Integrative Medicine for Colon Cancer

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Conventional Cancer Care Overview

The World Health Organization has estimated there will be more than ten million documented new cases of cancer next year. Since 1971 according to official figures, over $1 trillion has been spent on conventional cancer research and treatment in the U.S. The current cost is at least $110 billion a year - over 10 percent of all U.S. medical expenditures, and two percent of the entire GNP. Despite, or perhaps because of these unprecedented costs, the cancer establishment remains largely closed to most truly independent, innovative treatments. More people make a living from conventional cancer research and treatment than die from the disease on an annual basis. The average cancer patient spends in excess of $100,000 treating the disease via the conventional medical protocol. Thus, there is a tremendous vested interest in the status quo of current cancer therapy. A 1986 report in the *New England Journal of Medicine* assessed progress against cancer in the United States during the years 1950 to 1982. Despite progress against some rare forms of cancer, which account for 1 to 2 per cent of total deaths caused by the disease, the report found that the overall death rate had increased substantially since 1950. "The main conclusion we draw is that some 35 years of intense effort focused largely on improving treatment must be judged a qualified failure." The report further concluded, "we are losing the war against cancer."

Clearly, there are appropriate conventional treatments that seem able to remove the immediate threat to life. Surgery, chemotherapy and radiation are used with some degree of success in killing cancerous tissue. However, that degree of success must be weighed against the possible side effects and after effects that are to be expected. For a period of time in the mid-1970s, Nobel laureate James Watson, one of the world's most respected biologists, repeatedly called the war on cancer scientifically bankrupt, therapeutically ineffective and wasteful.[1] In 1975, reporter Daniel S. Greenberg broke a virtual media blockage with a celebrated piece in the *Columbia Journalism Review*. This was the first time a respected journalist had dared to openly criticize the cancer establishment. The article quoted criticisms by oncologists and statisticians working within the "war" itself. In March, Greenberg wrote a follow-up article for the *New England Journal of Medicine*. Both articles showed that many of the claims of progress in the "war against cancer" were a sham, a statistical construct.[2] What this research and current research today show, is that survival rates for the most common types of cancer (those that make up 90% of cases), have remained virtually unchanged, except in the forms of rare types of cancers and one or two other exceptions.[3,4] Patients with advanced disease are often told their treatment will do more good than it is likely to and chemotherapy is presented as more effective (and less toxic) than it really is.

The side effects of chemotherapy are routinely understated. Proof of this is the discrepancy between what oncologists tell patients to do, and what oncologists themselves do (or would do) if they have cancer. Do they believe in their own treatments so much that they would take it themselves? When celebrated chemotherapist Dr. Kettering found out he had advanced cancer, he told his colleagues, "Do anything you want – but no chemotherapy!" And when Dr. Ketting's mother

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got cancer, she was sent to Germany for unconventional treatment. Further proof in Medicine's own lack of belief in some forms of oncology was a shown in 1986 when McGill Cancer Center scientists sent a questionnaire to 118 doctors who treated cancer. All of them were affiliated with the Princess Margaret Hospital in Toronto or with the Ontario Cancer Research and Treatment Foundation, which operates seven cancer clinics. These Canadian specialists were asked to imagine that they themselves had cancer, were asked if they would they consent to chemotherapy. 74% of specialists would not consent to chemotherapy. The reason they gave: the ineffectiveness of chemotherapy and its unacceptable degree of toxicity.[5]

Generally, patients treated with chemotherapy have good initial results, but this results in a poorer long-term prognosis. For example, in two studies, previously untreated patients given paclitaxel with platinum compound, between 59% and 82% of treated patients responded to therapy. However, these patients showed recurrent disease rather quickly, with median progression free survival times of roughly 17 months being reported. In studies where this regimen was given to patients with recurrent cancer, results were more variable but generally worse. Moreover, median progression-free survival times as low as three months were reported, with median overall survival times ranging eight to 31 months.

The medical establishments open criticism of Integrative or Alternative Medicine is said to be its lack of research, specifically, the holy grail of Randomized Controlled Trials (RCTs). However, this criticism is largely unfounded, although it is true there are a lot of unsubstantiated therapies in the alternative medicine arena. Nonetheless, there is a lot of research on many integrative therapies; however, there is a bias against them. For instance, much of the research on these therapies is published outside the U.S. where alternative therapies are more accepted. American publications have shown that there is a research bias among U.S. medical doctors and the medical establishment against accepting non-U.S. articles or publications as valid–a kind of a scientific nationalism. Also, there is a bias among many medical journals against publishing research on natural therapies. Furthermore, there is a financial disincentive against funding such studies, since most natural therapies cannot be patented they are not attractive to pharmaceutical companies, which fund a significant portion of all research in the U.S. Finally, although many of these studies on integrative therapies appear in peer-reviewed journals, many are journals that conventional doctors do not read.

The argument against a scientific basis for alternative medicine isn't valid and, in fact, is hypocritical. Less than 20% of all medical therapies are backed by the holy grail of RCTs. And in the case of chemotherapy and cancer treatment, that percentage may be less. Although RCTs are done on chemotherapeutic agents, 90% are done comparing one chemotherapeutic agent to another. There is little data comparing the effectiveness of chemotherapeutic agents to "nothing alone" or to "alternative therapies." Most chemotherapy agents aren't proven useful, they are just proven less harmful than another or more effective than another. And if statistical "gerrymandering" isn't enough, political pressure from lobbyists have convinced states and governing bodies to pass laws that make it a crime to treat cancer with anything but chemotherapy, radiation and surgery–intimidating those who would like to carry out valid research with non-*status quo* therapies.

Another way the data about the effectiveness of chemotherapy is twisted is "dose effect studies" which attempt to

find out whether higher doses of drugs cause longer survival. If patients in a high-dose study live longer than lower dose ones, one might assume the high-dose regimen is the better of the two. But this is not always true, for often the high-dose study requires that patients be in better overall physical condition before enrolling.

Another argument given by the medical establishment to validate the effectiveness of the "war on cancer" is historical trends, which show an increase in survival for almost all forms of cancer. However, there has been improvement in survival even of untreated patients over the years. This increase in survival across the board is more likely to be due to better supportive care, earlier detection, and a general increase in life-span.[6] Even though proponents of chemotherapy believe better chemotherapy is responsible for the increase in cancer survival, viewed historically, careful analysis of the statistical data show that age-adjusted cancer rates are actually stable or on the increase.[7] This sort of historical analysis used by proponents of chemotherapy is regarded by statisticians as the weakest form of indirect evidence. The National Cancer Institute, agrees with this.[8]

Unfortunately, in cancer research there is existence of bias and even fraud. For example, in 1994, one of the largest and most important chemotherapy testing trials, National Survival Adjuvant Breast and Bowel Project (NSABP), was the subject of investigations of unethical behavior and fraud. The issue was known three years prior by the Office of Federal Research Integrity, but never reported. What is so significant, however, about this one case is that the entire basis of chemotherapy is built upon the program which was the basis for the study. The program started in 1954 as the first randomized trial of chemotherapy for breast and bowel cancer and was the

outcrop of the formation of the Cancer Chemotherapy National Service Center, a division of the National Institutes of Health (NIH). Is this type of unfortunate conduct and misrepresentation representative of all cancer research? No. However, Dr. Bernard Fisher's response (the head of the project) was not very reassuring: "I challenge those in authority to audit other clinical trial databases and see how well they fare."[9] And it is likely, that many studies would not fair well. In order to make their results appear better than they really are some researchers often employ "strategies of torturing their data until it confesses."[10] Recent studies have shown that 50 percent of faculty members reported that they had been exposed to two or more types of misconduct and questionable research practices (*American Scientist,* 11-12/93).

