

## Chapter 1

# The Scientific Basis of Chinese Medicine and Cancer Care: A Western Medicine Perspective

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### **Abstract**

Traditional Chinese medicine (TCM) may be integrated with conventional Western medicine to enhance the care of patients with cancer. Recent evidence confirms a scientific basis for the use of acupuncture, herbs, diet and energy therapies. We suggest a holistic care plan based on the concepts of biological response modification, enhancement of psycho-immunological function, better symptom control, and improvement of psycho-spiritual well-being. There is enough preliminary evidence to encourage good quality clinical trials to evaluate the efficacy of integrating TCM into Western cancer care.

*Keywords:* Traditional Chinese Medicine (TCM); Western Medicine; Cancer Treatment.

### **1.1 Introduction**

Recent evidence suggests that many traditional Chinese medical therapies can be effective for the supportive care of cancer patients. This is a review of the published literature (indexed in Medline) and our own practical experience. It provides various levels of evidence that support further research into a developing model of integrative care. Most published studies are at evidence level III, in other words trials without randomization, single group pre-post, cohort, time series, or matched case-controlled studies. Levels I and II evidence from well designed randomized controlled trials of appropriate size is emphasized in the text of this review. In view

of the paucity of quality data from levels I and II evidence, meta-analysis of the data is usually not possible. Well-designed randomized controlled trials are encouraged in view of the promising initial observations. It is important not to discount TCM as a system simply because an individual study is negative. The same applies to Western biomedical medicine. A negative drug study does not negate the whole of biomedicine. The challenge for TCM is to develop repeatable and provable outcomes, standardization, and quality assurance. The scientific bases of herbs and acupuncture are rapidly being established, but well designed, pragmatic, controlled clinical studies are lacking in most domains.

Traditional Chinese medicine (TCM) may be practiced alongside conventional Western medicine to enhance patient care. The philosophy of TCM proposes novel hypotheses that will support the development of a science-based holistic medicine.

## 1.2 Cancer as a Systemic Disease

In Western medicine, cancer is conventionally viewed from the somatic point of view as a clone of cells which has outgrown its environmental constraints and control mechanisms. These cells are abnormal and are considered to be foreign to the body. The main philosophy of cancer treatment is direct annihilation of the cancer cells using aggressive and destructive therapies. Chinese medicine emphasizes the importance of the body-mind communication network. The science of psychoneuro-immunology (PNI) has demonstrated a potential physiological basis for cancer cell progression through the effects of emotions on cellular immunity and other mechanisms.

In TCM, the development of cancer is viewed as a part of the presenting features of a syndrome representing an imbalance of the whole body-mind network (Macek, 1984). In other words, cancer is a systemic disease from the start, and the terrain is considered to be as important as the tumor itself (Schipper *et al.*, 1995). It is believed that if one can strengthen and rebalance the body-mind network, the normal pattern will be restored and this will help to resolve the cancer. This concept is currently being incorporated into a more holistic science, where the whole picture is as important as the parts. To quote Hanahan and Weinberg

(2000), “The metaphors used to conceptualize cancer cell function will also shift dramatically. For decades now, we have been able to predict with precision the behavior of an electronic integrated circuit in terms of its constituent parts — its interconnecting components, processing, and emitting signals. Having fully charted the wiring of every cellular signaling pathway, it will be possible to lay out the complete ‘integrated’ circuit. We will then be able to apply the tools of mathematical modeling to cancer cells. With holistic clarity of mechanism, cancer prognosis and treatment will become a rational science.” Recent evidence suggests that bone marrow stem cells may play a significant role in the perpetuation of some cancers, including the production of pro-angiogenic peptides. Thus Western science is now exploring the possibility that both hematological and solid cancer may sometimes be a systemic disease from the outset (Rafii and Lyden, 2003; Kerbel and Kamen, 2004; Houghton *et al.*, 2004).

### 1.3 The Body-Mind Network

TCM recognizes that the human being functions as a body-mind network (Ikemi and Ikemi, 1986). The philosophy of TCM analyzes the *process* of body-mind communication, rather than a “snap shot” of structural, material entities such as molecules. If Western medicine is viewed as the hardware of a computer, then TCM could represent the software. It recognizes a correspondence between patterns of information that are independent of the carrier of the information. For example, the pattern of information may be similar regardless of whether it is mediated by pulses of hormones and neuropeptides, or the electrophysiological frequency pattern of the heart (Watkins, 1995; Dardik, 1996; Pennisi, 1997; Pert *et al.*, 1998; Song *et al.*, 1998). Acupuncture stimulation of specific points on the body releases neuropeptides (such as somatostatin and vasoactive intestinal peptide) within the central nervous system (Zhang *et al.*, 1997 and 1999). The body-mind information system may be partly regulated by the relative contributions of the sympathetic and parasympathetic components of the autonomic nervous system. This corresponds to the traditional Chinese concept of a balance between yin and yang, which represents a pattern of information, rather than concrete material entities. Analysis of the pulse, using the classical Chinese technique, may indicate the relative imbalance.

This has been demonstrated indirectly by spectral analysis of the electrocardiogram, using appropriate computer software. Acupuncture has been shown to rebalance the relative contributions of the sympathetic and parasympathetic nervous systems (Haker *et al.*, 2000). The patterns of information transfer may interact to entrain and reinforce information flow in a complex dynamical system (Lee and Wei, 1983; McCraty *et al.*, 1995; Rubik, 1995). The system is an autopoietic process. In other words, it can recreate itself and evolve through learning, so that the body can adapt to changing circumstances.

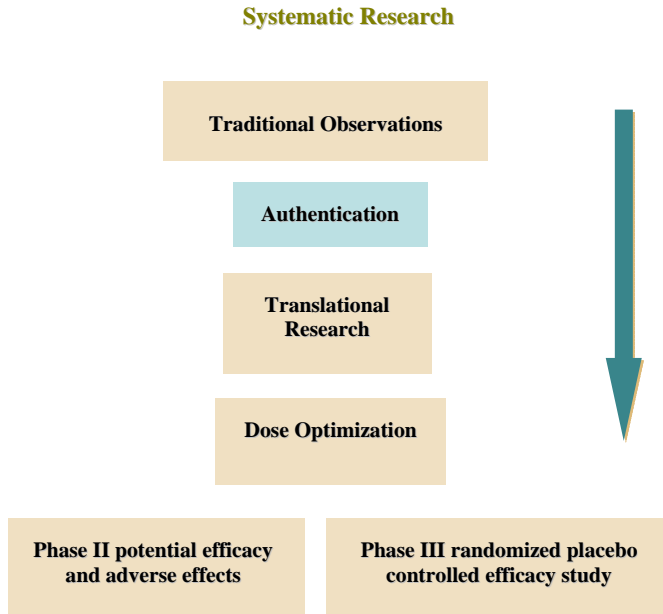
When the person is healthy, communication between systems flows freely through a complex, non-linear heterarchical and hierarchical process of information transfer, via physiological interactions. Metaphorically, mind-body communication is represented by an informatics system of energy-in-motion, in other words, “e-motion.” Cancer may be associated with a disturbance in information flow, manifest by an over-plastic system that loses process structure and becomes irreversibly chaotic (Coffey, 1998; Cuzick *et al.*, 1998). Experiments in rats show that chronic restraint stress promotes lymphocyte apoptosis through modulating CD95 gene expression via a pathway that involves opioid receptors (Yin *et al.*, 2000). In other words, stress can influence both the function and structure of the nervous system that, in turn, may modulate lymphocyte gene expression, thereby influencing immunity and resistance to cancer (Yin *et al.*, 2000). Intervention with a technique, such as acupuncture, may restore the imbalance in information flow, for example through the autonomic nervous system by balancing the sympathetic and parasympathetic components (Thomas *et al.*, 1992; Chao *et al.*, 1999). The same model may help us understand how the compassionate intentionality of a healer can restore health through entrainment and normalization of the imbalanced system (Watkins, 1996). In order to understand these processes, we will need to consider systems outside of our current reductionist pharmacological model. These may include electromagnetic and non-local effects between molecules, and the analysis of information flow between cells by novel mechanisms, such as quantum mechanics (Jovanovic-Ignjatic and Rakovic, 1999). In order to understand the concurrent, synergistic contributions of multiple systems, it is necessary to develop computerized algorithmic modeling, such as power spectral analysis (Haker *et al.*, 2000), neural networks (Riess and Abbas, 2000), and fuzzy logic (Kosko and Isaka, 1993).

