Cancer of the Pancreas

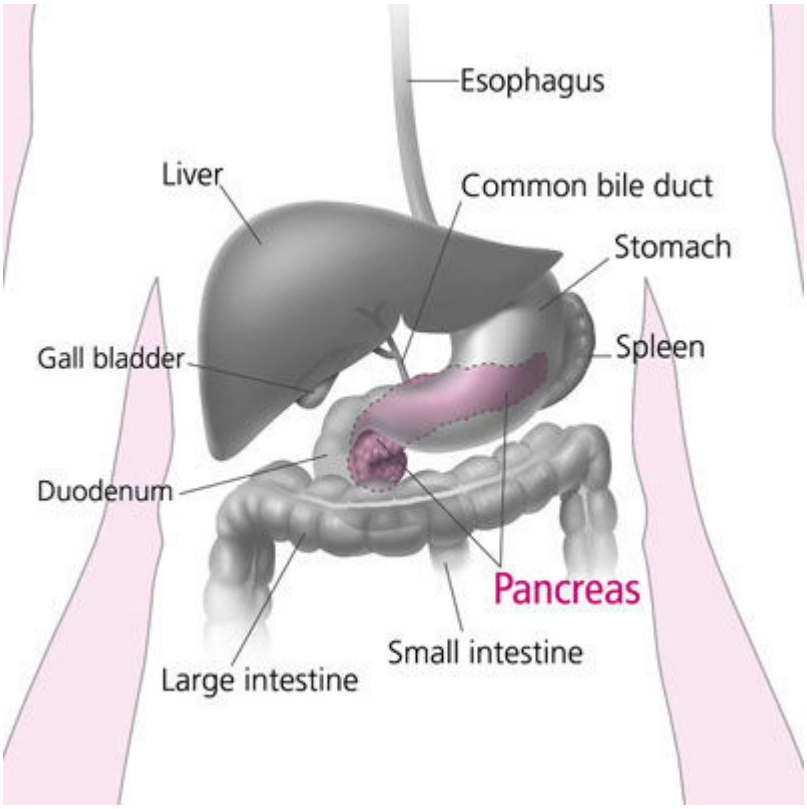
The pancreas is a spongy, tube-shaped organ about 6 inches long. It is located in the back of the abdomen, behind the stomach. The widest part of the pancreas is the head, the middle section is the body, and the thinnest part is the tail.

The head of the pancreas is on the right side of the abdomen. It is connected to the duodenum, the upper end of the small intestine. The narrow end of the pancreas, called the tail, extends to the left side of the body.

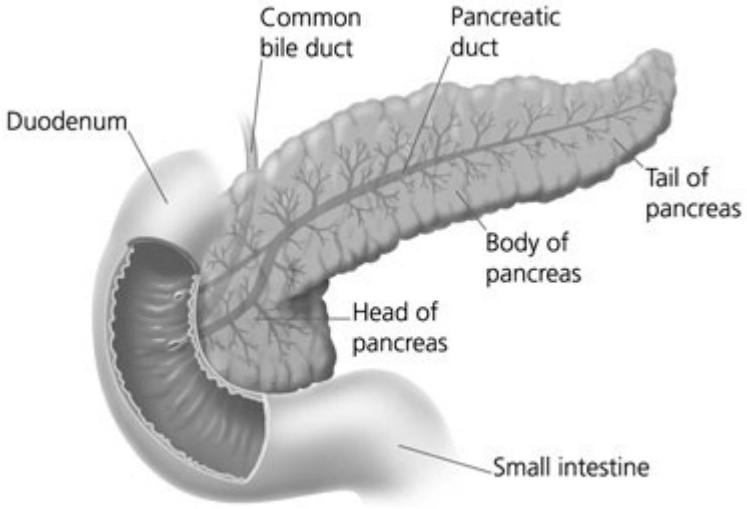
The pancreas makes pancreatic juices and hormones, including insulin. Pancreatic juices, also called enzymes, help digest food in the small intestine. Insulin controls the amount of sugar in the blood. Both enzymes and hormones are needed to keep the body working right.

As pancreatic juices are made, they flow into the main pancreatic duct. This duct joins the common bile duct, which connects the pancreas to the liver and the gallbladder. The pancreas releases the juices into a system of ducts leading to the common bile duct which carries bile (a fluid that helps digest fat). The common bile duct empties into the duodenum, the first section of the small intestine near the stomach.

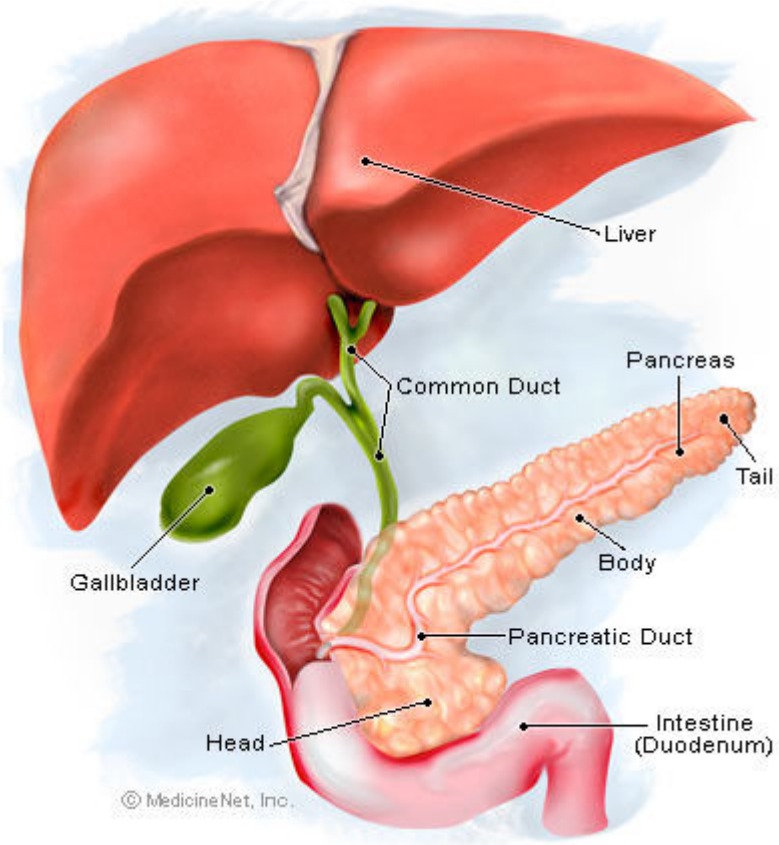
The pancreas is a gland located deep in the abdomen between the stomach and the spine (backbone). The liver, intestine, and other organs surround the pancreas.