Response Rates vs. Survival

It is one of the common misconceptions of chemotherapy that "shrinkage" or "response rates" have been proven to be correlated with increased survival time. Yet, in answer to a patient's question, "What are my chances?" The doctor may give impressive-sounding "response rates" of, say, 60 percent. You need to understand that response rates do not often correlate with increased survival or improved quality of life. Response rate alone is a poor parameter by which to assess therapeutic benefit in cancer and does not predict survival. And its effect on quality of life is very much determined by the nature of the treatment used.[11] This makes chemotherapy seem more effective than it is. The FDA defines a "response" in cancer as a reduction by 50 percent or more in all measurable tumors for 28 days or more. It is easy to see, how this terminology can be misunderstood, especially when talking about drugs that really don't increase life-span or absolute survival. Even more confusing is the talk

of "disease-free survival rates" which implies a cure, but really means something different. Even more confusing is that "disease-free survival" is not equivalent to "absolute survival." Response rates can be as high as 90%, but disease-free survival rates only 10%. Big difference! Much of the research done on chemotherapy today, solely uses "response rate" as the only criteria for gauging the effectiveness of that agent. Disease-free survival refers to an increase in time that the patient is free of cancer before a relapse occurs. Absolute survival is increased lifespan. Almost none of the studies on chemotherapy are measuring absolute survival.

Other biases, intentional and unintentional, exist in interpreting the usefulness of chemotherapy and include such things as lead time biases, stage migration, publication biases, and selection biases. Although beyond the scope of this paper, I highly recommend the book: *Questioning Chemotherapy,* by Ralph Moss, Ph.D., that illustrates the complex issues behind research and the fallacies of interpretation.

Chemotherapy is a dose-limiting treatment. That means at a certain point doctors have to stop giving it or it will kill the patient. Guyton's textbook on Medical Physiology (standard in many medical schools) states: "The goal of chemotherapy is to kill the cancer, before it [chemotherapy] kills the patient." Furthermore, some chemotherapy agents actually cause cancer. The International Agency for Research on Cancer (IARC) has identified 20 single chemo agents or regimens which cause cancer in humans, and about 50 more which are suspect. For example, one study showed that survivors of ovarian cancer treated with chemotherapy have a 100 times higher incidence of leukemia. This phenomenon is called "secondary cancers" which are caused by chemotherapy employed to treat the "primary cancer". By combining various forms of chemotherapy and then mixing those with radiotherapy, the risk of secondary cancers is increased. Chemotherapy can also promote the resistance of tumors to treatment, the occurrence of metastasis, and can suppress the immune system, damage the vascular system, and act directly in a thoroughly unpredictable way on tumor cells.[12]

Cancer is a Systemic, Not a Local Disease

"Let me tell you what really convinced me that the immune system has a lot to do with cancer," relates Neil Riordan, M.S., P.A.-C., Founder and Director of Aidan, Inc. "There was a paper published in the *Annals of the New York Academy of Sciences* in 1993 by Dr. James McCoy. It was a study of women with breast cancer. They had 77 women enrolled who were about to undergo surgery. When the surgery was performed they took tumor tissue and co-cultured this tissue with the patient's own lymphocytes (white blood cells). In some of the women, the lymphocytes had no reaction to the tumor tissue, and in other women the lymphocytes were stimulated and proliferated. This was nothing but the women's own natural immune response. Then they followed these women for more than 12 years. At that time, 47% of those women who showed no immune response had died. But of those women who had had an immune reaction, 95% were still alive." People develop cancer, says Riordan, because of "immune tolerance;" that is, their immune systems are tolerating these tumors or cancers to grow. "The whole idea is to break immune tolerance," Riordan says. "If you have a tumor, then your body's letting it be. Otherwise, it would have rid itself of the tumor a long time ago, before you could even feel it. And that immune tolerance is what we're all about. That's what we try to get rid of."

Riordan finds that by rescuing and rehabbing the immune system cells with unique, advanced methods, the patient's

immune tolerance transmutes into immune competence. This means that the patient's immune system recognizes, attacks and destroys tumors and cancer cells with lower doses, thus avoiding their destructive side effects. Cancer, therefore, is partly a failure of the immune system, and all forms of treating cancer should include support for the immune system. The problem with chemotherapy is that it destroys the immune system. Therefore, use of chemotherapy in my opinion is best if it is short-term, and in combination with scientifically sound nutritional strategies. Long-term chemotherapy increases the risk of side-effects.

Colon Cancer Overview

Colon cancer is the second biggest cancer killer in the United States and other industrialized countries, after lung cancer. It is strongly linked to a diet heavy in red meat and animal fat, as well as to smoking and heavy alcohol use, nutritional deficiencies and low fiber intake. A study, which appeared in the 1998 issue of the *Proceedings of the National Academy of Sciences* found a human gene that stops the growth of cancer cells when activated by fiber processing in the colon. In 1995, there was an estimated 140,00 new cases of colorectal cancer in the U.S. About that many die each year from colorectal cancer.

In its early stages, localized colon cancer is considered curable through surgery. Most if not all colon cancers are now believed to derive from premalignant polyps in the intestinal tract, which nutrient deficiencies are document to play a major role in their etiogenesis.[13] Unlike other cancers which use a staging system of roman numerals (e.g. stage I-IV), or the TNM system, colon cancer staging is based on what is known as Dukes' staging (named after pathologist, Cuthbert E. Dukes). Dukes' A is essentially the equivalent of state I, Dukes' B1 and B2 of stage II, Dukes' C1 and C2 of stage III, and Dukes' D of stage IV. While surgery is largely "curative" in early stages, the five

year survival rate in Dukes' D is only 5 percent. In stages Dukes' A, B and C, the primary treatment of choice is surgery. In Dukes' B, five-year survival rates are 70 to 80 percent. In Dukes' C, survival rates for five-years have been stated from 5 percent to 70 percent. The confusing issues stems from contradicting data, concerning the use of certain chemotherapeutic agents, 5-FU and levamisole. It has now been shown that 5-FU has benefit, whereas levamisole may be detrimental. Whether one or the other is used, or whether both are used in combination, determines the 5 year survival rate. 5-FU used alone shows the greatest positive impact.[14-18] In Dukes' D, where the cancer has already spread to distant sites, surgery is sometimes palliative but the disease is considered virtually incurable by conventional means.

Nutrition and Colon Cancer Overview

Long-term use of multi-vitamins may reduce the risk of colon cancer by 50 percent. Consumption of 200 IU of vitamin E per day may reduce the risk by 57 percent. A study published in the October, 1997, *Journal of Cancer, Epidemiology, Biomarkers and Prevention* shows there is a significant relationship between supplemental use of vitamins A, C, E, folic acid and calcium and lower colon cancer rates.

Another study, published in the journal *Nature Medicine* in 1997, found vitamin E enhanced the cancer-fighting effects of 5-fluorouracil (5FU), a chemotherapy drug regarded as the most effective treatment against colorectal cancer.