The beauty of this body-mind network model is that it can combine constitutional personality factors (such as emotions and feelings) with bodily symptoms, into a single diagnostic and treatment paradigm. This is represented in TCM terms by patterns of disharmonies in the main organ systems, as well as abnormalities of *qi* (energy flow), essence (energy reserves), blood, heat and moisture. It is interesting that there is correspondence with the TCM model of cancer predisposition being associated with rising *qi* (sheng qi) or Liver fire (representing anger), and the scientific evidence that repressed anger both suppresses the immune system and may increase the risk of breast cancer in the so-called Type C personality (Amkraut and Solomon, 1972; Temoshok, 1985; Temoshok and Dreher, 1992).

#### 1.4 Pharmacology of Chinese Herbs

In TCM, herbs are used in combinations that enhance their benefits while reducing their side effects (Rosenberg, 1997). In effect, multiple low dose pharmacological agents are being administered synergistically. Western medicine usually focuses on maximally tolerated doses of single agents. Although chemotherapy drugs are usually combined, the reason is to minimize drug resistance and the consequence can be to further increase drug toxicity. According to TCM practitioners, combinations of herbs can reduce the side effects of anti-cancer drugs, but further research is indicated to determine their pharmaco-kinetic interactions with drugs and any potential adverse effects.

A scientific approach to introducing Chinese herbs into Western practice involves a rigorous and systematic approach to phytochemical profiling, quality control, preclinical evaluation, safety evaluation, and Phases I to III clinical trials (Fig. 1.1). More data is required to establish optimal combinations of herbs that produce synergistic activity. Traditionally, Chinese herbs have been used as complex mixtures. One study evaluated the DNA microarray data for 12,600 genes to examine the anti-proliferative activity of the single herb *Coptidis rhizoma* and eight constituent molecules against eight human pancreatic cancer cell lines (Hara, 2005). They identified 27 genes showing a strong correlation with the 50% inhibitory dose (ID<sub>50</sub>) of *C. rhizoma* after 72-h exposure. Hierarchical cluster



**Figure 1.1.** Scientific approach to introducing Chinese herbs into Western practice.

analysis with correlation coefficients between expression levels of these 27 *C. rhizoma*-related genes and the ID<sub>50</sub> of each constituent molecule classified these test molecules into two clusters, one consisting of *C. rhizoma* and *berberine* and the other consisting of the remaining seven molecules. Their results suggest that one specific phytochemical, *berberine*, can account for the majority of the anti-proliferative activity of *C. rhizoma* and that DNA microarray analyses can be used to improve our understanding of the actions of an intact herb. In contrast, there appears to be merit in using combinations of herbs and their derivatives. For example, PHY106 (*Radix scutellariae*, *Paeonia lactiflora pall*, *Fructus, ziziphi*, *Radix glycyrrizae*) is an authenticated combination of herbs that may increase the efficacy and reduce the adverse effects of the cytotoxic drug, Capecitabine, which is used in treating colorectal cancer (Farrell, 2003). The biotech company, Phytoceutica Inc.<sup>®</sup> (Newhaven, CT, USA) has systematically profiled the phytochemical content of each herb and tested various combinations at the preclinical

stage to optimize the complex mixture. Quality has been assured by establishing profiles using chemical chromatography and spectroscopy, along with biologic, proteomic and genomic profiling. Through these techniques, they have developed a Phytomics Similarity Index.<sup>®</sup> Interestingly, their modern technological approach confirms traditional Chinese medical theory of optimizing efficacy through a hierarchy of herb combinations. The combination enhances anti-tumor activity, reduces toxicity, and enhances the pharmacokinetics of the chief herb (the Emperor herb). The mechanisms include inhibiting drug resistance proteins that may decrease absorption, inhibiting cytochrome p450 enzymes that metabolize phytochemicals, inhibiting microfloral beta-glucuronidase, chemical stabilization, and modification of solubility. Initial clinical trials demonstrate a reduction of gastrointestinal toxicity and enhancement of the tumoricidal effect of the chemotherapy. Many preclinical studies are now demonstrating that specific combinations of Chinese herbs can be synergistic with cytotoxic chemotherapy through pharmacodynamic, as well as pharmacokinetic, interactions. For example, *Phellinus linteus* is a mushroom, which mainly consists of polysaccharides. It sensitizes apoptosis induced by doxorubicin in an *in vitro* prostate cancer cell line (Collins, 2006). *P. linteus* or doxorubicin, at relatively low doses, do not independently induce apoptosis in the cells. However, combination treatment with both low doses of *P. linteus* and doxorubicin result in a synergistic effect on the induction of apoptosis. *P. linteus* has a synergistic effect with doxorubicin to activate caspases in prostate cancer LNCaP cells. Sensitization can be obtained at subtoxic concentrations of doxorubicin. *P. linteus* is an apoptotic synergiser for conventional chemotherapeutics such as doxorubicin, which can keep normal, surrounding cells unharmed.

Gene expression profiling coupled with promoter assays can evaluate the effect of a herbal mixture on cancer. Such approaches may be used for the standardization of herbal extract activity. An example is the comparison of the gene profile of PC-SPES with that of PC-CARE, a product with a similar herbal composition. Prior studies have shown that PC-SPES contains estrogenic organic compounds, and such compounds are known to affect prostate cancer. An important question is whether these are the primary drivers of the gene profile. The data suggest that gene expression profiles of LNCaP human prostate cancer cells in response

to PC-SPES are different from those found when diethylstilbestrol (DES), a synthetic estrogen, is used, suggesting that the estrogenic moieties within PC-SPES do not drive this expression signature (Bigler *et al.*, 2003). In contrast, the expression profile of PC-CARE is almost identical to that of DES, highlighting that mixtures containing similar herbal compositions do not necessarily result in similar biological activities. To validate the expression profiling data, the investigators evaluated the protein expression and promoter activity of prostate-specific antigen (PSA), a gene induced by PC-SPES but repressed by DES. In order to gain a mechanistic understanding of how PC-SPES and DES affect PSA expression differently, LNCaP cells were transiently transfected with wild-type and mutagenized PSA promoter, ARE concatemers and appropriate controls. The evidence suggests that the androgen response elements (ARE) II and III within the promoter region are responsible for the suppressive effects of DES and stimulatory effects of PC-SPES. The effects on PSA transcription are specific to ARE in the case of DES, while PC-SPES affects this promoter non-specifically. The expression profiling coupled with mechanistic target validation yields valuable clues as to the mode of action of complex botanical mixtures and provides a new way to compare objectively mixtures with similar components either for effect or quality assurance prior to their use in clinical trials. In the case of PC-SPES, the effectiveness of the complex mixture of herbs has been shown in a randomized controlled clinical trial to be more effective than DES alone (Oh, 2004).

Current technology is demonstrating the multi-dimensional activities of Chinese herbs as anti-cancer agents. Many are potent antioxidants that can induce apoptosis and others are anti-angiogenic agents (Cai, 2004; Yance, 2006). Many of the herbs that are traditionally considered effective against cancer cells are now being shown to have subtle effects on genetic expression and may play a key synergistic role in anti-cancer treatment through synergistic activity with cytotoxic agents and maintenance regimens for prevention of recurrence (Yonghe, 2004). Future research should maximize the use of technology to validate scientific mechanisms for quality assurance, safety, optimization and clinical effectiveness within the modern cancer treatment environment. Rigorous adherence to the development of research protocols and standards of reporting are necessary, as stated by a recent publication of the CONSORT group, which establishes

the standards for clinical trials (Gagnier, 2006). Further development of Chinese herbal medicine for administration in Western cancer clinics will require both international collaboration and an improved working relationship between national governments, industries and universities.

## 1.5 Physiology of Acupuncture

Acupuncture is a technique that allows us to modulate communication within the body-mind network through concurrent changes in multiple signaling pathways.

Most evidence suggests that acupuncture modulates neurotransmitters, cytokines and neuropeptides through electrophysiological changes in the nervous system (Bucinskaite *et al.*, 1996; Dawidson *et al.*, 1997). Interaction with the brain stem, hypothalamus, limbic system and autonomic nervous system occurs through either stimulating or suppressing the activity of afferent peripheral nerves (Kerr *et al.*, 1978; Kumar *et al.*, 1994; Alavi *et al.*, 1997; Cho *et al.*, 1998; Wu *et al.*, 1999; Zonenshayn *et al.*, 2000). Acupuncture may also modify the somatic electromagnetic field (Jessel-Kenyon *et al.*, 1992). Recent research suggests that the initial transduction of the acupuncture needle is through myofascial tissue planes. The network of acupuncture points and meridians can be viewed as a representation of the network formed by interstitial connective tissue. Langevin *et al.* (2002) mapped acupuncture points in serial gross anatomical sections through the human arm. They found an 80% correspondence between the sites of acupuncture points and the location of intermuscular or intramuscular connective tissue planes in postmortem tissue sections. The surface points appear to connect to a web of vessels that cover internal organs. This is demonstrated by special DNA staining (Shin *et al.*, 2005). The de qi or “needle grasp” may be due to mechanical coupling between the needle and connective tissue with winding of tissue around the needle during needle rotation. Needle manipulation could transmit a mechanical signal to connective tissue cells via mechanotransduction (Langevin *et al.*, 2001). This may be converted into an electrophysiological response through a change in electrical impedance that spreads through the connective tissue planes, interacts with cellular genomic expression, and releases local cytokines and other messenger molecules that may initiate neurological transmission (Ahn *et al.*, 2005).