This picture shows the pancreas and nearby organs.



This picture shows the pancreas, common bile duct, and small intestine.



The pancreas has two main jobs in the body:

- To produce juices that help digest (break down) food.
- To produce hormones, such as insulin and glucagon, that help control blood sugar levels. Both of these hormones help the body use and store the energy it gets from food.

The digestive juices are produced by exocrine pancreas cells and the hormones are produced by endocrine pancreas cells.

Cancer that starts in the pancreas is called pancreatic cancer. Pancreatic cancer is a disease in which malignant (cancer) cells form in the tissues of the pancreas. About 95% of pancreatic cancers begin in exocrine cells.

Cancer

Cancer is a group of diseases. More than 100 different types of cancer are known, and several types of cancer can develop in the pancreas. They all have one thing in common: abnormal cells grow and destroy body tissue.

Healthy cells that make up the body's tissues grow, divide, and replace themselves in an orderly way. This process keeps the body in good repair. Sometimes, however, some cells lose the ability to control their growth. They grow too rapidly and without any order. Too much tissue is made, and tumors are formed. Tumors can be benign or malignant.

Benign tumors are not cancer. They do not spread to other parts of the body and are seldom a threat to life. Often, benign tumors can be removed by surgery, and they are not likely to return.

Malignant tumors are cancer. They can invade and destroy nearby healthy tissues and organs. Cancer cells also can break away from the tumor and spread to other parts of the body. The spread of cancer is called metastasis.

Cancer cells can also be carried through the bloodstream to the liver, lungs, bone, or other organs.

Pancreatic cancer

Cancer that starts in the pancreas is called pancreatic cancer. When pancreatic cancer spreads, it usually travels through the lymphatic system. The lymphatic system includes a network of thin tubes that branch, like blood vessels, into tissues all over the body. Cancer cells are carried through these vessels by lymph, a colorless, watery fluid that carries cells that fight infection. Along the network of lymphatic vessels are groups of small, bean-shaped organs called lymph nodes. Surgeons often remove lymph nodes near the pancreas to learn whether they contain cancer cells.

Pancreatic cancer that spreads to other organs is called metastatic pancreatic cancer.

About 95% of exocrine pancreatic cancers are adenocarcinomas (M8140/3). The remaining 5% include adenosquamous carcinomas, signet ring cell carcinomas, hepatoid carcinomas, colloid carcinomas, undifferentiated carcinomas, and undifferentiated carcinomas with osteoclast-like giant cells. Exocrine pancreatic cancers are far more common than endocrine pancreatic cancers (also known as islet cell carcinomas), which make up about 1% of total cases.

Risk Factor

- Anything that increases your risk of getting a disease is called a risk factor. Having a risk factor does not mean that you will get cancer; not having risk factors does not mean that you will not get cancer. People who think they may be at risk should discuss this with their doctor.

Risk factors for pancreatic cancer include:

- Age (particularly over 60)
- Male sex
- Ethnicity
- Smoking.
- Diets low in vegetables and fruits
- Diets high in red meat
- Obesity
- Diabetes mellitus is both risk factor for pancreatic cancer, and, as noted earlier, new onset diabetes can be an early sign of the disease.
- Chronic pancreatitis has been linked, but is not known to be causal. The risk of pancreatic cancer in individuals with familial pancreatitis is particularly high.
- *Helicobacter pylori* infection
- Family history, 5–10% of pancreatic cancer patients have a family history of pancreatic cancer. The genes responsible for most of this clustering in families have yet to be identified. Pancreatic cancer has been associated with the following syndromes; autosomal recessive ataxia-telangiectasia and autosomal dominantly inherited mutations

in the BRCA2 gene and PALB2 gene, Peutz-Jeghers syndrome due to mutations in the STK11 tumor suppressor gene, hereditary non-polyposis colon cancer (Lynch syndrome), familial adenomatous polyposis, and the familial atypical multiple mole melanoma-pancreatic cancer syndrome (FAMMM-PC) due to mutations in the *CDKN2A* tumor suppressor gene.
- Gingivitis or periodontal disease.

Alcohol

It is controversial whether alcohol consumption is a risk factor for pancreatic cancer. Drinking alcohol excessively is a major cause of chronic pancreatitis, which in turn predisposes to pancreatic cancer, but chronic pancreatitis that is due to alcohol does not increase risk as much as other types of chronic pancreatitis. Overall, the association is consistently weak and the majority of studies have found no association.

Some studies suggest a relationship, with risk increasing with increasing amount of alcohol intake. Risk is greatest in heavy drinkers mostly on the order of four or more drinks per day. But there appears to be no increased risk for people consuming limited amounts of alcohol a day.

Several studies caution that their findings could be due to confounding factors. Even if a link exists, it could be due to the contents of some alcoholic beverages other than the alcohol itself.

Causes

While it can seldom be explained why one person gets pancreatic cancer and another does not, it is clear that the disease is not contagious. No one can 'catch' cancer from another person.

Although scientists do not know exactly what causes cancer of the pancreas, they are learning that some things increase a person's chance of getting this disease. Smoking is a major risk factor. Research shows that cigarette smokers develop cancer of the pancreas two to three times more

often than nonsmokers. Quitting smoking reduces the risk of pancreatic cancer, lung cancer, and a number of other diseases.

Symptoms and Signs

Pancreatic cancer has been called a 'silent' disease because early pancreatic cancer usually does not cause symptoms. If the tumor blocks the common bile duct and bile cannot pass into the digestive system, the skin and whites of the eyes may become yellow, and the urine may become darker. This condition is called jaundice.

As the cancer grows and spreads, pain often develops in the upper abdomen and sometimes spreads to the back. The pain may become worse after the person eats or lies down. Cancer of the pancreas can also cause nausea, loss of appetite, weight loss, and weakness. A rare type of pancreatic cancer, called islet cell cancer, begins in the cells of the pancreas that produce insulin and other hormones. Islet cells are also called the islets of Langerhans. Islet cell cancer can cause the pancreas to produce too much insulin or hormones. When this happens, the patient may feel weak or dizzy and may have chills, muscle spasms, or diarrhea. These symptoms may be caused by cancer or by other, less serious problems. If an individual is experiencing symptoms, a doctor should be consulted.

