meditation
- Spirituality and religion
- Multimodality programmes
- Tai Qi and Qi Gong
- Others.

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