In view of the power of the placebo effect, a sham acupuncture control arm is required as a standard for randomized controlled trials of acupuncture. Sham needles have been validated to a limited extent. The results may depend on whether the subject has past experience of acupuncture. These devices, withdraw a blunt needle back into the sheath during application. This is a more valid sham technique than using superficial penetration of the skin or randomly assigning points away from known meridians. Evaluation of the widely used Streitberger sham needle concluded that most patients were unable to discriminate between the needles by penetration; however, nearly 40% were able to detect a difference in treatment type between needles. No major differences in outcome between real and placebo needling could be found. The fact that nearly 40% of subjects did not find that the two interventions were similar, however, raises some concerns with regard to the wholesale adoption of this instrument as a standard acupuncture placebo. The authors conclude that further work on inter-tester reliability and standardization of technique is highly recommended before we can be confident about using this needle in further studies (White *et al.*, 2003).

## **1.6 Roles of TCM in Cancer Supportive Care**

The goals of cancer treatment should be to increase patients' survival, when possible, and to improve their quality of life. TCM is able to support patients being treated with conventional Western medicine (surgery, radiotherapy and chemotherapy) through four major approaches:

- (1) modification of biological response to improve therapeutic gain;
- (2) improved psycho-neuro-immunological response;
- (3) enhancement of symptom control;
- (4) psychospiritual integration.

Very often, TCM therapy works through more than one approach synergistically.

### **(1) Biological Response Modification**

#### **[I] Adjunctive Cancer Treatment**

## (a) Modification of Tumor Physiology

### (i) Herbs

There is increasing evidence that suggests TCM can favorably modify the tumor response to conventional Western cancer treatment. There is a correspondence between the TCM theory of cancer and recent medical research findings.

TCM herbs have been extensively investigated in the laboratory and are known to have multiple pharmacological effects (Wang *et al.*, 1992; Tode *et al.*, 1993; Lao *et al.*, 1994; Boik, 1996 and 1997; Kang *et al.*, 2000). It is often important to specify the botanical parts from which the herbal agent is prepared, since the active pharmacological agents depend on their source. Radix (Rx) denotes the root, Cortex (Cx) denotes the bark or rind, and Rhizome (Rh) denotes the rhizome. There are plenty of examples of anti-cancer multiplicity. *Rx Ginseng* has anti-tumor activity, inhibits platelet aggregation, and inhibits chemotherapy-induced immunosuppression. *Glycyrrhizic acid* has anti-tumor activity, is anti-inflammatory through increasing serum cortisol, and also increases natural killer (NK) cell activity against cancer cells. *Rx Astragali membranaceus* is a powerful stimulator of the immune system, has anti-tumor activity and inhibits platelet aggregation. *Rx Angelica sinensis* stimulates the immune system, has anti-tumor activity, inhibits platelet aggregation, and inhibits vascular permeability. *Rh Atractylodis macrocephala* has anti-tumor activity, and is an anti-thrombotic and fibrinolytic agent. *Ginkgo biloba* has multiple effects including inhibition of platelet activation factor (PAF), stimulation of the immune system, fibrinolysis and anti-thrombosis, scavenging of free radicals, and dilation of blood vessels to increase perfusion. The effects on the hemostatic coagulation system are interesting as we learn more about the interactive roles of the bone marrow, hemopoietic system, and angiogenesis in the progression of cancer (Yance and Sagar, 2006).

Extracts of multiple Chinese herbs traditionally used for anti-cancer therapy (*Anemarrhena asphodeloides*, *Atractylodes argyi*, *Commiphora myrrha*, *Duchesnea indica*, *Gleditsia sinensis*, *Ligustrum lucidum*, *Rheum palmatum*, *Rubia cordifolia*, *Salvia chinensis*, *Scutellaria barbata*, *Uncaria rhyzophylla*, *Vaccaria segetalis*) demonstrate growth inhibitory activity against various cancer cell lines, but limited inhibitory

activity against normal cell proliferation (Shoemaker *et al.*, 2005). Occasionally herbs alone are associated with tumor regression. For example, a 51-year-old lady with pathological proven squamous cell carcinoma of the lung attained complete regression with sole treatment using a combination of herbs (*Herba Hedyotis diffusae*, *Radix ophiopogonis*, *Herba taraxaci*, *Radix notoginseng*, *Pseudobulbus cremastrae seu pleiones*, *Radix panacis quinquefolii*, *Herba houttuyniae*, *Bulbus Fritillariae thunbergii*, *Rhizoma Pinelliae preparata*) (Liang *et al.*, 2004).

These herbs contain a variety of chemicals that may act synergistically to inhibit tumor cell division, increase tumor cell death (apoptosis), increase the proportion of immune cells within the tumor, and increase blood flow through the tumor. This is associated with a change in the balance of cytokines (communicating peptides released by the immune cells) that may improve the *therapeutic gain*. This means that they reduce the proliferation of tumor cells, increase tumor cell death, whilst minimizing many side effects for normal tissues. Recent meta-analyses confirm the utility for Chinese herbs to both enhance the control of particular cancers (particularly viral-induced cancers such as hepatocellular carcinoma and nasopharyngeal cancers) and reduce side effects of chemotherapy (Taixang *et al.*, 2005; Shu *et al.*, 2005). This synergy appears to be secondary to inducing apoptosis, anti-angiogenesis, antagonism of the viral genome, and induction of an immune response. In addition, some herbs can reverse multidrug resistance (Zhou and Liu, 2005). Examples of some studies that illustrate these principles are discussed elsewhere in this chapter.

In TCM, the malignant tumor is viewed as being associated with stagnation of *qi* (energy) and blood. *Qi* may be viewed as a model for intra- and intercellular information and potential energy transfer. This would correlate with the known abnormalities of signal transduction, cell contact, and electrophysiology of cancer cells (Coffey, 1998; Cuzick *et al.*, 1998; Kang *et al.*, 2000). It has been shown that there is increased fluid content and a stagnant blood supply in malignant tumors (Baxter and Jain, 1989; Boucher and Jain, 1992; Sagar *et al.*, 1993; Milosevic *et al.*, 1998). The microcirculation within a tumor is very abnormal, and there are regions within the tumor where the blood flow is sluggish. In TCM, stagnation of blood is classically associated with tumors. The impaired

blood circulation leads to areas of poor oxygenation in the tumor. Cancer cells that survive in a low oxygen tension environment are also found to be more resistant to radiotherapy and some types of chemotherapy (Brizel *et al.*, 1997; Fyles *et al.*, 1998).

In TCM, destagnation or detoxification herbs are used to move the blood and *qi* within the malignant tumor. Interestingly, the use of anti-coagulants, such as heparin and coumadin (warfarin), as an adjunctive treatment to chemotherapy, has been shown to prevent the development of blood-borne metastases in animal laboratory studies, and to improve the survival of cancer patients in clinical studies (Lebeau *et al.*, 1994; Hejna *et al.*, 1999). Many of these herbs are proving to be anti-angiogenic agents (Yance and Sagar, 2006).

The possible usefulness of *destagnation herbs* was demonstrated in a randomized controlled clinical trial evaluating the combined modality treatment of Chinese herbal destagnation formula and radiotherapy in patients with nasopharyngeal carcinoma (Xu *et al.*, 1989). In this trial, 90 patients received combined herbal and radiation treatment compared to 98 patients who were randomized to receive radiation treatment alone. The ingredients of the herbal formula included *Rx Astragali membranaceus*, *Rx Paeoniae rubrae*, *Rx Ligustici Chuan xiong*, *Rx Angelicae sinensis*, *Semen persica*, *Flos Carthami tinctorii*, *Rx et Caulis Jixueteng*, *Rx Puerariae*, *Pericarpium citri reticulatae*, and *Rx Codonopsis pilosulae*. The combined treatment group showed a statistically significant increase in local tumor control and overall five-year survival as compared with the group treated with radiation alone ( $p$ -value < 0.05). The rate of local recurrence in the intervention group was halved from 29% in those receiving radiation alone, to 14% in the group receiving destagnation herbs as well. The five-year disease free survival was increased from 37% in the control group to 53% in the group receiving destagnation herbs. It is postulated that this herbal destagnation formula may have improved tumor microcirculation and increased tumor blood flow leading to an improvement in the oxygen tension inside the tumor. The oxygen tension increases the radiosensitivity of the tumor. In other words, the destagnation formula has acted as a radiation sensitizer.