Pancreatic cancer is difficult to detect (find) and diagnose early. It is difficult to detect and diagnose for the following reasons:

- There are no noticeable signs or symptoms in the early stages of pancreatic cancer.
- The signs of pancreatic cancer, when present, are like the signs of many other illnesses.
- The pancreas is hidden behind other organs such as the stomach, small intestine, liver, gallbladder, spleen, and bile ducts.

Pancreatic cancer is sometimes called a 'silent killer' because early pancreatic cancer often does not cause symptoms, and the later

symptoms are usually non-specific and varied. Therefore, pancreatic cancer is often not diagnosed until it is advanced.

Common symptoms include:

- Pain in the upper abdomen that typically radiates to the back (seen in carcinoma of the body or tail of the pancreas)
- Loss of appetite and/or nausea and vomiting
- Significant weight loss
- Painless jaundice (yellow skin/eyes, dark urine) when a cancer of the head of the pancreas (about 60% of cases) obstructs the common bile duct as it runs through the pancreas. This may also cause pale-colored stool and steatorrhea.
- Trousseau sign, in which blood clots form spontaneously in the portal blood vessels, the deep veins of the extremities, or the superficial veins anywhere on the body, is sometimes associated with pancreatic cancer.
- Diabetes mellitus or elevated blood sugar levels. Many patients with pancreatic cancer develop diabetes months to even years before they are diagnosed with pancreatic cancer, suggesting that new onset diabetes in an elderly individual may be an early warning sign of pancreatic cancer.

Clinical depression has been reported in association with pancreatic cancer, sometimes presenting before the cancer is diagnosed. However, the mechanism for this association is not known.

Alterations of Function

Pancreatic cancer can alter the normal function of the pancreas by:

- Creating a deficiency of pancreatic enzymes, bicarbonate, and bile salt.
- Causing poor absorption of nutrients from food.
- Impairing the use of pancreatic enzymes.

The activity of pancreatic enzymes is impaired by an acidic environment, which is partly determined by dietary intake. Each day, the exocrine tissue secretes about 2 liters of bicarbonate (a buffer) to neutralize stomach acid in the small intestine. Reduced bicarbonate levels create an acidic microenvironment that weakens the activity of pancreatic enzymes. Some evidence suggests that antacids, alkaline diet, and essential fatty acids may be beneficial in treating pancreatic cancer.

Diagnoses

Most patients with pancreatic cancer experience pain, weight loss, or jaundice.

Pain is present in 80 to 85 percent of patients with locally advanced or advanced metastic disease. The pain is usually felt in the upper abdomen as a dull ache that radiates straight through to the back. It may be intermittent and made worse by eating. Weight loss can be profound; it can be associated with anorexia, early satiety, diarrhea, or steatorrhea. Jaundice is often accompanied by pruritus and dark urine. Painful jaundice is present in approximately one-half of patients with locally unresectable disease, while painless jaundice is present in approximately one-half of patients with a potentially resectable and curable lesion.

The initial presentation varies according to location of the cancer. Malignancies in the pancreatic body or tail usually present with pain and weight loss, while those in the head of the gland typically present with steatorrhea, weight loss, and jaundice. The recent onset of atypical diabetes mellitus, a history of recent but unexplained thrombophlebitis (Trousseau sign), or a previous attack of pancreatitis are sometimes noted.

Courvoisier sign defines the presence of jaundice and a painlessly distended gallbladder as strongly indicative of pancreatic cancer, and may be used to distinguish pancreatic cancer from gallstones.

Tiredness, irritability and difficulty eating due to pain also exist. Pancreatic cancer is usually discovered during the course of the evaluation of aforementioned symptoms.

Liver function tests can show a combination of results indicative of bile duct obstruction (raised conjugated bilirubin, γ-glutamyl transpeptidase and alkaline phosphatase levels).

CA19-9 (carbohydrate antigen 19.9) is a tumor marker that is frequently elevated in pancreatic cancer. However, it lacks sensitivity and specificity. When a cutoff above 37 U/mL is used, this marker has a sensitivity of 77% and specificity of 87% in discerning benign from malignant disease. CA 19-9 might be normal early in the course, and could be elevated due to benign causes of biliary obstruction.

In the September 2009 issue of the journal Cancer Prevention Research, scientists from the University of Texas M.D. Anderson Cancer Center identified microRNAs associated with pancreatic cancer from blood samples of pancreatic cancer patients, leading to a new and minimally invasive approach to early detection. Expression of higher levels of miR-155 circulating in blood was identified as a potential early stage biomarker, and expression of miR196a was shown to increase during disease progression. Using a panel of 4 miRNA biomarkers, miR-21, miR-210, miR-155, and miR-196a, the study achieved 64% sensitivity and 89% specificity in a sample of 28 pancreatic cancer patients and 19 healthy controls.

To diagnose pancreatic cancer, the doctor does a complete physical exam and asks about the patient's personal and family medical history. In addition to checking general signs of health (temperature, pulse, blood pressure, and so on), the doctor usually orders blood, urine, and stool tests. The doctor may also ask for a 'barium swallow,' or 'upper GI series.' For this test, the patient drinks a barium solution before x-rays of the upper digestive system are taken. The barium shows an outline of the pancreas on the x-rays.

Other tests may be ordered, such as:

- An angiogram, a special x-ray of blood vessels.
- Trans-abdominal ultrasound to view the pancreas. In this procedure, an instrument that sends out high-frequency sound

waves, which cannot be heard, is passed over the abdomen. The sound waves echo off the pancreas. The echoes form a picture on a screen that looks like a television.

Biopsy

A biopsy is the only sure way for the doctor to know whether cancer is present. In a biopsy, the doctor removes some tissue from the pancreas. It is examined under a microscope by a pathologist, who checks for cancer cells.

One way to remove tissue is with a long needle that is passed through the skin into the pancreas. This is called a needle biopsy. Doctors use x-rays or ultrasound to guide the placement of the needle.

Another type of biopsy is a brush biopsy. This is done during the ERCP. The doctor inserts a very small brush through the endoscope into the bile duct to rub off cells to examine under a microscope.

Sometimes an operation called a laparotomy may be needed. During this operation, the doctor can look at organs in the abdomen and can remove tissue. The laparotomy helps the doctor determine the stage, or extent, of the disease. Knowing the stage helps the doctor plan treatment.

Tissue samples that are obtained with one kind of biopsy may not give a clear diagnosis, and the biopsy may need to be repeated using a different method.