Intestinal Ecology and Colon Cancer

A paper in *Nutrition and Cancer* (1997;27:250) studied high- and low- risk diets and their relationship to gut flora-associated biomarkers of colon cancer, and increased beta glucuronidase activity. The study showed that a high-fat, low-fiber, high-refined-carbohydrate diet increased beta glucuronidase, whereas a diet high in

protein, higher in unrefined carbohydrate, lower in fat, and rich in fiber (particularly fibers such as those of the fructo-oligosaccharide family like inulin) lowered the beta glucuronidase and the risk of colon cancer. One benefit of the indigestible carbohydrates found in fiber is that they can be fermented by friendly bacteria in the gut to produce short-chain fatty acids like acetate, propionate, and (probably most important) the 4-carbon, short-chain fatty acid butyrate. Colonocytes (intestinal cells) use butyrate as a fuel. Butyrate is produced by gut bacteria through fermentation of non-digestible carbohydrate, is also very important as an anti-cell-transforming agent. It helps keep genes in the colonocytes in order, so to speak, to prevent the up-regulation of oncogenes. Therefore, production in the stool of the "friendly" short-chain fatty acids, acetate, propionate, and butyrate is very important and can be assessed with commercially available laboratory testing.

The intestinal microflora number in the trillions and are comprised of 100 to 400 different bacterial species. Maintaining the delicate balance of intestinal microflora is critical. Microbial balance is a key factor that determines whether substances in the intestine are converted into compounds that are beneficial or detrimental to the host.[19] There is considerable interest in the metabolic activities of the intestinal microflora, especially in relation to the etiology of colon cancer.[20] Epidemiological studies indicate a correlation between regular consumption of fermented dairy products and low incidence of colon cancer.[21,22] To investigate this, several studies measured fecal bacterial enzymes, such as ß-glucuronidase, nitroreductase, and azoreductase, which have been shown to catalyze reactions that convert procarcinogens to carcinogens. In one study oral administration of L. acidophilus to meat-fed rats substantially reduced the activities of these fecal bacterial enzymes. Similarly,

in a study with 7 human subjects, it was found that supplementing the diet with L. acidophilus for one month significantly reduced fecal ß-glucuronidase and nitroreductase activities. In a larger study with 21 human subjects, reductions of 2- to 4-fold in the activities of the three fecal enzymes were observed during a 4-week period of L. acidophilus supplementation. To investigate the role of L. acidophilus in prevention of chemically induced colon tumors in rats, two groups of rats were challenged with a colon cancer inducing agent. The experimental group, which was fed a supplement of the L. acidophilus strain, showed a lower incidence of colon cancer after a 20-week induction period than the control group.

In researching how diet affects colon cancer British and American subjects on a typical Western diet with a high proportion of meat in their diet were compared with Indian and Ugandan subjects who consumed strict vegetarian diets. Subjects with significant amounts of meat in the diet were found to have many more gram negative, non-spore forming anaerobes such as bactericides in their feces, whereas subjects who consumed a vegetarian diet were found to have a higher proportion of streptococci and enterobacteriaceae. Therefore, the anaerobe to aerobe bacterial ratio was higher in those people consuming a typical Western diet, manifesting in individuals as an increased risk of colon cancer.[23] Kruis et al reported significant increases in gut transit time, fermentative colonic bacterial activity, and intestinal bile acids in healthy subjects who were fed a diet high in refined sugar. The lengthened transit time caused an increase in secondary bile acid concentration, which may be associated with the development of colorectal cancer.[24]

Two papers discussing lactobacillus acidophilus stimulating production of trophic factors from murine macrophages

and bifidobacteria showed they inhibited colon cancer by modulating intermediate biomarkers of colon carcinogenesis.[25,26] These studies looked at various kinds of biochemical markers for colon carcinogenesis and showed they are lower after supplementation with bifidobacteria, and improved after supplementation with lactobacillus acidophilus.

The Effect of Modified Citrus Pectin (MCP) Fiber and the Phytonutrient/ Antioxidant Quercetin on Colon Cancer

The health benefits of fruits and vegetables have been the subject of numerous investigations over many years. Two natural substances, quercetin (a flavonoid) and citrus pectin (a polysaccharide found in the cell wall of plants) are of particular interest to cancer researchers. Research confirms that quercetin exhibits antitumor properties, likely due to immune stimulation, free radical scavenging, alteration of the mitotic cycle in tumor cells, gene expression modification, antiangiogenesis activity, or apoptosis induction (or a combination of these effects). MCP has also been shown to inhibit metastases. Early research conducted on the effect of oral administration of quercetin on colon-25 tumors in mice showed a significant reduction (50%) in size.[27] In one study, administration of MCP and quercetin reduced solid tumor size by 29-70%.[28] The largest amount of tumor size reduction was seen when both natural compounds were used together. Again, it is important to realize, however, that reduction in size alone is not a good predictor for extrapolating increases in absolute survival.

MCP is a water-soluble polysaccharide extracted from orange peel citrus pectin and is further pH-modified in the laboratory.[16] Previous studies have shown a link between administration of modified citrus pectin (MCP) and decreased metastasis of prostate tumors in rats and melanoma in mice.[29,30] Certain cancer cell types, such as prostate cancer, breast cancer, colon cancer, lymphoma, melanoma, glioblastoma, and laryngeal epidermoid carcinoma, all have specific protein molecules on their cell surface, called galectins. It has also been observed that metastatic cells express significantly more galectin-3 than the original primary tumor cells from which they were derived. Galectins are known for their carbohydrate-binding abilities. These proteins on the cancer cell surface are involved in binding between cells. They play an important role in cellular interactions during the metastatic process, binding to galactose on neighboring cancer cells and oligosaccharides on the surface of normal cells.[31] Human studies of colon, stomach and thyroid cancers showed that the amounts of galectin produced increased proportionally as the cancers progressed from their early to advanced stages.[32] Higher galectin levels permit greater adhesion of cancer cells and increases the ability of these cells to bind to non-cancerous cells at a distant site, where metastasis occurs. Thus, these binding sites and their ability to bind to cancer cell surface carbohydrates appear to be the basis by which cancer cells aggregate together and bind to metastatic target sites.

It is felt that MCP works by blocking tumor cell surface galectins, so that tumor cells cannot adhere to other cells. The galactose branch chains on the modified pectin molecule appear to be the part, which has an affinity for galectins on the tumor cell surface.[33] The impact of this galectin blockage is twofold: (1) to inhibit aggregation of cancer cells and (2) to inhibit adhesion of cancer cells to host cell surfaces. Due to these affects, MCP may also prevent the formation of organized tumor emboli. Although these results are very promising, more research is needed.

Quercetin

Quercetin is a flavonoid, found in many plants, fruits and vegetables, are of particular interest for their anticancer properties. In his text *"Natural Compounds in Cancer Therapy,"* Boik divides the flavonoids into five categories: anthocyanins, minor flavonoids, flavones or flavonoids, isoflavonoids, and tannins.[34] Quercetin, a member of the flavones group, is thought to be the most widely distributed in nature; approximately 25-50 mg of quercetin is consumed in a normal daily diet.[35] Bioflavonoids have been reported to be involved in several important biological processes including antihistamine effects, immunological modulation, inhibition of platelet aggregation, and anti-tumor activity.