In animal experiments, *Gingko biloba* has also been shown to increase perfusion and radiosensitivity (Kleijnen and Knipschild, 1992; Sung *et al.*,

1996). Chinese herbs, such as *Salviae miltiorrhizae*, which inhibit tumor edema caused by free radicals may also increase tumor perfusion, oxygenation and response to radiotherapy (Sagar *et al.*, 1995; Peigen *et al.*, 1996). Other herbs may directly sensitize neoplastic cells to radiotherapy (Huali *et al.*, 1994). Some herbs may protect normal tissues from radiotherapy. For example, *Panax ginseng* and *Panax quinquefolium* water extract (especially Rh2 ginsenoside) may radioprotect through mechanisms involving antioxidative and immunomodulating properties (Lee *et al.*, 2005).

More clinical trials need to be done to further evaluate this promising role of herbs in potentially improving the therapeutic gain. Novel non-invasive techniques such as functional MRI and positron emission tomography may be useful (Sagar *et al.*, 1993).

## (ii) *Acupuncture*

The interaction of acupuncture with appropriate acupoints modulates blood flow (Thomas *et al.*, 1992; Chao *et al.*, 1999; Zhou *et al.*, 1995; Stener-Victorin *et al.*, 1996). This may be through a local effect via release of cytokines, or through neurological reflexes that adjust the balance between the sympathetic and parasympathetic nervous system. Its effect on tumor physiology and response to therapy remains to be investigated. However, we do know that electric pulses to the tumor can increase the response to chemotherapy. A Phase II study of electrochemotherapy using cisplatin in patients with skin nodules from malignant melanoma demonstrated a significantly increased control rate compared to cisplatin alone (Sersa *et al.*, 2000). However, the effect of acupuncture may be more diverse through the promotion of local cytokines at physiological levels.

## (b) Enhancement of Immunity

### (i) *Herbs*

Another strategy that TCM uses in cancer therapy is to strengthen the whole body-mind system by enhancing and harmonizing the energy balance between all the organs. This may be viewed as correcting an imbalance in the body-mind communication network and is reflected by an enhancement in immunity. This is called *Fu Zheng* treatment and is mediated by the specific group of TCM herbs called *Fu Zheng* herbs

(Ning *et al.*, 1988; Ling *et al.*, 1989; Chen, 1990; Yu *et al.*, 1990; Hou *et al.*, 1991; Rao *et al.*, 1991; Li, 1992; Yu *et al.*, 1993; Cao *et al.*, 1994; Cheng, 1994; Horie *et al.*, 1994; Lin *et al.*, 1995). There is some limited evidence that improvement of the immunological function of cancer patients is associated with an improvement in their survival. In China, *Fu Zheng* herbs have been reported to increase survival when combined with radiotherapy for patients with nasopharyngeal cancer, and when combined with chemotherapy for patients with stomach and liver cancer (Macek, 1984; Wang, 1990).

*Fu Zheng* herbs, including *Rx Ginseng*, *Ganoderma*, *Rx Astragali membranaceus*, *Rx Angelicae sinensis*, *Cordyceps sinensis* and *Fructus Lycii*, have been shown to enhance the body's defense mechanisms. Clinical studies, including two randomized trials, have found that the NK cell and OKT4 (immune-enhancing lymphocyte) cell counts were increased with the use of *Fu Zheng* herbs (Ning *et al.*, 1988; Ling *et al.*, 1989; Chen, 1990; Yu *et al.*, 1990; Hou *et al.*, 1991; Rao *et al.*, 1991; Li, 1992; Yu *et al.*, 1993; Cao *et al.*, 1994; Cheng, 1994; Horie *et al.*, 1994; Lin *et al.*, 1995). These immunocytes are known to attack cancer cells. In a study of gastric cancer patients, increased survival was found in the combined treatment group receiving both *Fu Zheng* herbs and chemotherapy versus the chemotherapy alone group. Many of these herbs are associated with an increase in cytokines, such as interferon and interleukin (Kawakita *et al.*, 1990; Jin *et al.*, 1994; Feng *et al.*, 1995). Chinese studies also suggest that healing of normal tissues may be enhanced. Anti-inflammatory constituents may diminish radiation-induced ulcers and chemotherapy-induced stomatitis (Zhu and Zhang, 1993; Zhu, 1994). However, these studies still need to be verified in the West, using acceptable standards and quality assurance.

Recently, the concept of immune enhancement has gained new ground with the discovery that both the cytotoxic therapies and the cancer suppress immunity, and that low immune levels may increase the probability of relapse. In addition, an intact innate immune system is necessary for the activity of new cancer vaccines. The interaction of host immunity with the natural history of cancer is suggested by Burnet's immune surveillance theory; the fact that immunodeficiency diseases are associated with an increased risk of cancer; and the fact that immune-enhancing therapies in

malignant melanoma and renal cell carcinoma have produced anti-tumor responses. There is evidence that the healthy immune system is necessary for the control of malignant disease and that immune suppression associated with cancer contributes to its progression. Natural immune mediators are implicated in resistance against tumor development (Whiteside, 2006). Adaptive immunity is often suppressed in tumor-bearing hosts, and specially designed agents are required to boost this defense (Berkzy *et al.*, 1998). Hormonal manipulation of the host can result in the elevation of immune defenses against cancer. Such manipulation strengthens both the adaptive and natural immune defenses of the host, both of which play significant roles. Cytokines and hormones boost natural defense mechanisms during febrile reactions, which are now known as the acute phase response. Hormonal stimulation of immune mechanisms coupled with the other immunostimulants may be employed to good advantage for the combination immunotherapy of cancer. Many Chinese herbs contain glycoproteins and polysaccharides that can modulate metastatic potential and the innate immune system. Metastasis of malignant tumors may be a specific receptor-mediated process in which organ-specific lectins play a role in the adhesion of disseminated tumor cells. Glycoprotein-mediated membrane identity is part of the HLA antigen histocompatibility system. The abnormal carbohydrate group on the tumor cell could have formed during malignant transformation. The metastatic tumor cell, with its membrane-associated glycoprotein (often identical with the tumor marker) is recognized by the organ specific lectins as belonging to the organ, and is thereby captured. *In vitro* experiments show that galactoglycoconjugates can inhibit the adhesion of tumor cells to hepatocytes (Beuth, 1988). Immune suppression in cancer contributes to progression and relapse (Kebudi *et al.*, 1995; Vucković-Deki *et al.*, 1992; Maier *et al.*, 1995; Miyazaki *et al.*, 1995; Baniyash, 2006; Whiteside, 2006; Sasada *et al.*, 2003; Wichmann *et al.*, 2003; Bang *et al.*, 2006; Koukourakis *et al.*, 2003). There are currently multiple strategies to identify candidate tumor antigens, and we now understand more about activation and regulation of immunity against cancer. Vaccines can target tumor-specific antigens, but adjuvants are required to boost the innate immune response, especially in patients who already have depressed immunity from tumor-derived signaling molecules and the effects of cytotoxic therapies (Stevenson, 2005; Minev, 2002; Hoffmann