Imaging

Pancreatic cancer is usually diagnosed with tests and procedures that produce pictures of the pancreas and the area around it. The process used to find out if cancer cells have spread within and around the pancreas is called staging. Tests and procedures to detect, diagnose, and stage pancreatic cancer are usually done at the same time. In order to plan treatment, it is important to know the stage of the disease and whether or not the pancreatic cancer can be removed by surgery.

The following tests and procedures may also be used:

- CT scan (CAT scan): A procedure that makes a series of detailed pictures of areas inside the body, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography. A spiral or helical CT scan makes a series of very detailed pictures of areas inside the body using an x-ray machine that scans the body in a spiral path.
- MRI (magnetic resonance imaging): A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI).
- PET scan (positron emission tomography scan): A procedure to find malignant tumor cells in the body. A small amount of radionuclide glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumor cells show up brighter in the picture because they are more active and take up more glucose than normal cells do.

- Endoscopic ultrasound (EUS): Endoscopic ultrasound is a relatively new procedure that can be used to diagnose pancreatic cancer. An endoscope is inserted into the body, usually through the mouth or rectum. An endoscope is a thin, tube-like instrument with a light and a lens for viewing. A probe at the end of the endoscope is used to bounce high-energy sound waves (ultrasound) off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. This procedure is also called endosonography. The ultrasound probe scans the pancreas for cancers. Because the ultrasound probe is closer to the pancreas than with trans-abdominal ultrasound, it is possible to identify small cancers within the pancreas. The cancers also can be biopsied through the endoscope.

- Laparoscopy: A surgical procedure to look at the organs inside the abdomen to check for signs of disease. Small incisions (cuts) are made in the wall of the abdomen and a laparoscope (a thin, lighted tube) is inserted into one of the incisions. Other instruments may be inserted through the same or other incisions to perform procedures such as removing organs or taking tissue samples for biopsy.
- Endoscopic retrograde cholangiopancreatography (ERCP): A procedure used to x-ray the ducts (tubes) that carry bile from the liver to the gallbladder and from the gallbladder to the small intestine. Sometimes pancreatic cancer causes these ducts to narrow and block or slow the flow of bile, causing jaundice. An endoscope (a thin, lighted tube) is passed through the mouth, esophagus, and stomach into the first part of the small intestine. A catheter (a smaller tube) is then inserted through the endoscope into the pancreatic ducts. A dye is injected through the catheter into the ducts and an x-ray is taken. If the ducts are blocked by a tumor, a fine tube may be inserted into the duct to unblock it. This tube (or stent) may be left in place to keep the duct open. Tissue samples may also be taken.
- Percutaneous transhepatic cholangiography (PTC): A procedure used to x-ray the liver and bile ducts. A thin needle is inserted through the skin below the ribs and into the liver. Dye is injected into the liver or bile ducts and an x-ray is taken. If a blockage is found, a thin, flexible tube called a stent is sometimes left in the liver to drain bile into the small intestine or a collection bag outside the body. This test is done only if ERCP cannot be done.

Prevention

According to the American Cancer Society, there are no established guidelines for preventing pancreatic cancer, although cigarette smoking has been reported as responsible for 20–30% of pancreatic cancers.

In September 2006, a long-term study concluded that taking Vitamin D can substantially cut the risk of pancreatic cancer (as well as other

cancers) by up to 50%, but this study needs to evaluate fully the risks, costs and potential benefits of taking Vitamin D.

Several studies, including one published on 1 June 2007, indicate that B vitamins such as B12, B6, and folate, can reduce the risk of pancreatic cancer when consumed in food, but not when ingested in vitamin tablet form.

Treatment

Cancer of the pancreas is very hard to control with current conventional treatment methods. At this time, pancreatic cancer can be cured only when it is found at an early stage, before it has spread.

Conventional medicine's inability to treat pancreatic cancer effectively is illustrated by the fact that more than 90 percent of patients die within 12 months of diagnosis.

Fewer than 5 percent of pancreatic cancer patients survive five years beyond diagnosis of the disease. Surgery is the only hope for cure; however, due to the aggressive nature of pancreatic tumors, only 5 percent to 20 percent of patients are candidates for surgery. Chemotherapy and radiation therapy produce only minor increases in survival rates.

Treatment for pancreatic cancer depends on a number of factors. Among these are the type, size, and extent of the tumor as well as the patient's age and general health. A treatment plan is tailored to fit each patient's needs. Treatment of pancreatic cancer depends on the stage of the cancer.

Cancer of the pancreas is curable only when it is found in its earliest stages, before it has spread. Otherwise, it is very difficult to cure. However, it can be treated, symptoms can be relieved, and the quality of the patient's life can be improved.

Pancreatic cancer is treated with surgery, radiation therapy, or chemotherapy. Researchers are also studying biological therapy to see whether it can be helpful in treating this disease. Sometimes several methods are used, and the patient is referred to doctors who specialize in different kinds of cancer treatment.

Pain can occur when the tumor presses on nerves or other organs near the pancreas. When pain medicine is not enough, there are treatments that act on nerves in the abdomen to relieve the pain. The doctor may inject medicine into the area around affected nerves or may cut the nerves to block the feeling of pain. Radiation therapy with or without chemotherapy can also help relieve pain by shrinking the tumor.

When a cure or control of the disease is not possible, some patients and their doctors choose palliative therapy. *Palliative therapy* aims to improve *quality of life* by controlling pain and other problems caused by this disease.

Along with lifestyle changes and nutritional approaches, novel therapeutic strategies are needed for the treatment of pancreatic cancer.

It will not be out of place to mention here that other approaches such as Orthomolecular Treatment for cancer may be a far better option which the patient can and should explore before deciding on a treatment strategy.

Surgery

Surgery may be done to remove all or part of the pancreas. Sometimes it is also necessary to remove a portion of the stomach, the duodenum, and other nearby tissues. This operation is called a Whipple procedure. In cases where the cancer in the pancreas cannot be removed, the surgeon may be able to create a bypass around the common bile duct or the duodenum if either is blocked.

The Whipple procedure is the most common surgical treatment for cancers involving the head of the pancreas. This procedure involves removing the pancreatic head and the curve of the duodenum together (pancreatoduodenectomy), making a bypass for food from stomach to jejunum (gasto-jejunostomy) and attaching a loop of jejunum to the cystic duct to drain bile (cholecysto-jejunostomy). It can only be performed if the patient is likely to survive major surgery and if the cancer is localized without invading local structures or metastasizing. It can therefore only be performed in the minority of cases.