Quercetin has been found to inhibit production of heat shock proteins in several malignant cell lines, including colon cancer.[36] Heat shock proteins form a complex with mutant p53, which allows tumor cells to bypass normal mechanisms of cell cycle arrest. Quercetin (10 microM) has been found to inhibit the expression of the p21-ras oncogene in cultured colon cancer cell lines.[37] Mutations in this important gene usually impair cellular GTP-ase, which has the effect of continual activation of the signal for DNA replication. Mutations of ras proto-oncogenes are found in over 50 percent of colon cancers, as well as many other tumor types.[38] Quercetin has a history of use by nutritional physicians as an anti-inflammatory and anti-allergy agent.[39] This action is thought to be largely due to the inhibition of lipoxygenase and cyclooxygenase, leading to a reduced production of eicosanoid inflammatory mediators. Quercetin is thought to inhibit cyclooxygenase more potently than lipoxygenase.[40] Inhibitors of cyclo-oxygenase (NSAIDS) are currently under research as potential chemotherapeutic agents, particularly for colon cancer.[41]

Biological Response Modifiers (Brms) Proteoglycan Molecules (PGMs) and Muraly Polysaccharide Complex (MPG)

Recently, anti-angiogenesis properties of a common weed, *Convolvulus arvensis,* has been discovered. Convolvulus is derived from the Latin, *convolere,* meaning to entwine, and arvensis means "of fields".[42] The genus *Convolvulus* contains about 250 species. *Convolvulus* is a ubiquitous weed but, arvensis is understood to contain alkaloids that are toxic. However, extracts of the plant largely comprised of proteoglycan molecules (termed PGMs) appear non-toxic in animal studies and have been shown to have potent anti-angiogenesis effects.[43]

Many lay and professional people assume weeds have no therapeutic value. However, the difference between "weeds" and "herbs" may merely be our understanding of them. The basic definition of a weed is that it is an unwanted plant. Weeds are also considered harmful, as they often compete with crops for light, moisture and nutrients and harbor insects and diseases harmful to crops. For farmers and agriculture specialists, weeds are unwanted plants; but for herbalists, all weeds are useful plants.[44] Such is the case of *Convolvulus arvensis,* as new research is showing it has great promise as a useful, safe and non-toxic chemotherapeutic agent.

As tumors grow they secrete substances that promote new blood vessel growth (angiogenesis). Recruitment of new blood vessels plays a crucial role in tumor survival and growth and every aspect of tumor growth require rapid vascular development. Tumors secrete substances which block local regulatory control measures and allow for unnaturally fast growth and replication. Many natural and chemical agents have been employed with the aim to halt or block angiogenesis in an attempt to arrest malignant growth, development and metastasis. One well

known natural substance promoted for its ability to halt tumor growth is shark cartilage. The data supporting shark cartilage is conflicting and its popularity has made it a high-price item due to supply and demand laws of economics and the lack of abundant availability of the source. Finally, environmental and ecological concerns limit the usefulness of shark cartilage as a chemotherapeutic agent. However, PGMs have been found to inhibit angiogenesis 100 times more than shark cartilage and is widely available due to its ubiquitousness. Because of this, extracts of this common weed (*Convolvulus arvensis*) hold great promise as a tool in the fight against cancer. Ironically, this herb has great promise in cancer but has a common name of "the cancer of weeds" among others.

After an anecdotal report of complete remission of human ovarian carcinoma after ingestion of an extract of *Convolvulus arvensis,* this "weed" was tested for its anti-angiogenic and immunogenic effects. It was found that a high molecular weight water extract of the plant contains almost no appreciable amount of alkaloids (devoid of its inherent toxicity) which are depleted during the extraction or manufacturing process. This proprietary extract is comprised primarily of proteoglycan molecules, termed PGMs, and marketed in the U.S. under the brand name C-Statin®.

In models of angiogenesis, mouse sarcoma, mouse Lewis lung carcinoma and human lyphocytoma, PMG was found to have potent anti-angiogenic and tumor inhibitory effects. Inhibition on angiogenesis was from 18-73%. Inhibition of tumor growth was 35-80% in the cancer models represented and lymphocytes were increased 12-46% in respective models.

Angiogenesis plays a significant role in tumor growth and metastasis. New blood vessels that develop locally as a result of angiogenic signaling allow for tumor growth by transporting nutrients and metabolic waste. Tumors cannot grow larger than 2 mm (the size of a pea) without inducing angiogenesis. The larger the volume of viable tumor in the body the more angiogenesis occurs, in turn increasing the amount of tumor. This circuitous process can ultimately lead to the demise of the host. There are many molecular factors in the human body that exhibit angiogenic activity. The family of vascular endothelial growth factors (VEGF) are the most potent endogenous angiogenic peptides presently known. Three characteristics of VEGF make it an interesting target for cancer treatment: 1) It stimulates endothelial cell proliferation and chemotaxis, thus acting as a "recruitment signal" to induce cell migration towards the signal and subsequent formation of capillaries therein; 2) It suppresses the immune system, most particularly by inhibiting dendritic cell maturation in vivo; 3) Abnormally high VEGF levels have been shown to correlate with poor prognosis and decreased survival time in people with cancer.

VEGF suppression is being studied as an anti-tumor strategy. Most recently a clinical trial of an anti-VEGF monoclonal antibody as a treatment for inflammatory breast cancer is underway under sponsorship of the National Institutes of Health. As part of a comprehensive approach to treating people with metastatic disease, 10 patients (with a variety of primary tumors) were prescribed two angiogenesis inhibitors, PGM and MPGC, at an average dose of 4 capsules 3 times per day by mouth. Baseline plasma VEGF concentration was determined prior to treatment. At intervals ranging from 12 to 42 days, a second plasma VEGF was measured. There was a significant ($p<.05$) reduction in plasma VEGF in this population. Interestingly, the subjects with the highest plasma concentration dropped the most. 4 of 5 subjects whose concentration was

outside of the reference normal range (33-86 pg/mL) had normalization.

Bindweed Extract, or *Convolvulus arvensis,* contains proteoglycans known to inhibit angiogenesis. MPGC is a cell wall extract from the bacterium Lactobacillus fermentum. MPGC upregulates the production of interleukin 12 (IL-12) by peripheral mononuclear cells. IL-12 is a potent angiogenesis inhibitor via downstream cytokine regulation. This is interesting in that a significant reduction of plasma VEGF was seen in a relatively short treatment interval. VEGF plays a role in 1) Angiogenesis, 2) Suppression of the localized immune response in and around tumor tissue. In particular VEGF in combination with other molecules - most notably interleukin 10 - suppresses antigen presentation from dendritic cells to cytotoxic T lymphocytes. It does this by inhibiting the maturation of dendritic cells; and 3) Mediation of lymphangiogenesis in tumors-a major component of the metastatic process.

Freidrich Douwes, M.D., head of the German Oncological Society and Chief Medical Officer of St. George Clinic, has clinically used and tested a PGM containing extract called C-Statin® in patients with cancer. He has the following to say on the usefulness of PGM extracts in cancer: "Using new technology, we are now capable of culturing tumor cells from patient's blood. We can then culture those cells and test whether they are likely to be susceptible to a variety of treatments: cytostatic agents, hormones and angiogenesis inhibitors. We tested PGM (bindweed extract), and several other angiogenesis inhibitors, including pharmaceutical angiogenesis inhibitors, for their ability to inhibit the expression of VEGF (vascular endothelial growth factor). VEGF is a powerful inducer of new blood vessel growth in tumors. Without angiogenesis, no new metastases can occur. In the majority of patients tested, PGM is the most effective suppressor of VEGF. Because of this new information, we are using PGM in the management of most our patients."