*et al.*, 2004). Phytochemicals, such as specific polysaccharides, have been shown to boost the innate immune system, especially through interaction with Toll-like receptors (TLRs) in mucosa associated lymphoid tissue (MALT) (Tsan, 2006; Sen *et al.*, 2005; Rezaie, 2006). TLRs evolved to interact with polysaccharides found in the walls of bacteria and are an essential part of developing and maintaining a competent immune system (Heine and Almer, 2005). Polysaccharide extracts and complexes from Chinese medicinal herbs and mushrooms may have a potential role for enhancing innate immunity. There is some evidence from clinical trials that they can improve survival (Chang, 2002). The polysaccharide complexes and extracts include constituents of *Coriolus versicolor* (extract is Krestin, PSK or PSP) (Zeng *et al.*, 2005; Ito *et al.*, 2004; Ohwada *et al.*, 2004; Koda *et al.*, 2003; Tsang *et al.*, 2003; Kanazawa *et al.*, 2004; Wong *et al.*, 2004 and 2005; Munemoto *et al.*, 2002; Hayakawa *et al.*, 1997; Ogoshi *et al.*, 1995; Mitomi *et al.*, 1992; Nakazato *et al.*, 1994), *Ganoderma lucidum* (Shao *et al.*, 2004a; Lin, 2005; Kuo *et al.*, 2006; Gao *et al.*, 2003; Kodama *et al.*, 2005a), *Grifola frondosa* (maitake MD-fraction) (Kodama *et al.*, 2002, 2003, 2005a and b; Atsuyuki *et al.*, 2002), *Astragalus membranaceus* (Shao *et al.*, 2004b), *Panax ginseng* (Shin *et al.*, 2002 and 2004; Han *et al.*, 2005; Lim *et al.*, 2004), and various other medicinal mushrooms (Ooi and Liu, 2000; Zaidman *et al.*, 2005; Lindquist *et al.*, 2005). Molecular mechanisms for the immunobiological functions may be through various receptors on macrophages, monocytes and NK cells, which activate NF- $\kappa$ B and anti-tumor cytokine secretion. Interactions may include complement receptor type 3, CD14, mannose, and beta-glucan receptors. There is evidence of interaction with TLRs, especially TLR4, with polysaccharides derived from *Astragalus membranaceus*, *Acanthopanax senticosus/koreanum*, *Ganoderma lucidum* and *Platyloden grandiflorum* (Han *et al.*, 2003; Schepetkin and Quinn, 2006; Ahn *et al.*, 2006). Immuno-suppression in cancer patients can reduce the efficacy of anti-cancer vaccines and increase complications from opportunistic infections. Polysaccharides (mainly beta-D-glucans alone or linked to proteins) from the cell walls of various traditional Chinese medicinal mushrooms and plants show anti-tumor and anti-infection activities through activation of monocytes, macrophages and NK cells. A future research strategy should authenticate

the source of these polysaccharide extracts and screen them for interaction with TLRs in the gastrointestinal tract of animals. Oral agents that boost cell-mediated immunity through the MALT may be subsequently evaluated in human Phase I studies for dose-response (cytokine and immune cell assays) and safety. Optimized, authenticated polysaccharides may play a role in enhancing the potency of anti-cancer vaccines and other therapeutic modalities. These non-cytokine molecules appear to signal primarily through the TLRs, which are expressed by dendritic cells. In the MALT, these agonists can induce a host of proinflammatory cytokines such as tumor necrosis factor-alpha, IL-12, and IL-6, as well as CD4+ and CD8+ T cells. Combining radiation therapy and TLR agonists may reduce the amount of radiation therapy required to eradicate tumors, thus acting as an “immunosensitizer” (Koski and Czerniecki, 2005; DeMaria *et al.*, 2005). Further evidence of the potential usefulness of polysaccharides in stimulating an enhanced immune response comes from a study of orally administered betaglucons (from maitake mushroom) that demonstrates an enhancement of anti-tumor effects of monoclonal antibodies (Cheung *et al.*, 2002). Ganopoly (a *Ganoderma lucidum* polysaccharide extract) modulated immune function in advanced-stage cancer patients. Treatment for 12 weeks resulted in a significant increase in the mean plasma concentrations of IL-2, IL-6, and IFN- gamma, whereas IL-1 and TNF-alpha were decreased. NK activity was increased, but there was no significant change in the levels of CD4+, CD8+ or the CD4+/CD8+ ratio (Gao *et al.*, 2003). Lymphoproliferative neoplasms, such as lymphomas and leukemias, may be particularly sensitive to changes in cytokine balance. The Memorial Sloan-Kettering Cancer Center (New York, NY, USA) has commenced an NCI-sponsored Phase I study of beta-glucan and rituximab in pediatric patients with relapsed or progressive CD-20 positive lymphoma or leukemia (Clinical Trials Government, 2006).

Evidence indicates that the healthy immune system is necessary for control of malignant disease and that immune suppression associated with cancer contributes to its progression. Tumors have developed strategies to successfully evade the host immune system, and various molecular and cellular mechanisms responsible for tumor evasion have been identified. Some of these mechanisms target immune anti-tumor effector cells. Dysfunction and apoptosis of these cells in the tumor-bearing host creates

an immune imbalance that cannot be corrected by immunotherapies aimed only at activation of anti-tumor immune responses. Reversal of existing immune dysfunction and normalization of lymphocyte homeostasis in patients with cancer needs to be a part of future cancer immunotherapy (Whiteside, 2006). Therapeutic strategies are being designed to correct the immune imbalance, deliver adequate *in vivo* stimulation, transfer effector T cells capable of *in vivo* expansion and provide protection for the immune effector cells re-populating the host. Survival of these cells and long-term memory development in patients with malignancy are necessary for improving clinical benefits of cancer immunotherapies. Polysaccharides derived from Chinese herbs and mushrooms are emerging agents that seem to enhance cytotoxic drugs, radiotherapy, surgery, and the newer targeted therapies and vaccines (Chang, 2002; Chan, 2005a and b; McCulloch, 2006).

#### (ii) *Acupuncture*

Multiple animal and clinical studies have also suggested that acupuncture has a positive immune-modulating effect in cancer patients (Bianchi *et al.*, 1991; Yuan and Zhou, 1993; Wu *et al.*, 1994 and 1996a; Yang *et al.*, 1994; Liu *et al.*, 1995; Wu, 1995; Sato *et al.*, 1996; Petti *et al.*, 1998; Zhou *et al.*, 1999a). In these studies, acupuncture has been shown to increase T-lymphocyte proliferation, increase NK cell activities, activate the complement system and heat-stable mitogenic humoral factor, and increase OKT4 cell counts. Inhibition of the growth of transplanted mammary cancer has also been shown in mice with the use of acupuncture. The main acupoints that were used in these studies were those that support blood formation and Spleen function. These points include LI 4, LI 11, St 36, Sp 6, Sp10, P6, UB 20, GB39 and GV14. An increased level of all components (red blood cells, white blood cells and platelets) was found.

#### (c) *Hormonal effects*

Some Chinese herbs inhibit hormone-responsive tumor cells. PC-SPES is a combination of herbs with partial estrogenic activity associated with activity against prostate cancer. One study correlated laboratory activity with clinical response (DiPaola *et al.*, 1998). On the basis of these findings, a National Cancer Institute (NCI) randomized controlled trial was initiated. Unfortunately, the clinical trial was terminated when a

batch of PC-SPES was contaminated with the hormone stilboestrol and other pharmacological agents. It is not certain whether there was deliberate adulteration or accidental contamination (Guns, 2002).

Acupuncture may stimulate steroid levels and other hormones, such as melatonin, somatostatin, and vasoactive intestinal peptide, which could potentially have anti-tumor effects (Massion *et al.*, 1995; Zhang *et al.*, 1997 and 1999). Exposure of the popliteal fossa (over the Bladder meridian) to bright light modulates the circadian release of melatonin from the pineal gland (Campbell and Murphy, 1998).

### [II] Cancer Prevention

TCM also emphasizes appropriate nutrition according to specific constitutional and disease patterns. Green tea (*Camellia sinensis*) and *Panax Ginseng* are two dietary supplements which have been extensively investigated in both the laboratory and in epidemiological studies. Both reduce the risk of cancer induction, and they both may prevent cancer recurrence (Yang and Wang, 1993; Kaegi, 1998; Yun and Choi, 1998).

Green tea (*Camellia sinensis*) contains isoflavones and a powerful antioxidant called epigallocatechin (EGC) (McKenna *et al.*, 2000). The latter may potentiate the destruction of cancer cells through the process of apoptosis (natural programmed cell death) and by inhibiting angiogenesis (new blood vessel formation that enhances tumor growth and metastasis) (Cao and Cao, 1999; Fujiki *et al.*, 1999). *Panax Ginseng* may induce the differentiation of neoplastic cells into normal tissue (Lee *et al.*, 1996). Both EGC and Ginseng appear to restore normal intercellular communication through the gap junctions (Kang *et al.*, 2000). Both dietary supplements seem to work through novel mechanisms of signaling and communication through the body-mind network.