Spleen-preserving distal pancreatectomy can also be used as a method to remove a cancer running through centre of pancreas; this is invasive surgery, resulting in loss of body and tail. Cancers of the tail of the pancreas can be resected using a procedure known as a distal pancreatectomy. Recently, localized cancers of the pancreas have been resected using minimally invasive (laparoscopic) approaches.

Surgery can be performed for palliation, if the malignancy is invading or compressing the duodenum or colon. In that case, bypass surgery might overcome the obstruction and improve quality of life, but it is not intended as a cure.

Radiation therapy

Radiation therapy (also called radiotherapy) uses high-powered rays to damage cancer cells and stop them from growing. Radiation is usually given 5 days a week for 5 to 6 weeks. This schedule helps to protect normal tissue by spreading out the total dose of radiation. The patient does not need to stay in the hospital for radiation therapy.

Radiation is also being studied as a way to kill cancer cells that remain in the area after surgery. In addition, radiation therapy can help relieve pain or digestive problems when the common bile duct or duodenum is blocked.

Chemotherapy

Chemotherapy uses drugs to kill cancer cells. The doctor may use just one drug or a combination. Chemotherapy may be given by mouth or by injection into a muscle or vein. The drugs enter the bloodstream and travel through the body. Chemotherapy is usually given in cycles; a treatment period followed by a recovery period, then another treatment period, and so on.

After surgery, *adjuvant* chemotherapy with gemcitabine has in several large randomized studies been shown to significantly increase the 5-year survival (from approximately 10 to 20%), and should be offered if the

patient is fit after surgery. There is a study being done currently by Washington University that is using interferon to treat the cancer, and it has boosted survival times somewhat further. Addition of radiation therapy is a hotly debated topic, with groups in the US often favoring the use of adjuvant radiation therapy, while groups in Europe do not, due to the lack of any large randomized studies to show any survival benefit of this strategy.

In patients not suitable for resection with curative intent, palliative chemotherapy may be used to improve quality of life and gain a modest survival benefit. However no large randomized study has shown significant survival benefit from this treatment. The survival improvement with the combination of chemo drugs is on the order of less than four weeks, leading some cancer experts to question the incremental value of such action. It may cause higher rates of high blood pressure, bleeding in the stomach and intestine, and intestinal perforations.

Biological therapy

Biological therapy is a new type of cancer treatment that uses natural and laboratory-produced substances to stimulate or restore the body's immune system so it can fight disease more effectively. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defenses against cancer. This type of cancer treatment is also called biotherapy or immunotherapy.

This kind of treatment is being studied in patients with advanced or recurring cancer of the pancreas.

Side effects of the treatment

The methods used to treat pancreatic cancer are very powerful. It is hard to limit the effects of treatment so that only cancer cells are destroyed. Healthy tissue may also be damaged. That is why treatment often causes unpleasant side effects. Side effects depend on the type of treatment used and on the part of the body being treated.

Surgery for cancer of the pancreas is a major operation. While in the hospital, the patient will need special medications and may be fed only liquids. During recovery from surgery, the patient's diet and weight will be checked carefully.

During radiation therapy, the patient may become very tired as the treatment continues. Resting as much as possible is important. Skin reactions (redness or dryness) in the treated area are also common. Good skin care is important at this time, but the patient should not use any lotions or creams on the skin without checking with the doctor. Radiation therapy to the upper abdomen can cause nausea and vomiting. Usually, dietary changes or medications can ease these problems.

The side effects of chemotherapy depend on the drugs that are given. In addition, each person reacts differently. Chemotherapy affects rapidly growing cells, such as blood-forming cells, those that line the digestive tract, and those in the skin and hair. As a result, patients can have side effects such as a lowered resistance to infection, less energy, loss of appetite, nausea, vomiting, or mouth sores. Patients may also lose their hair.

Weight loss can be a serious problem for patients being treated for cancer of the pancreas. Researchers are learning that well- nourished patients usually feel better and may be better able to withstand the side effects of their treatment.

Therefore, nutrition is an important part of the treatment plan, and doctors may have a number of suggestions to help their patients get enough calories and protein. In many cases, patients feel better if they take food and beverages in very small amounts. Many patients find that eating several small meals and snacks throughout the day is easier than having three large meals.

In addition, treatment for cancer of the pancreas may interfere with production of insulin and pancreatic juices. The patient must take medicines to replace these; otherwise the level of blood sugar may be wrong and digestion may be affected. Even so, taking these medicines can

often upset digestion. Careful planning and checkups are important to help the patient avoid weight loss and the weakness and lack of energy caused by poor nutrition.

Patients and family members are often afraid that cancer will cause pain. Cancer patients do not always have pain, but if it does occur, there are many ways to relieve or reduce it. It is important for the patient to let the doctor know about pain, because uncontrolled pain can cause loss of sleep and poor appetite. These problems can make it difficult for the patient to respond to treatment.

The side effects that patients have during cancer therapy vary for each person. They may even be different from one treatment to the next. Attempts are made to plan treatment to keep problems to a minimum. Fortunately, most side effects are temporary. Doctors and dietitians can explain the side effects of cancer treatment and can suggest ways to deal with them.

Prognosis

Certain factors affect prognosis (chance of recovery) and treatment options.

Patients diagnosed with pancreatic cancer typically have a poor prognosis partly because the cancer usually causes no symptoms early on, leading to locally advanced or metastatic disease at time of diagnosis. Median survival from diagnosis is around 3 to 6 months; 5-year survival is less than 5%. Pancreatic cancer has one of the highest fatality rates of all cancers and is the fourth highest cancer killer in the United States among both men and women. Although it accounts for only 2.5% of new cases, pancreatic cancer is responsible for 6% of cancer deaths each year.

Pancreatic cancer may occasionally result in diabetes. Insulin production is hampered and it has been suggested that the cancer can also prompt the onset of diabetes and vice versa. Thus diabetes is both a risk factor for the development of pancreatic cancer and diabetes can be an early sign of the disease in the elderly.

The prognosis (chance of recovery) and treatment options depend on the following:

- Whether or not the tumor can be removed by surgery.
- The stage of the cancer (the size of the tumor and whether the cancer has spread outside the pancreas to nearby tissues or lymph nodes or to other places in the body).
- The patient's general health.
- Whether the cancer has just been diagnosed or has recurred (come back).

Pancreatic cancer can be controlled only if it is found before it has spread, when it can be removed by surgery. If the cancer has spread, palliative treatment can improve the patient's quality of life by controlling the symptoms and complications of this disease.