In summary, an extract of a common weed, *Convolvulus arvensis,* shows profound promise as an anti-cancer agent, largely through its ability to inhibit angiogenesis and its stimulatory effect on the immune system. The exact details regarding the anti-angiogenesis mechanism of bindweed extract are not completely understood. This extract should be studied further to elucidate its anti-tumor effects and mechanisms of action. Whether or not a decrease in plasma VEGF correlates with clinical response remains to be seen. There is encouraging data demonstrating that VEGF suppression results in a more positive prognosis. Well-designed clinical trials will help elucidate the effects of VEGF suppression in people with cancer.

Omega-3 Fatty Acids

Omega-3 fats inhibit expression of other gene agents, such as farnesyl protein transferases.[45,46] That relates to reduced colon cancer, reduced cytokine production, and reduced inflammation.[47] Omega-3 fatty acids have proven immune modulating and inflammatory modulating effects.

Enzymes

In 1902, John Beard (an embryologist at a Scottish medical school) wrote several texts and published many papers. His premise was that cancer cells are much like the trophoblasts of a pregnant woman in that they grow wildly. What makes the trophoblasts stop growing at three months and stop invading the uterus? He found that was the same time as the pancreatic enzymes of the embryo kicked into synthesis. So he argued that using high doses of pancreatic enzymes could turn off cancer. That's exactly what we saw, and there's data to support this. In many studies, it has been shown that bromelain is a better protease inhibitor

than the protease-inhibiting drugs. One study showed that enzymes will actually dissolve off the sialoglycoproteins that coat a cancer cell making it immune from the immune system so that now it can be seen and destroyed by the enzyme.

"A cohort of 1,242 patients with colorectal cancer was documented in 213 centres; 616 patients receiving complementary treatment with oral enzymes (182 OE only; 405 other complementary drugs; 29 protocol violators), and 626 patients not receiving OE (368 control only; 229 other complementary drugs; 29 protocol violators). 1,162 patients underwent primary surgery of whom 526 received adjuvant chemotherapy and 218 radiotherapy. The median follow-up time for the OE-group was 9.2 months; for the control group 6.1 months. The primary test criterion of efficacy for OE treatment was the multivariate effect size (Wei, Lachin, 1992) of the changes from baseline of the disease, and therapy-associated signs and symptoms (nausea, vomiting, changes in appetite, stomach pain or stomach disorder, tiredness, depression, memory or concentration disorder, sleep disturbance, dizziness, irritability, dyspnea at rest, dyspnea during activity, headache, tumor pain, cachexia, skin disorders and infections). Tumor related events, e.g. death, were evaluated by the number of events observed and time to event. Safety of treatment with OE was analyzed by number and severity of adverse events, their duration, treatment and outcome.

A significant reduction in disease associated signs and symptoms was observed in patients treated with OE alone, but not in those patients receiving OE in addition to other complementary treatments. Adverse reactions of chemo- or radiotherapy were diminished in all patients receiving OE. Analysis of survival did not demonstrate a reduced number of deaths in the OE group. However, a trend to prolongation of survival could be demonstrated, particularly in the patients with disease stage Dukes' D, receiving OE treatment in the subgroup receiving OE in addition to other complementary treatments. Similar but less pronounced trends were observed for disease stages Dukes' B and C. In the OE-group, 21 of 616 patients (3.4%) experienced OE associated adverse reactions, all of them reported as mild to moderate gastrointestinal symptoms.

Complementary treatment of colorectal cancer patients with OE improves their quality of life by reducing both the signs and symptoms of the disease, and the adverse reactions associated with adjuvant antineoplastic therapies. This epidemiological retrolective cohort analysis provides evidence that the patients may also benefit by a prolongation of survival time. OE preparations were generally well tolerated."[48-53]

Artemisinin

Artemisinin has been used for about 30 years in Vietnam and China for cancer treatment. And the experience with artemisinin for this purpose is increasing. This history probably lead to the recent cited cancer research with artemisinin. For the past ten years, the Hoang medical family, with three generations of sophisticated physicians, have used artemisinin in combination with several other herbs to treat cancer, and eliminate necrotic material from the body. In 1995, a paper by Lai appeared in *Cancer Letters* concerning the use of artemisinin against numerous cancer cell lines *in vitro.* This article has mobilized interest in artemisinin as an addition to anticancer treatment.[54] There are a number of properties shared by cancer cells which favor the selective toxicity of artemisinin against cancer cell lines, and against cancer *in vivo.* Cancer cells have higher rates of iron flux via transferring (iron) receptors, than normal cells and are particularly sensitive to oxygen radicals.[55] A subsequent article appeared in *Life Science* in 2001 by Singh and Lai on the selective toxicity of artemisinin and holotransferrin towards human breast cancer cells.[56] Artemisinin becomes cytotoxic in the presence

of ferrous iron. Since they showed iron influx is naturally high in cancer cells, artemisinin and its analogs selectively kill cancer cells under conditions *in vivo*. Further, it is possible to increase or enhance iron flux in cancer cells using the conditions that increase intracellular iron concentrations. They report on the incubation of holotransferrin, which increases ferrous iron in cancer cells, in combination with artemisinin, and demonstrate its effectiveness in a type of radiation resistant human breast cancer cell line in vitro. A third paper, by Efferth, et al. published in *Oncology* in 2001 stated that the anti-malarial artesunate is also active against cancer.[57] Artesunate (ART) is a semi-synthetic derivative of artemisinin, and has been analyzed for it's anticancer activity against fifty-five cell lines by the Developmental Therapeutics program of the National Cancer Institute, USA. ART was most active against leukemia and colon cancer cell lines. Mean growth inhibition was 50%. Intermediate GI 50 values were obtained for melanomas, breast, ovarian, prostate, CNS, and renal cancer cell lines. Most important, a comparison of ART's cytotoxicity with those standard cytostatic drugs showed that ART was active in molar ranges comparable to those of established anti-tumor drugs. Leukemia lines resistant to either doxorubicin, vincristine, methotrexate, or hydroxyurea were tested. None of these drug resistant lines showed any resistance to ART.

Nutrients and Anti-oxidants in Cancer

Folic Acid (Folate): Higher intake of folic acid is associated with lower risk of colon and breast cancer, particularly in individuals who possess specific polymorphisms like the C677T polymorphism in methylenetetrahydrofolate reductase (30-60% of the population). This is due to the role folate plays in methyl donation in the body. Methylation defects, caused by folate and other methyl donor insufficiency, are thought to underlie colon

cancer. Some studies show promise of administration of folate, and correction of methylation defects in colorectal cancer.[58] Note: Folic acid is contraincidated during treatment with the chemotherapy drug 5-FU. During this time, use other methyl donors, such as SAMe.

Vitamin A and Carotenoids In the Colorectal Cancer Study at the University of Modena, 255 subjects with a history of colonic adenoma were randomized to receive treatment with either (1) vitamin A (axerophthol palmitate, 30,000 IU per day), vitamin C (1 gram per day), and vitamin E (d,l-alpha-tocopheryl acetate, 70 mg per day); (2) lactulose; or (3) placebo for an average of 18 months.[46] At the end of the treatment period, adenoma recurrence had occurred in 5.7 percent of the antioxidant vitamin group compared to 35.9 percent of the placebo group (p < 0.001).[59]

The integrity of the intestinal mucosa depends not only on the state of the immune system, the GALT and MALT, but also on the nutritional status and vitality of the rapidly turning epithelial tissue. As Dr. Butterworth reminded us, this tissue needs to be replaced every few days. Regeneration of this tissue is highly dependent on nutritional status of the parent cells. Insufficiencies of vitamin A, folic acid, B_{12}, and B_6 can result in imperfections in cellular regulation and dysplasia. Vitamin A plays an important role in cell differentiation and cell turnover. This may explain why individuals who have colorectal polyps and certain types of dysplastic gut mucosa are found to have low levels of serum vitamin A and the carotenoid zeaxanthin.