The soy bean contains genistein, which is an isoflavone with multiple anti-cancer effects demonstrated in the laboratory (Boik, 1996). These include the induction of tumor cell death through the process of apoptosis, inhibition of cancer cell proliferation through decreasing the availability of sex hormones, inhibition of angiogenesis, inhibition of tyrosine kinase (involved in intracellular signaling from the membrane to the nucleus), and inhibition of platelet aggregation (Kim *et al.*, 1998; Li *et al.*, 1999a and b). Some epidemiological studies suggest that populations with a high soy or

tofu content in their diet may have a reduced risk of breast cancer (Wu *et al.*, 1996b; Witte *et al.*, 1997; Lu *et al.*, 2000), whereas other studies cannot confirm this link (Key *et al.*, 1999). The phytoestrogens contained within soy may reduce the symptoms of hot flashes associated with chemotherapy-induced menopause (Scambia *et al.*, 2000), although not all studies support this (Quella *et al.*, 2000). The isoflavones and phytoestrogens in soy also appear to reduce the incidence of prostate cancer, and may play a role in prevention and as an adjunctive therapy to reduce the risk of recurrence (Jacobsen *et al.*, 1998; Kamat and Lamm, 1999; Moyad, 1999; Stephens, 1999; Adlercreutz *et al.*, 2000). Cell culture and animal xenograft studies show that treatment with soy is associated with inhibition of prostate specific antigen, deactivation of NF-kappa B (a nuclear transcription factor), induction of apoptosis (programmed cell death), and inhibition of angiogenesis (Aronson *et al.*, 1999; Davis *et al.*, 1999 and 2000; Zhou *et al.*, 1999b).

TCM herb combinations may reduce the risk of lung cancer in ex-smokers. An NCI sponsored study through the British Columbia Cancer Agency, led by Dr. Stephen Lam, is recruiting participants aged 45–74 years, who are ex-smokers, to evaluate the efficacy of a herbal combination called Anti-Cancer Preventive Health Agent (ACAPHA) (personal communication). This contains *Sophora tonkinensis*, *Polygonum bistorta*, *Prunella vulgaris*, *Sonchus brachyotus*, *Dictamnus dasycarpus*, and *Dioscorea bulbifera*. In Chinese studies, ACAPHA reduced the risk of esophageal cancer by 50%, through reversing severe esophageal dysplasia. In addition, a pilot study of 20 former heavy smokers with bronchial dysplasia treated with ACAPHA showed that, after 6 months, 50% had complete regression of dysplasia, compared to only 13% in the placebo group. *Panax quinquefolium* (American ginseng) appears to reduce death and increases quality of life in survivors of breast cancer, suggesting that some botanicals may prevent recurrence (Cui *et al.*, 2005).

## (2) Psychoneuroimmunology (PNI)

Psychoneuroimmunology (PNI) is a scientific discipline that has produced evidence for a dynamic mutual interaction between the mind, nervous system, endocrine system, and immunity. The interaction of emotions and immunocytes through molecules, such as neuropeptides, is now well

recognized. In fact, the immune system can be viewed as a complex evolutionary communication system within the body-mind network (Page and Ben-Eliyahu, 1997; Jessop, 1998; Nutt, 1998; Pert *et al.*, 1998; Rabin, 1999). TCM recognizes this complex interaction between personality, mood states, and susceptibility to illness through malfunction of the body-mind network.

There is accumulating evidence that psychological function is linked with outcomes in cancer patients (Shekelle *et al.*, 1981; Levy and Wise, 1987; Ramirez *et al.*, 1989; Orsi *et al.*, 1996; Anderson *et al.*, 1998; Watson *et al.*, 1999). There is evidence to suggest a link between mood disorders and function of the immune system. Indeed, the experience of pain and suffering is intimately connected to immunity. A mood disorder such as helplessness and hopelessness may lead to a depressed immune system. Treatment of depression and feelings of hopelessness may not only increase quality of life, but may also increase survival (Spiegel *et al.*, 1989; Fawzy *et al.*, 1995; Fawzy, 1999). In a cancer practice, 50% of patients suffer from clinically recognized depression. In 15% of these patients, the degree of depression is severe. Therefore treatment of depression is an important intervention in the management of the body-mind network of cancer patients.

Conventionally, clinical depression is treated with oral medication, such as amitriptyline or the newer serotonin reuptake inhibitor drugs. Studies indicate that acupuncture treatment may be an equally effective alternative treatment modality to drugs in patients suffering from mild depression. In one study, the profile of side effect associated with acupuncture treatment was shown to be better than amitriptyline (Han, 1986). In a single-blind placebo-controlled study of the antidepressant, mianserin, supplementary acupuncture improved the course of depression more than pharmacological treatment with the drug alone (Roschke *et al.*, 2000). Since pharmaceutical antidepressants are not usually effective until two weeks after starting therapy, their combination with acupuncture may enable more rapid results with less side effects.

### **(3) Symptom Control**

Cancer patients experience multiple symptoms related either to the cancer itself or late treatment side effects. Even if a patient's cancer were

clinically “cured”, the person may still be suffering from late treatment side effects. For example, radiation may cause xerostomia, trismus and skin ulceration. These side effects have an adverse effect on quality of life, and are often not effectively managed by conventional Western medicine.

Chinese medicine plays a useful role in symptom supportive care for cancer patients. Symptoms that can be effectively managed include general constitutional symptoms, such as fatigue and depression, pain, and specific symptoms such as gastrointestinal side effects and myelosuppression.

Cancer patients receiving chemotherapy usually develop myelosuppression (with risk of infection and bleeding) and gastrointestinal side effects (nausea, vomiting and diarrhea). They easily become fatigued and develop a reduced appetite. In TCM terms, the chemotherapeutic agents are causing Spleen and Kidney deficiency leading to a general decrease in *qi* and blood. Radiotherapy and chemotherapy act as “heat toxins” that damage the *yin* and *qi*. “Heart fire” is expressed as stomatitis; “deficient Spleen *qi*” is manifest as diarrhoea. Chemotherapy drugs “disturb Spleen and Stomach *qi*”, expressed physically as damage to the lining of the stomach and intestines (Rosenberg, 1997). These physical expressions are only part of the disturbance in the body-mind network and will inevitably be accompanied by emotional disorders (such as depression, anxiety, insomnia), and constitutional change (such as fatigue or hyper-excitability and poor concentration). After an evaluation and diagnosis of the disturbance in the body-mind network, appropriate combinations of herbs, acupuncture, nutrition, and Qigong may be utilized.

#### (i) Herbs

Spleen and Stomach *qi* are supported by appropriate formulas containing *Rx Ginseng*, *Poria*, and *Rh atractylodis macrocephala* (Rosenberg, 1997). Depleted *yin* leads to dry and sore mouth, thirst, constipation and scanty dark urine. The harmonious relationship between Kidney and Heart is disturbed, leading to insomnia, restlessness, disorientation, palpitations and low back pain. This combination of symptoms is traditionally alleviated with combinations of *Rh Anemarrhenae*, *Cx Phellodendron*, and *Rx Rehmanniae*. The weakening of *qi* is associated with depressed immunity and susceptibility to infection and cancer progression. Medicinal mushrooms, such as *Ganoderma*, *Cordyceps sinensis*, and *Shitaki* strengthen the *qi*,

which is associated with an improved immune profile and anti-tumor activity. Another herb with potent immune-stimulating properties is *Rx astragali membranaceus*.

At least five randomized controlled trials have shown that Chinese herbal treatment can decrease the degree of myelosuppression, reduce gastrointestinal side effects and increase the patient's appetite (Ning *et al.*, 1988; Ling *et al.*, 1989; Chen, 1990; Yu *et al.*, 1990; Wang, 1990; Hou *et al.*, 1991; Rao *et al.*, 1991; Li, 1992; Yu *et al.*, 1993; Cao *et al.*, 1994; Cheng, 1994; Horie *et al.*, 1994; Lin *et al.*, 1995). Importantly, it can also increase the probability of patients completing the scheduled chemotherapy. One randomized trial recruited 669 patients with late-stage gastric cancer (Yu *et al.*, 1993). One group of patients was treated with herbs that support the Spleen and Kidney function (*Jian Pi Yi Shen prescription*) twice daily for four to six weeks with concurrent chemotherapy, while another group was treated with the same type of chemotherapy alone. The combined treatment group showed significantly higher leukocyte and platelet counts with less general and gastrointestinal side effects. The percentage of patients completing the scheduled chemotherapy was 95% in the combined treatment group versus 74% in the chemotherapy alone group ( $p$ -value < 0.01). Unfortunately, the quality and verification of the data from these studies, which were reported from China, are not at a high enough standard that a definitive meta-analysis can be done at this stage.

In TCM, systemic Chinese herbal treatments and topical herbal applications appear to be effective in treating cancer-related pain. In one study, the effectiveness in pain control was shown to be over 90% (Yang *et al.*, 1995).

Ginger root has been shown in many clinical studies to have anti-emetic activity (Mowrey and Clayson, 1982; Grontved and Hentzer, 1986; Grontved *et al.*, 1988; Bone *et al.*, 1990; Fischer-Rasmussen *et al.*, 1991). It appears to particularly help nausea that may be intransigent to standard anti-emetics. Ginger syrup is shown to be effective in a randomized controlled trial (Keating and Chez, 2002). Caution should be used with patients on anticoagulants and those with low platelet levels, since it does have anticoagulant effects at higher doses.