There are three ways that cancer spreads in the body:

- Through tissue. Cancer invades the surrounding normal tissue.
- Through the lymph system. Cancer invades the lymph system and travels through the lymph vessels to other places in the body.
- Through the blood. Cancer invades the veins and capillaries and travels through the blood to other places in the body.

When cancer cells break away from the primary (original) tumor and travel through the lymph or blood to other places in the body, another (secondary) tumor may form. This process is called metastasis. The secondary (metastatic) tumor is the same type of cancer as the primary tumor. For example, if breast cancer spreads to the bones, the cancer cells in the bones are actually breast cancer cells. The disease is metastatic breast cancer, not bone cancer.

Staging

When pancreatic cancer [or any other cancer] is diagnosed, the doctor needs to know the *stage*, or extent, of the disease to plan the best treatment. *Staging* is a careful attempt to find out the size of the tumor in

the pancreas, whether the cancer has spread, and if so, to what parts of the body.

The doctor may determine the stage of pancreatic cancer at the time of diagnosis, or the patient may need to have more tests. Such tests may include blood tests, a CT scan, ultrasonography, *laparoscopy*, or *angiography*. The test results will help the doctor decide which treatment is appropriate.

The following stages are used for pancreatic cancer:

Stage 0 (Carcinoma in Situ)

In stage 0, abnormal cells are found in the lining of the pancreas. These abnormal cells may become cancer and spread into nearby normal tissue. Stage 0 is also called carcinoma in situ.

Pea, peanut, walnut, lime (tumor sizes.)

Stage I

In stage I, cancer has formed and is found in the pancreas only. Stage I is divided into stage IA and stage IB, based on the size of the tumor.

- Stage IA: The tumor is 2 centimeters or smaller.
- Stage IB: The tumor is larger than 2 centimeters.

Stage II

In stage II, cancer may have spread to nearby tissue and organs, and may have spread to lymph nodes near the pancreas. Stage II is divided into stage IIA and stage IIB, based on where the cancer has spread.

- Stage IIA: Cancer has spread to nearby tissue and organs but has not spread to nearby lymph nodes.
- Stage IIB: Cancer has spread to nearby lymph nodes and may have spread to nearby tissue and organs.

Stage III

In stage III, cancer has spread to the major blood vessels near the pancreas and may have spread to nearby lymph nodes.

Stage IV

In stage IV, cancer may be of any size and has spread to distant organs, such as the liver, lung, and peritoneal cavity. It may have also spread to organs and tissues near the pancreas or to lymph nodes.

Recurrent pancreatic cancer is cancer that has recurred (come back) after it has been treated. The cancer may come back in the pancreas or in other parts of the body.

Nutrition

People with pancreatic cancer may not feel like eating, especially if they are uncomfortable or tired. Also, the side effects of treatment such as poor appetite, nausea, or vomiting can make eating difficult. Foods may taste different. Nevertheless, patients should try to get enough calories and protein to control weight loss, maintain strength, and promote healing. Also, eating well often helps people with cancer feel better and have more energy.

Careful planning and checkups are important. Cancer of the pancreas and its treatment may make it hard for patients to digest food and maintain the proper blood sugar level. The doctor will check the patient for weight loss, weakness, and lack of energy. Patients may need to take medicines to replace the enzymes and hormones made by the pancreas. The doctor will watch the patient closely and adjust the doses of these medicines.

The doctor, dietitian, or other health care provider can advise patients about ways to maintain a healthy diet. Patients and their families may want to read the National Cancer Institute booklet *Eating Hints for Cancer Patients*, which contains many useful suggestions and recipes.

Followup care after treatment for pancreatic cancer is an important part of the overall treatment plan. Patients should not hesitate to discuss followup with their doctor. Regular checkups ensure that any changes in health are noticed. Any problem that develops can be found and treated. Checkups may include a physical exam, laboratory tests, and *imaging procedures*.

Patients with pancreatic cancer have special nutritional needs.

Surgery to remove the pancreas may interfere with the production of pancreatic enzymes that help to digest food. As a result, patients may have problems digesting food and absorbing nutrients into the body. To prevent malnutrition, the doctor may prescribe medicines that replace these enzymes.

For some patients, taking part in a clinical trial may be the best treatment choice. Clinical trials are part of the cancer research process. Clinical trials are done to find out if new cancer treatments are safe and effective or better than the standard treatment.

Many of today's standard treatments for cancer are based on earlier clinical trials. Patients who take part in a clinical trial may receive the standard treatment or be among the first to receive a new treatment.

Patients who take part in clinical trials also help improve the way cancer will be treated in the future. Even when clinical trials do not lead to effective new treatments, they often answer important questions and help move research forward.

Patients can enter clinical trials before, during, or after starting their cancer treatment.

Some clinical trials only include patients who have not yet received treatment. Other trials test treatments for patients whose cancer has not gotten better. There are also clinical trials that test new ways to stop cancer from recurring (coming back) or reduce the side effects of cancer treatment.

Clinical trials are taking place in many parts of the country. See the Treatment Options section that follows for links to current treatment clinical trials. These have been retrieved from NCI's clinical trials database.

Follow-up tests may be needed

Some of the tests that were done to diagnose the cancer or to find out the stage of the cancer may be repeated. Some tests will be repeated in order to see how well the treatment is working. Decisions about whether to continue, change, or stop treatment may be based on the results of these tests. This is sometimes called re-staging.

Some of the tests will continue to be done from time to time after treatment has ended. The results of these tests can show if your condition has changed or if the cancer has recurred (come back). These tests are sometimes called follow-up tests or check-ups.

Treatment Options by Stage

Stages I and II Pancreatic Cancer
Stage III Pancreatic Cancer
Stage IV Pancreatic Cancer

A link to a list of current clinical trials is included for each treatment section. For some types or stages of cancer, there may not be any trials listed. Check with your doctor for clinical trials that are not listed here but may be right for you.

Stages I and II Pancreatic Cancer

Treatment of stage I and stage II pancreatic cancer may include the following:

- Surgery alone.
- Surgery with chemotherapy and radiation therapy.
- A clinical trial of surgery followed by radiation therapy with chemotherapy. Chemotherapy is given before, during, and after the radiation therapy.
- A clinical trial of surgery followed by chemotherapy.