This was addressed in a recent study published in the *European Journal of Gastroenterology and Hepatology*. The authors found a very close inverse correlation between the serum level of vitamin A and colorectal polyps.[60] Colorectal polyps are associated statistically with increased colonic cancer risk. One might say that low

levels of intake and absorption of vitamin A and carotenoids may be associated with increased dysplasia of the gut mucosa and increased risk of colon carcinogenesis. J.L. Schwartz from Harvard shows that high doses of beta carotene will cause a reprogramming of the mutant p53 gene back to the normal p53 gene. It actually reverses from the mutant form that triggered cancer to the cancer-protective gene. Other studies have shown that high doses of carrot juice – for example, 11 oz of carrot juice a day –will decrease chromosome breakage by a third.

Changing to a diet with a lot of phytochemicals and brassica vegetables is also important. Phytochemicals, such as glucosinolates and nutrients in brassica vegetables help the body to detoxify. For instance, just changing two vegetables a day to brassicas increases the metabolism of Tylenol by seventeen percent. We have tremendous power over our genes and our detoxification ability by just with what we put in our mouths.

Vitamin C (ascorbate / ascorbic acid) and Colon Cancer. The theoretical concern of antioxidant use concurrently during chemotherapy lies in the knowledge that many current clinical oncology drugs induce cellular toxicity and death through mechanisms of intracellular free radical generation and it is thought that antioxidants may block this action. In the September 1999 issue of *Oncology,* an article appeared in which the authors discuss possible theoretical negative interactions of cancer chemotherapy drugs and concurrent use of antioxidants.[61] The experimental evidence for such a hypothesis is lacking and, in the majority of cases, shows the opposite. There are only three presently known examples in which any agent classifiable as an antioxidant has been shown to decrease effectiveness of radiation or chemotherapy in vivo, none of which apply to Vitamin C.[62] Vitamin C has been shown in either animal or human studies to either increase the efficacy and/or decrease the toxicity of the following chemotherapeutic agents: Alkylating agents (cyclophosphamide, ifosfamide, busulphan, melphan), Antibiotic type agents (doxorubicin (adriamycin), bleomycin, epirubicin, daunorubicin), Anti-metabolites (5-Fluorouracil, methotrexate), Platinum compounds (cisplatin), Radiotherapy, Hormone Therapies (tamoxifen), and Plant Alkaloids (etoposide, vincristine, paclitaxel).[63] For further review, the reader is referred to the study by Lamson and Brignall, *Alternative Medicine Review,* April 2000.

The ideal agent to treat cancer would be cytotoxic to tumor cells, but non-toxic to normal cells. Vitamin C has long been known to fulfill these requirements but is obscured, ridiculed and criticized by conventional medicine in favor of more powerful and toxic chemotherapeutic agents.[64]

Colonic polyps are recognized as a frequent precursor to colorectal cancer. In a group of 36 patients with polyps, 19 received 3 grams ascorbate daily and 17 received placebo. The researchers noted a decrease in polyp area after nine months of treatment with ascorbate but not placebo. In addition, a trend toward decrease in polyp number was noted.[65] Other researchers have used antioxidants to prevent recurrence of polyps in patients who had undergone surgical removal of their polyps.

Clinical data demonstrates that ascorbic acid potentiate chemotherapy effects. However, there are still theoretical concerns from conventional oncology questioning the use of antioxidants, such as vitamin C, concurrently with chemotherapy.[66-69] The majority of clinical evidence indicates the usefulness of anti-oxidants, like Vitamin C, concurrently with most types of chemotherapy.[70,71] In a recent review paper in The *Journal of American Nutraceutical Association,* Block and Evans reviewed all English articles listed in *Index Medicus*

between the years 1990-2000 related to antioxidant and interactions with anticancer drugs or radiation and concluded, "...there is a rational basis for the continued use of antioxidant agents as a therapeutic adjunct in cancer therapy."[72]

Vitamin C has been extensively tested *in vitro* and *in vivo* for its ability to prevent the adverse effects of, decrease resistance to, and increase the effects of chemotherapeutic agents.[73] Combined administration of vitamin C (1g/kg) and vitamin K given prior to chemotherapy increased survival and the effect of several chemotherapeutic agents in a murine ascitic liver tumor model.[74] The vitamin combination did not increase the toxicity of these agents to healthy tissue. Splenic and thymic weights of the vitamin-treated animals were higher than those receiving cytotoxic treatment alone, suggesting an immune-stimulating action of these vitamins.

As well as being safe to use concurrently with chemotherapeutic agents, vitamin C has also been shown safe to be used concurrently with Radiation. Vitamin C has been shown to have a radio-protective effect on normal cells while concurrently having a radio-sensitizing effect on malignant ones.[75,76]

Vitamin D3. Numerous studies have shown Vitamin D to be associated with a lower incidence of cancers, and colon cancer. The mechanism of Vitamin D's association with a lower colon cancer risk was not understood until recently, when it was discovered that laboratory animals given doses of vitamin D and then given lithocholic acid do not get colon cancer. It was also discovered that colon cancer patients have a high incidence of lithocholic acid. David Mangelsdorf, a professor of pharmacology and a researcher at the Howard Hughes Medical Institute at the University of Texas Southwestern in Dallas, recently published findings in the journal, *Science* that vitamin D helps the body to break down lithocholic acid. Recent evidence suggests colon cancer may largely be caused by bile acid produced to help digest fat, specifically lithocholic acid. Lithocholic acid occurs naturally and can be broken down by the body. However, a high fat diet and dysbiosis (alterations in gut ecology) may allow the accumulation of lithocholic acid, which acts as an oxidant, irritant, mutagen and procarcinogens.

Calcium and vitamin D are synergistic minerals, and taking too much of either can throw off the balance of the other. Vitamin D should be taken with calcium, which has also been shown to have benefit in colon cancer. Supplementation with 1200 mg of calcium (as calcium carbonate) for four years was associated with a significant, 15 percent reduction in the risk of adenoma recurrence (p = 0.03).[48] In this double-blind trial (n=832), the average number of adenomas seen in calcium-supplemented patients was 24-percent lower than in those taking placebo (p=0.02).[77]

Selenium. The mineral and micronutrient selenium has been shown benefit in preventing and treating cancer and colon cancer. Observational and experimental studies have suggested that dietary supplementation with selenium can inhibit the development of colon cancer.[78] Patients with colon cancer have been shown to have decreased levels of selenium in their diet and tissues.[79] A landmark study found significant reductions in certain cancer incidence among individuals using 200 mcg of selenium supplementation for more than four years. Researchers at the University of Arizona found that people who took the selenium supplements versus those that took a placebo, had 63 percent fewer cases of prostate cancer, 58 percent fewer colon and rectal cancers, and 45 percent fewer lung cancers. Furthermore, the selenium group suffered 50 percent fewer cancer deaths over all than the placebo group.[80]

Summary

Abram Hoffer, who has seen over 970 patients suffering from cancer in the last 20 years, has concluded that, "... the optimum treatment for cancer today is a combination of xenobiotic and orthomolecular therapy and that the treatment must be started as soon as possible." Hoffer's view is that orthomolecular treatment improves the quality of life, decreases side effects and is palatable. Furthermore, he states, "There can be no logical reason today why most of the research funds should go only toward the examination of more chemotherapy and more ways of giving radiation. There must be a major expansion into the use of orthomolecular therapy to sort out the variables and to determine how to improve the therapeutic outcome of treatment." Furthermore, conventional and alternative medicine both need to scrutinize their own treatments and consider working together and integrating sound, rational approaches from both camps.