Vitexina (*Vigna radiata*) is a flavonoid herb with radio-protective effects that may be useful for reducing some side effects of radiotherapy.

It treats the heat or yin-deficiency side effects of anti-cancer treatment, such as fatigue, restlessness, insomnia and constipation. This empty heat syndrome is characterized through tongue diagnosis, which reveals a red, denuded and cracked tongue. Since the tongue is the most densely innervated organ in the body, it may reflect the imbalance between yin and yang, via the autonomic nervous system, which in turn may influence blood flow and epithelial cell turnover through the local release of neuropeptides and cytokines. A randomized controlled trial of breast cancer patients receiving radiotherapy showed that Vitexina prevented the empty heat syndrome, reduced weight loss, and protected against a reduction in peripheral lymphocytes and platelets (Tran, 2002).

The role of Chinese herbs, together with conventional Western pharmaceuticals, for symptom control is currently unclear. Laboratory data suggests that they can be effective modifiers of biochemical pathways, immunostimulants, and signal transduction modulators. Potential detrimental interactions and idiosyncratic toxicity are possible. Future studies need to be done using more rigorous methodology and quality assurance. The use of appropriate modeling and suitable evaluative methodologies should enable the integration of Chinese herbology into an emerging model of holistic Western medicine.

#### (ii) *Acupuncture*

Acupuncture treatment at acupoint P6 has been shown to increase the anti-emetic effect of drugs for peri-operative and chemotherapy-induced nausea and vomiting (Dundee *et al.*, 1986 and 1989). Innovative randomized single blind controlled trials have since confirmed these results (Al-Sadi *et al.*, 1997; Schlager *et al.*, 1998; Lee and Done, 1999) and led to the NIH (US) consensus statement that, “acupuncture is a proven effective treatment modality for nausea and vomiting” (NIH Consensus Development Panel on Acupuncture, 1998). A three-arm randomized controlled trial of conventional modern anti-emetics (such as the 5-HT<sub>3</sub> antagonists), versus electro-acupuncture, versus the combination of anti-emetic drugs plus acupuncture, clearly demonstrated that the combination arm was the most effective for preventing nausea and vomiting (Shen *et al.*, 2000). Stimulation of P6 may be done more conveniently with a small transcutaneous nerve stimulation (TENS) device, such as the

Reliefband™. A recent randomized controlled trial could not confirm its efficacy in the control of chemotherapy-induced nausea in women with breast cancer (Roscoe *et al.*, 2005). This may have been due to tolerance or because these patients were already maximally controlled by pharmaceutical anti-emetics, and therefore provided no advantage over medication alone. A meta-analysis of acupuncture-point stimulation for chemotherapy-induced nausea or vomiting shows a benefit over and above drug therapy (Ezzo *et al.*, 2005). However, not all the studies used optimal drug therapy, and this may need to be optimized before using acupuncture for refractory cases. Self-administered acupressure appears to have a protective effect for acute nausea.

Pain is a common symptom of cancer. Causes of pain can be disease- or treatment-related. Acupuncture has been shown to be effective in managing pain and other symptoms in cancer patients (Thompson and Filshie, 1998). In a retrospective study from the Royal Marsden Hospital (London, UK), 183 cancer patients with malignant pain, iatrogenic pain and radiation-induced chronic ulcers were treated with acupuncture (Filshie, 1984; Filshie and Redman, 1985). There was an improvement in 82% of the patients, but effectiveness only lasted for more than three days in half of the patients. Iatrogenic pain (for example, pain due to radiation fibrosis or skin ulceration) and pain due to secondary muscle spasm responded better than malignant pain. Furthermore, increased blood flow with improved healing of skin ulcers was demonstrated after treatment with acupuncture. A randomized controlled trial using ear acupuncture showed a profound effect on cancer pain (Alimi *et al.*, 2003). We also have similar experience with the high but short lasting effectiveness of acupuncture treatment in malignant pain. We suggest that acupuncture is a useful treatment modality that may best be combined with other treatments to improve pain control, resulting in reduced doses of pharmaceutical analgesics. This has the benefit of reducing the incidence and degree of drug-induced side effects. A systematic review could not demonstrate the effectiveness of acupuncture as an adjunctive analgesic method for cancer patients (Lee, 2005). However, there was only the one randomized controlled trial (Alimi *et al.*, 2003), and all the other studies were generally of poor scientific quality (Lee *et al.*, 2005). The intensity of stimulation, especially electrostimulation, may be important (Barlas, 2006).

Some patients may not be able to access an acupuncturist because of geographic restrictions or poor performance status. In addition, some patients may not tolerate needle insertions. For these patients, a transcutaneous nerve stimulator (TENS) has the advantage of easy administration by patients or staff with minimal basic training. Recently acupuncture-like TENS (AL-TENS) devices have been developed to mimic the treatment of acupuncture using low-frequency (e.g. 4 Hz), high-intensity stimulation (Pomeranz and Niznik, 1987). The goal is to recruit the high threshold type III afferent nerve fibers that are potent releasers of endorphins. Recent meta-analyses (including a Cochrane Database systematic review) have shown that AL-TENS is more effective than placebo, and improves function more than standard TENS, when treating chronic pain (Patel *et al.*, 1989; Gadsby and Flowerdew, 1997; Ernst and White, 1998; Ghoname *et al.*, 1999). AL-TENS devices are very simple machines that patients can learn to operate in less than an hour's training. An acupoint prescription may then be given to the patient who can administer the appropriate treatments with AL-TENS at home. The Codetron™ is a sophisticated AL-TENS device that has the advantage of reducing tolerance to its analgesic effect, by electronically rotating through a series of random electrical stimulation patterns and acupoint locations.

Other symptoms that may be helped by acupuncture include constipation, trismus (post-radiotherapy contracture of the masseter muscle) (Ernst and White, 1999), radiotherapy-associated proctitis (Zhang, 1987), hiccups (Yan, 1988), persistent yawning (Wong and Sagar, 2000), chemotherapy-induced peripheral neuropathy (Wong and Sagar, 2006), and dysphagia secondary to an esophageal neoplasm (Feng, 1984). Although observational studies by Filshie *et al.* (1996) showed that acupuncture may improve cancer-associated dyspnoea, this was not supported by a later randomized controlled study using semi-permanent acupuncture studs (Vickers *et al.*, 2005). Suppression of anxiety by acupuncture may be associated with an increase in the pain threshold (Widerstrom-Noga *et al.*, 1998). Acupuncture may also play a role in the treatment of fatigue and malignant cachexia through the modulation of cytokines and hormones (Lissoni *et al.*, 1996; Campbell and Murphy, 1998; Glaus, 1998; Stone *et al.*, 1998). A Phase II study of acupuncture for post-chemotherapy fatigue (average of two years) showed a mean improvement of 30% on

the Brief Fatigue Inventory (Vickers *et al.*, 2004). This met the research group's pre-specified criterion of clinical importance that has prompted the initiation of a randomized sham acupuncture controlled trial.

Patients who are in remission from their cancer may still continue to suffer from late treatment side effects with reduced quality of life. Radiation-induced xerostomia (dry mouth) is one of the distressing late side effects seen in patients who received radiation treatment that involved the parotid glands. The presence of this condition renders patients with loss of taste and difficulty in speaking and swallowing. Recently, acupuncture treatment has been found to increase blood flow to the parotid glands and may stimulate tissue regeneration in parotid glands damaged by radiotherapy (Blom *et al.*, 1992 and 1993; Talal *et al.*, 1992). A randomized controlled trial of 38 patients with radiation xerostomia was reported from the Karolinska Institute (Sweden) (Blom *et al.*, 1996). Subjects were randomized to either deep acupuncture treatment or superficial acupuncture treatment. The latter group was used as the control, despite previous evidence that superficial acupuncture treatment can have a certain degree of effectiveness and should not be used as a control in acupuncture treatment trials. In this study it was found that in both groups, there was more than a 20% increase in saliva flow rate in more than 50% of patients. In the deep acupuncture group, 68% of patients demonstrated an increase in salivary flow rate. Changes in the control group were smaller and appeared after a longer latency phase. Moreover, patients in the treatment group reported less dryness, less hoarseness and improved taste. In another study, 70 patients with xerostomia due to either Sjögren's syndrome or irradiation were treated with acupuncture (Blom and Lundeberg, 2000). A statistically significant increase in unstimulated and stimulated salivary flow rates (SFR) was found in all patients immediately after acupuncture treatment, and up to six months follow-up. After a review at three years, those patients who chose to be treated with additional acupuncture demonstrated a consistently higher median SFR, compared to those not having additional acupuncture. Despite, some limitations in the study design, both studies provide evidence suggesting acupuncture can be effective in treating radiation-induced xerostomia, with minimal side effects. In a prospective single cohort, visual analogue assessed study of acupuncture in palliative care patients with xerostomia, there was a highly significant alleviation of subjective

xerostomia (Rydholm and Strang, 1999). Other studies are confirming the clinical use of acupuncture for relief of radiation-induced xerostomia (Johnstone *et al.*, 2001).