Check for U.S. clinical trials from NCI's PDQ Cancer Clinical Trials Registry that are now accepting patients with stage I pancreatic cancer and stage II pancreatic cancer. For more specific results, refine the search by using other search features, such as the location of the trial, the type of treatment, or the name of the drug. General information about clinical trials is available from the NCI Web site.

Stage III Pancreatic Cancer

Treatment of stage III pancreatic cancer may include the following:

- Palliative surgery or stent placement to bypass blocked areas in ducts or the small intestine.
- Chemotherapy with gemcitabine.
- A clinical trial of new anticancer therapies together with chemotherapy or chemoradiation.
- A clinical trial of radiation therapy given during surgery or internal radiation therapy.

Check for U.S. clinical trials from NCI's PDQ Cancer Clinical Trials Registry that are now accepting patients with stage III pancreatic cancer. For more specific results, refine the search by using other search features, such as the location of the trial, the type of treatment, or the name of the drug. General information about clinical trials is available from the NCI Web site.

Stage IV Pancreatic Cancer

Treatment of stage IV pancreatic cancer may include the following:

- Chemotherapy with gemcitabine with or without erlotinib.
- Palliative treatments for pain, such as nerve blocks, and other supportive care.
- Palliative surgery or stent placement to bypass blocked areas in ducts or the small intestine.
- Clinical trials of new anticancer agents with or without chemotherapy.

Treatment of recurrent pancreatic cancer may include the following:

- Chemotherapy.
- Palliative surgery or stent placement to bypass blocked areas in ducts or the small intestine.
- Palliative radiation therapy.
- Other palliative medical care to reduce symptoms, such as nerve blocks to relieve pain.
- Clinical trials of chemotherapy, new anticancer therapies, or biologic therapy.

Understanding Cancer

Cancer is a group of many related diseases. All cancers begin in *cells*, the body's basic unit of life. Cells make up *tissues*, and tissues make up the organs of the body.

Normally, cells grow and divide to form new cells as the body needs them. When cells grow old and die, new cells take their place.

Sometimes this orderly process breaks down. New cells form when the body does not need them, or old cells do not die when they should. These extra cells can form a mass of tissue called a growth or *tumor*.

Tumors can be *benign* or *malignant*:

- **Benign tumors** are not cancer. Usually, doctors can remove them. In most cases, benign tumors do not come back after they are removed. Cells from benign tumors do not spread to tissues around them or to other parts of the body. Most important, benign tumors are rarely a threat to life.
- **Malignant tumors** are cancer. They are generally more serious and may be life threatening. Cancer cells can invade and damage nearby tissues and organs. Also, cancer cells can break away from a malignant tumor and enter the bloodstream or *lymphatic system*. That is how cancer cells spread from the original cancer (*primary tumor*) to form new tumors in other organs. The spread of cancer is called *metastasis*.

Most pancreatic cancers begin in the ducts that carry pancreatic juices. Cancer of the pancreas may be called *pancreatic cancer* or *carcinoma* of the pancreas.

A rare type of pancreatic cancer begins in the cells that make insulin and other hormones. Cancer that begins in these cells is called *islet cell cancer*. This booklet does not deal with this rare disease. The Cancer Information Service (1-800-4-CANCER) can provide information about islet cell cancer.

When cancer of the pancreas spreads (*metastasizes*) outside the pancreas, cancer cells are often found in nearby *lymph nodes*. If the cancer has reached these nodes, it means that cancer cells may have spread to other lymph nodes or other tissues, such as the liver or lungs. Sometimes cancer of the pancreas spreads to the *peritoneum*, the tissue that lines the abdomen.

When cancer spreads from its original place to another part of the body, the new tumor has the same kind of abnormal cells and the same name as the primary tumor. For example, if cancer of the pancreas spreads to the liver, the cancer cells in the liver are pancreatic cancer cells. The disease is metastatic pancreatic cancer, not liver cancer. It is treated as pancreatic cancer, not liver cancer.

Pancreatic Cancer: Who's at Risk?

No one knows the exact causes of pancreatic cancer. Doctors can seldom explain why one person gets pancreatic cancer and another does not. However, it is clear that this disease is not contagious. No one can "catch" cancer from another person.

Research has shown that people with certain *risk factors* are more likely than others to develop pancreatic cancer. A risk factor is anything that increases a person's chance of developing a disease.

Studies have found the following risk factors:

- **Age** -- The likelihood of developing pancreatic cancer increases with age. Most pancreatic cancers occur in people over the age of 60.
- **Smoking** -- Cigarette smokers are two or three times more likely than nonsmokers to develop pancreatic cancer.
- ***Diabetes*** -- Pancreatic cancer occurs more often in people who have diabetes than in people who do not.
- **Being male** -- More men than women are diagnosed with pancreatic cancer.
- **Being African American** -- African Americans are more likely than Asians, Hispanics, or whites to get pancreatic cancer.
- **Family history** -- The risk for developing pancreatic cancer triples if a person's mother, father, sister, or brother had the disease. Also, a family history of colon or ovarian cancer increases the risk of pancreatic cancer.
- **Chronic *pancreatitis*** -- Chronic pancreatitis is a painful condition of the pancreas. Some evidence suggests that chronic pancreatitis may increase the risk of pancreatic cancer.

Other studies suggest that exposure to certain chemicals in the workplace or a diet high in fat may increase the chance of getting pancreatic cancer.

Most people with known risk factors do not get pancreatic cancer. On the other hand, many who do get the disease have none of these factors. People who think they may be at risk for pancreatic cancer should discuss this concern with their doctor. The doctor may suggest ways to reduce the risk and can plan an appropriate schedule for checkups.

Symptoms

Pancreatic cancer is sometimes called a "silent disease" because early pancreatic cancer often does not cause *symptoms*. But, as the cancer grows, symptoms may include:

- Pain in the upper abdomen or upper back
- Yellow skin and eyes, and dark urine from *jaundice*
- Weakness
- Loss of appetite
- Nausea and vomiting
- Weight loss

These symptoms are not sure signs of pancreatic cancer. An infection or other problem could also cause these symptoms. Only a doctor can diagnose the cause of a person's symptoms. Anyone with these symptoms should see a doctor so that the doctor can treat any problem as early as possible.