References

1. Greenberg D: A critical look at cancer coverage. *CJR,* 1975; Jane-Feb: 40-44.
2. Greenberg D: Progress in cancer research - don't say it isn't so. *NEJM,* 1975; 292: 707-708.
3. Illich: I: *Medical nemesis: the expropriation of health.* NY: Bantam Books, 1976.
4. Braverman A: Medical oncology in the 1990s. *Lancet,* 1991;337:901-902
5. Hansen HH: Advanced non-small cell lung cancer: to treat or not to treat? *JCO,* 1987;5:1711-1712.
6. Rankin EM: Non-small-cell lung cancer. In: *Slevin and Staquest,* 1986: 447-491.
7. Ries LAG et al: *Cancer Statistics Review,* 1973-1990, Bethesda: NCI, 1990.
8. Miller BA, et al: [eds.] SEER Cancer Statistics review: 1973-1990 *(NIH Pub. No. 93-2789),* Bethesda, MD: NCI, 1993.
9. Crewdson J: Head of federal cancer institute plans to resign. *Chicago Tribune,* 12/22/94
10. Smigel K: Experts agree to disagree on adjuvant therapy for breast cancer. *JNCI,* 1990; 82: 640-641.
11. Macaulay V, Smith IE: Advanced breast cancer. In: *Slevin and Staquest,* 1986: 273-258.
12. McMillan TJ, Hart IR: Can cancer chemo-
therapy enhance the malignant behavior of tumors? *Cancer and Metast Rev,* 1987; 6: 503-520.
13. Weir DG, Scott JM: Colonic mucosal folate concentrations and their association with colorectal cancer. *Am J Clin Nutr,* 1998; 68: 763-4.
14. Mortel CG, et al: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *NEJM,* 1990; 322: 352-358.
15. Steele GDJ, et al: National cancer data base: annual review of patient care. Atlanta: *Am Cancer Soc,* 1994.
16. Chlebowski RT, et al: Late mortality and levamisole adjuvant therapy in colorectal cancer. *Brit J Cancer,* 1994; 69: 1094-1097.
17. Davis S, et al: Combination cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy for extensive non-small cell carcinomas of the lung. *Cancer Treat Rep,* 1981; 65: 955-958.
18. *National Cancer Institute,* PDQ. Statement on colon cancer, 4/14/94.
19. Donaldson RM: Normal Bacterial Populations of the Intestine and Their Relation to Intestinal Function. *NEJM,* 1964;270:1050-56.
20. Goldin BR, Gorbach SL: The effect of milk and Lactobacillus feeding on human intestinal bacterial enzyme activity. *Am J Clin Nutr,* 1984; 39: 756-61.
21. Goldin B, Gorbach SL: Alterations in fecal microflora enzymes related to diet, age, Lactobacillus supplements, and dimethylhydrazine. *Cancer,* 1977; 40: 2421-26.
22. Goldin BR, Swenson L, Dwyer J, et al: Effect of diet and Lactobacillus acidophilus supplements on human fecal bacterial enzymes. *J Natl Cancer Inst,* 1980; 64: 255-61.
23. Hentges R: Does diet influence human fecal microflora composition? *Nutr Rev,* 1980; 38: 329-335.
24. Kruis W, Forstmaier G, Sheurlen C, Stellard F. Effects of diets low and high in refined sugars on gut transit, bile acid metabolism, and bacterial fermentation. *Gut,* 1991; 32: 367-371.
25. Hambly RJ, Rumney CJ, Fletcher JM, Rijken PJ, Rowland IR: Effects of high- and low-risk diets on gut microflora-associated biomarkers of colon cancer in human flora-associated rats. *Nutr Cancer,* 1997; 27(3): 250-255.
26. Singh J, Rivenson A, Tomita M, et al: Bifidobacterium longum, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates the intermediate biomarkers of colon carcinogenesis. *Carcinogenesis,* 1997; 18(4): 833-841.

27. Lott J, Hayashi A: Effect of daily oral administration of quercetin on implanted colon-25 tumor growth in balb-c mice. *Unpublished.*

28. Hayashi A, Gillen AC, Lott JR: Effects of Daily Oral Administration of Quercetin Chalcone and Modified Citrus Pectin on Implanted Colon-25 Tumor Growth in Balb-c Mice. *Alt Med Rev,* 2000; 5(6): 546-552.

29. Pienta KJ, Naik H, Akhtar A, et al. Inhibition of spontaneous metastasis in a rat prostate cancer model by oral administration of modified citrus pectin. *J Natl Cancer Inst,* 1995;87:348-353.

30. Platt D, Raz A. Modulation of the lung colonization of B16-F1 melanoma cells by citrus pectin. *J Natl Cancer Inst,* 1992;84:438-442.

31. Raz A, Lotan R. Endogenous galactoside-binding lectins: a new class of functional tumor cell surface molecules related to metastasis. *Cancer Metastasis Rev,* 1987; 6:433-452.

32. Robert S, Bresalier RS, Yan PS, et al. Expression of the endogenous galactose-binding protein galectin-3 correlates with the malignant potential of tumors in the central nervous system. *Cancer,* 1997; 80:776-787

33. Inohara H, Raz A: Effects of natural complex carbohydrate (citrus pectin) on murine melanoma cell properties related to galectin-3 functions. *Gllycoconj J,* 1994 Dec; 11(6):527-32.

34. Boik J: *Cancer and Natural Medicine: A Textbook of Basic Science and Clinical Research.* Princeton, MN: Oregon Medical Press; 1995:155.

35. Kang Z, Tsai S, Lee H: Quercetin inhibits benzo[a]pyrene-induced DNA adducts in human Hep G2 cells by altering cytochrome P-450 1A1 gene expression. *Nutr Cancer,* 1999; 35: 175-179.

36. Koishi M, Hosokawa N, Sato M, et al: Quercetin, an inhibitor of heat shock protein synthesis, inhibits the acquisition of thermotolerance in a human colon carcinoma cell line. *Jpn J Cancer Res,* 1992; 83: 1216-1222.

37. Ranelletti FO, Maggiano N, Serra FG, et al: Quercetin inhibits p21-ras expression in human colon cancer cell lines and in primary colorectal tumors. *Int J Cancer,* 1999; 85: 438-445.

38. DeVita NT, Hellman S, Rosenberg SA, (eds): *Cancer: Principles and Practice of Oncology,* 5th ed. Philadelphia, PA: Lippencott-Raven; 1997.

39. Quercetin (Monograph). *Altern Med Rev,* 1998; 3: 140-143.

40. Welton AF, Hurley J, Will P: Flavonoids and arachidonic acid metabolism. *Prog Clin Biol Res,* 1988; 280: 301-312.

41. Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis (part II). *J Natl Cancer Inst,* 1998; 90: 1609-1620.