At the Hamilton Regional Cancer Centre (Canada), a Phases I and II study of AL-TENS in the treatment of radiation-induced xerostomia has been completed (Wong *et al.*, 2003). Forty-five patients were randomized into three treatment groups with AL-TENS stimulation using the Codetron™ to three different sets of acupuncture points: Group A — CV 24, St 36, Sp 6, LI 4; Group B — CV 24, St 36, Sp 6, P6; and Group C — CV 24, St 5, St 6, Sp 6, P6. The goal of this study was to determine the optimum pattern of stimulation (based on TCM theory) prior to designing a placebo-controlled study. AL-TENS treatment was administered twice a week for a total of 12 weeks. Unstimulated and stimulated salivary flow rates before, during and after treatment were measured, and a survey of the patients' quality of life was assessed during a follow-up of one year. There was an improvement in xerostomia symptoms with a mean increase in the visual analogue score at three and six months after treatment completion. All patients demonstrated a significant increase in the mean basal and citric acid primed saliva production. The results suggest that Codetron™ treatment improves saliva production and related symptoms in patients suffering from radiation-induced xerostomia. Treatment effects are sustained at least six months after completion of treatment. A recent fMRI study showed activation of the insula region of the brain, the location associated with gustatory function (Deng *et al.*, 2006).

Acupuncture can reduce the hot flushes associated with anti-cancer hormone therapy. Three prospective uncontrolled cohort studies have been done, one in men castrated for prostate cancer, and two others in women taking tamoxifen for breast cancer. They all demonstrated a reduction in vasomotor symptoms (Hammar *et al.*, 1999; Tukmachi, 2000; Cumins and Brunt, 2001). Long-term administration using semi-permanent studs or with needles, especially at SP6 appears to be associated with more long-term relief of symptoms (Filshie *et al.*, 2005).

#### **(4) Improved Function and Quality of Life Through Psycho-Spiritual Integration**

Psycho-spiritual philosophy plays an important role in Chinese medicine. It is a complex philosophy beyond the scope of this chapter. Corresponding

concepts between Eastern and Western philosophies include the mind or *shen* (in the Heart meridian), the intellect or *yi* (in the Spleen meridian), the will power or *zhi* (in the Kidney meridian), the corporeal soul or *po* (in the Lung meridian), and the ethereal soul or *hun* (in the Liver meridian). Balancing of the Five Elements, associated with these psycho-spiritual concepts, through herbs and acupuncture, may improve psychological and spiritual well-being. The philosophy is well described in the literature (Hammer, 1990), but no scientific studies have addressed the interaction of herbs and acupuncture with psycho-spiritual adaptation. However, we previously quoted studies of acupuncture being effective for some patients with depressive-anxiety states, and treatment of these symptoms may have a positive effect on psycho-spiritual transformation and transcendence (Han, 1986; Roschke *et al.*, 2000).

Both Eastern and Western cultures have evolved different forms of “hands-on-healing”, prayer, and intention to heal through altered states of mind. The philosophy of Chinese medicine encourages an appropriate state of mind, such as compassion and healing intent, to accompany a practical procedure such as acupuncture (Rapgay *et al.*, 2000). Meditation is important for both the practitioner and the patient. It induces beneficial physiological adaptations. For example, meditation can restore a balance between the sympathetic and parasympathetic nervous systems (Benson, 1975). It can also increase melatonin levels that can relieve insomnia, and may have an anti-neoplastic effect (Massion *et al.*, 1995). There are currently multiple hypotheses that scientifically support the rationale of healing through influencing the patient’s body-mind memory and information system. These include manipulation of the systemic memory system (Schwartz and Russek, 1999), electromagnetic entrainment (Zimmerman, 1990; Seto *et al.*, 1992; Walleczek, 1992; Sisken and Walder, 1995; Cuzick *et al.*, 1998; Benford *et al.*, 1999; Childre and Cryer, 1999), interaction with subtle energy (Childre and Cryer, 1999), and non-local positive intention through compassion and centering (Grinberg-Zylberbaum *et al.*, 1994; Tiller and Pecci, 1997; Nadeau and Kafatos, 2000). Clinical trials of the effect of intent through prayer have shown efficacy in reducing side-effects and complications (Dossey, 1995; Harris *et al.*, 1999), and a recent systematic review and meta-analysis has confirmed the positive effects of “distant healing” (Astin *et al.*, 2000).

A similar process is seen in the practice of Reiki (from Japan), external Qigong (from China), Polarity Therapy and Therapeutic Touch. There is some evidence that they can all reduce the side effects of cancer and its treatment, and possibly even help to inhibit neoplastic cells (Macek, 1984; Feng *et al.*, 1988; Quizi and Li, 1988; Cohen, 1997; Olson and Hanson, 1997; Shah *et al.*, 1999).

These practices involve the practitioner laying-on her hands at a short distance from the patient, with a positive and loving intent to heal. The patient's "energy field" is assessed for the presence of any disturbance, which may be detected over areas of the body involved by disease processes. If an area of disturbance is detected, the practitioner will "smooth" the disturbance with her hands and channel "external energy" to heal the patient's disturbed somatic energy field.

Many studies have been done to evaluate the usefulness of this practice. Therapeutic touch can reduce anxiety and pain in dying cancer patients. It can be associated with an objective reduction of biochemical and biophysical indicators (Cox and Hayes, 1999). A meta-analysis has also suggested that therapeutic touch has a low to moderate positive effect size with an average effect ratio of 0.39 (Winstead-Fry and Kijek, 1999). Although there are still a lot of controversies regarding the effectiveness of therapeutic touch (Rosa *et al.*, 1998), particularly with respect to technique, end points and controls, the patients' subjective experience should be considered as important since it influences quality of life and immunological status (Engebretson and Wardell, 2000; Wardell and Weymouth, 2004). A recent randomized controlled trial of polarity therapy demonstrated a reduction of fatigue associated with radiotherapy (Roscoe *et al.*, 2005).

Qi gong, tai chi and awareness meditation are scientifically demonstrated to affect physiological processes, including electromagnetic changes that may represent the flow of *qi* (Tiller and Pecci, 1997; Syldona and Rein, 1999). These techniques encourage a personal sense of control, improve mood, reduce side effects of treatment, increase immunity, and may be associated with an improved outcome from cancer treatment (Meares, 1978; Young *et al.*, 1999). Tai chi is a simple exercise for cancer survivors that deserves further investigation. It is a widely practiced movement exercise combining characteristics of meditative practice and

aerobic exercise. Cancer survivors may benefit most from a mind-body intervention such as tai chi. While studies previously have compared changes of physiologic parameters comparing tai chi and aerobic exercise, representing the “body” aspect of tai chi, studies are lacking that may demonstrate differential effects of a mind-and-body activity compared to aerobic exercise programs. As the concept of the human being as a mental-spiritual-physical entity is widely held and fundamental to many health systems, there is a need to establish ways of investigating the mind and body effects, as well as their benefits for disease and well-being. A review of published randomized trials of tai chi suggests benefits in the elderly and in cardiovascular diseases (Mansky *et al.*, 2006). It is also likely to help cancer survivors and to contribute to their rehabilitation.

## 1.7 Conclusions

There is emerging scientific evidence that Chinese medicine can play an important role in the supportive care of cancer patients. There is enough preliminary evidence to encourage good quality clinical trials to evaluate the efficacy of integrating Chinese medicine into Western cancer care (Fontanarosa and Lundberg, 1998; Sagar, 1998 and 1999; Tagliaferri *et al.*, 2001). Currently, the evidence for the utility of TCM in cancer care is promising, but prospective randomized clinical trials for specific clinical scenarios are necessary to obtain reliable and generalizable data. Appropriate stratification and individualization according to TCM diagnostic criteria is possible within the context of a randomized controlled trial (Bensoussan *et al.*, 1998). We believe that an evidence-based approach can be integrated into an individualized therapeutic plan and that there is still a major role for individual belief-systems and psycho-spiritual experience. Assessment and measurement of coping strategies, maintenance of function, quality of life, and patient satisfaction is important. We are hopeful that future integration of different models of health, such as TCM, may lead to further improvement of cancer patients’ survival and quality of life (Sagar, 2001).

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