42. Gray, A: *Gray's Manual of Botany; a handbook of the flowering plants and ferns of central and northeastern United States and adjacent Canada,* 8th ed, 1970: D. VanNostrand Co., New York.

43. Riordan NH, Menh X, Taylor P, Riordan HD: Anti-angiogenic, anti-tumor and immuno-stimulatory effects of a non-toxic plant extract *(PMG).*

44. Oudhia P, Tripathi RS: Medicinal weeds of kharif crops in the plains of Chhattisgarh. *Bhartiya Krishi Anusandhan Patrika.* 1998; 13(1/2) : 33-38.

45. Singh J, Hamid R, Reddy BS: Dietary fish oil inhibits the expression of farnesyl protein transferase and colon tumor development in rodents. *Carcinogenesis,* 1998; 19(6): 986-989.

46. Xi S, Cohen D, Chen LH: Effects of fish oil on cytokines and immune functions of mice with murine AIDS. *J Lipid Res,* 1998;39(8):1677-1687.

47. DS Alberts, C Ritenbaugh, JA Story, et al: Randomized, double-blinded, placebo-controlled study of effect of with Intravenous Vitamin C. *J Orthomol Med, Special Issue, Proceedings from Vitamin C as Cancer Therapy Workshop. Montreal,* 1999; 15(4): 201-13.

65. Bussey HJ, DeCosse JJ, Deschner EE, et al: A randomized trial of ascorbic acid in polyposis coli. *Cancer,* 1982; 50: 1434-1439.

66. Cohen M, Krasnow H: Cure of advanced Lewis lung carcinoma (LL): a new treatment strategy. *Proceedings of AACR.* 1987; 28: 416.

67. Lupulesco A: Vitamin C inhibits DNA< RNA and protein synthesis in epithelial neoplastic cells. Intl J Vit Res. wheat bran fiber and calcium on fecal bile acids in patients with resected adenomatous colon polyps. *J Natl Cancer Inst,* 1996 88: 81a-92a.

48. Piela T, Kulig J, Hanisch J, Bock PR: Influence of a complementary treatment with oral enzymes on patients with colorectal cancers - an epidemiological retrolective cohort study. *Chemother Pharmacol,* 47 (suppl) S55-S63, 2001

49. Popiela T, Kulig J, Klek S et al: Enzyme therapy in patients with advanced colorectal cancer. *Przegl Lek,* 2000; 57 Suppl 5: 138-9.

50. Popiela T, Kulig J, Klek S, et al: Double-blind pilot-study on the efficacy of enzyme therapy in advanced colorectal cancer. *Przegl Lek,* 2000; 57 Suppl 5:142

51 Wenning HG, Stauder G: Complementary Enzyme Treatment in Patients with Colon or

Gastric Cancer. *Int J Oncology,* 1995: 996.

52. Kim, JP, W. S. Hah, and S. J. KIm. Effect on rossette forming T-lymphocyte level in immuno-chemotherapy using Picibanil and Wobe-Mugos in gastric cancer patients. *J Korean Surg Soc,* 1981; 23.

53. W. Werk. Klinische und immunologische Wirkung von Enzymen bei einer Kombinations Chemotherapie des Kolonkarzinoms. *Krebs-geschehen,* 1980; 1: 15-18.

54. Lai H., Narendra S. *Cancer Letters,* 91:41-46, 1995.

55. May WS: *J Membr Biol,* 88:205-215, 1985.

56. Singh NP, Lai H. *Life Sci,* Nov 21, 70(1):49-56, 2001.

57. Efferth T, Dunstan H, Sauerbrey A, Miyachi H, Chitambar CR. Antimalarial artesunate is also active against cancer, *Oncol,* 2001, Apr; 18(4): 767-73.

58. Cravo ML, Pinto AG, Chaves P, et al. Effect of folate supplementation on DNA methylation of rectal mucosa in patients with colonic adenomas: Correlation with nutrient intake. *Clin Nutr,* 1998; Apr; 17(2):45-9.

59. In the *Colorectal Cancer Study at the University of Modena,* 255 subjects with a history of colonic adenoma were randomized to receive treatment with either (1) vitamin A (axerophthol palmitate, 30,000 IU per day), vitamin C (1 gram per day), and vitamin E (d,l-alpha-tocopheryl acetate, 70 mg per day); (2) lactulose; or (3) placebo for an average of 18 months.46 At the end of the treatment period, adenoma recurrence had occurred in 5.7 percent of the antioxidant vitamin group compared to 35.9 percent of the placebo group (p < 0.001).

60. Rumi G, Szabo I, Vincze A, et al: Decrease in serum levels of vitamin A and zeaxanthin in patients with colorectal polyp. *Eur J Gastroenterol Hepatol,* 1999;11:305-308.

61. Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. *Oncology,* 1999; 13: 1003-1012.

62. Davis W. Lamson, MS, ND, Matthew S. Brignall, ND. Antioxidants and Cancer Therapy II: Quick Reference Guide. *Altern Med Rev,* 2000; 5(2).

63. Davis W. Lamson, MS, ND, Matthew S. Brignall, ND. Antioxidants and Cancer Therapy II: Quick Reference Guide. *Altern Med Rev,* 5(2), 2000

64. Riordan N, Riordan H, Casiari J: *Clin Exper Experiences,* 1991; 61: 125-29.

68. Varga M, Airoldi L: Inhibition of transplantable melanoma tumor development in mice by prophylactic administration of Ca-ascorbate.

Life Sci, 1983; 32: 1559-64.

69. Pierson H, Meadows G: Sodium ascorbate enhancement of carbidopalevodopa methyl ester antitumor activity against pigmented B-16 melanoma. *Cancer Res,* 1983; 43: 2047-51.

70. Prasad K, et al: High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy, *J Am Coll Nutr,* 1999; 18:13-5.

71. Chinery R, et al: Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer: a p53-independent induction of p21WAF1/CIP1 via C/EBPbeta. *National Med,* 1997; 3: 1233-41.

72. Block J, Evans S: A review of recent results addressing the potential interactions of antioxidants with cancer drug therapy. *JANA.* 4(1):11-20, 2001.

73. Shimpo K, Nagatsu T, Yamada K, et al: Ascorbic acid and adriamycin toxicity. *Am J Clin Nutr* 1991;54:1298S-1301S.

74. Taper HS, de Gerlache J, Lans M, et al: Nontoxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. *Int J Cancer,* 1987; 40: 575-579.

75. Okunieff P. Interactions between ascorbic acid and the radiation of bone marrow, skin, and tumor. *Am J Clin Nutr,* 1991;54:1281S-1283S.

76. Okunieff P, Suit HD. Toxicity, radiation sensitivity modification, and combined drug effects of ascorbic acid with misonidazole in vivo on FSall murine fibrosarcomas. *J Natl Cancer Inst,* 1987;79:377-381.

77. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med,* 1999;340:101-107.

78. BS Reddy, A Rivenson, K El-Bayoumy, P Upadhyaya, B Pittman, and CV Rao. Chemoprevention of colon cancer by organoselenium compounds and impact of high- or low-fat diets. *J Natl Cancer Inst,* 1997 89: 506-512.

79. Van den Brandt PA, GoldbohmRA, Van Veer P et al: A prospective cohort study on toenail selenium levels and risk of gastrointestinal cancer. *J Natl Canc Inst,* Vol 85, 224-229

80. Clark LC, Combs GF, Turnbull BW, et al: Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. *JAMA,*1996; 276(24): 1957-1963.