Diagnosis

If a patient has symptoms that suggest pancreatic cancer, the doctor asks about the patient's medical history. The doctor may perform a number of procedures, including one or more of the following:

- **Physical exam** -- The doctor examines the skin and eyes for signs of jaundice. The doctor then feels the abdomen to check for changes in the area near the pancreas, liver, and *gallbladder*. The doctor also checks for *ascites*, an abnormal buildup of fluid in the abdomen.
- **Lab tests** -- The doctor may take blood, urine, and stool samples to check for *bilirubin* and other substances. Bilirubin is a substance that passes from the liver to the gallbladder to the intestine. If the common bile duct is blocked by a tumor, the bilirubin cannot pass through normally. Blockage may cause the level of bilirubin in the blood, stool, or urine to become very high. High bilirubin levels can result from cancer or from noncancerous conditions.
- ***CT scan*** **(Computed tomography)** -- An x-ray machine linked to a computer takes a series of detailed pictures. The x-ray machine is shaped like a donut with a large hole. The patient lies on a bed that passes through the hole. As the bed moves slowly through the hole, the machine takes many x-rays. The computer puts the x-rays together to create pictures of the pancreas and other organs and blood vessels in the abdomen.
- ***Ultrasonography*** -- The ultrasound device uses sound waves that cannot be heard by humans. The sound waves produce a pattern of echoes as they bounce off internal

organs. The echoes create a picture of the pancreas and other organs inside the abdomen. The echoes from tumors are different from echoes made by healthy tissues.

The ultrasound procedure may use an external or internal device, or both types:

  - ***Transabdominal ultrasound***: To make images of the pancreas, the doctor places the ultrasound device on the abdomen and slowly moves it around.
  - ***EUS (Endoscopic ultrasound)***: The doctor passes a thin, lighted tube (*endoscope*) through the patient's mouth and stomach, down into the first part of the small intestine. At the tip of the endoscope is an ultrasound device. The doctor slowly withdraws the endoscope from the intestine toward the stomach to make images of the pancreas and surrounding organs and tissues.

- **ERCP (*endoscopic retrograde cholangiopancreatography*)** -- The doctor passes an endoscope through the patient's mouth and stomach, down into the first part of the small intestine. The doctor slips a smaller tube (*catheter*) through the endoscope into the bile ducts and pancreatic ducts. After injecting dye through the catheter into the ducts, the doctor takes x-ray pictures. The x-rays can show whether the ducts are narrowed or blocked by a tumor or other condition.
- **PTC (*percutaneous transhepatic cholangiography*)** -- A dye is injected through a thin needle inserted through the skin into the liver. Unless there is a blockage, the dye should move freely through the bile ducts. The dye makes the bile ducts show up on x-ray pictures. From the pictures, the doctor can tell whether there is a blockage from a tumor or other condition.
- ***Biopsy*** -- In some cases, the doctor may remove tissue. A *pathologist* then uses a microscope to look for cancer cells in the tissue. The doctor may obtain tissue in several ways. One way is by inserting a needle into the pancreas to remove cells. This is called *fine-needle aspiration*. The doctor uses x-ray or ultrasound to guide the needle. Sometimes the doctor obtains a sample of tissue during EUS or ERCP. Another way is to open the abdomen during an operation.

Staging

When pancreatic cancer is diagnosed, the doctor needs to know the *stage*, or extent, of the disease to plan the best treatment. *Staging* is a careful attempt to find out the size of the tumor in the pancreas, whether the cancer has spread, and if so, to what parts of the body.

The doctor may determine the stage of pancreatic cancer at the time of diagnosis, or the patient may need to have more tests. Such tests may include blood tests, a CT scan, ultrasonography, *laparoscopy*, or *angiography*. The test results will help the doctor decide which treatment is appropriate.

Treatment

Many people with pancreatic cancer want to take an active part in making decisions about their medical care. They want to learn all they can about their disease and their treatment choices. However, the shock and stress that people may feel after a diagnosis of cancer can make it hard

for them to think of everything they want to ask the doctor. Often it helps to make a list of questions before an appointment. To help remember what the doctor says, patients may take notes or ask whether they may use a tape recorder. Some patients also want to have a family member or friend with them when they talk to the doctor-to take part in the discussion, to take notes, or just to listen.

Cancer of the pancreas is very hard to control with current treatments. For that reason, many doctors encourage patients with this disease to consider taking part in a *clinical trial*. Clinical trials are an important option for people with all stages of pancreatic cancer. The section on "The Promise of Cancer Research" has more information about clinical trials.

At this time, pancreatic cancer can be cured only when it is found at an early stage, before it has spread. However, other treatments may be able to control the disease and help patients live longer and feel better. When a cure or control of the disease is not possible, some patients and their doctors choose palliative therapy. *Palliative therapy* aims to improve *quality of life* by controlling pain and other problems caused by this disease.

The doctor may refer patients to an *oncologist*, a doctor who specializes in treating cancer, or patients may ask for a referral. Specialists who treat pancreatic cancer include *surgeons*, *medical oncologists*, and *radiation oncologists*. Treatment generally begins within a few weeks after the diagnosis. There will be time for patients to talk with the doctor about treatment choices, get a second opinion, and learn more about the disease.

Preparing for Treatment

The doctor can describe treatment choices and discuss the results expected with each treatment option. The doctor and patient can work together to develop a treatment plan that fits the patient's needs.

Treatment depends on where in the pancreas the tumor started and whether the disease has spread. When planning treatment, the doctor also considers other factors, including the patient's age and general health.

These are some questions a person may want to ask the doctor before treatment begins:

- What is the diagnosis?
- Where in the pancreas did the cancer start?
- Is there any evidence the cancer has spread? What is the stage of the disease?
- Do I need any more tests to check whether the disease has spread?
- What are my treatment choices? Which do you recommend for me? Why?
- What are the expected benefits of each kind of treatment?
- What are the risks and possible *side effects* of each treatment?
- What is the treatment likely to cost? Is this treatment covered by my insurance plan?
- How will treatment affect my normal activities?

- Would a clinical trial (research study) be appropriate for me?

People do not need to ask all of their questions or understand all of the answers at one time. They will have other chances to ask the doctor to explain things that are not clear and to ask for more information.

Methods of Treatment

People with pancreatic cancer may have several treatment options. Depending on the type and stage, pancreatic cancer may be treated with *surgery*, *radiation therapy*, or *chemotherapy*. Some patients have a combination of therapies.

Surgery may be used alone or in combination with radiation therapy and chemotherapy.

The surgeon may remove all or part of the pancreas. The extent of surgery depends on the location and size of the tumor, the stage of the disease, and the patient's general health.

- ***Whipple procedure***: If the tumor is in the head (the widest part) of the pancreas, the surgeon removes the head of the pancreas and part of the small intestine, bile duct, and stomach. The surgeon may also remove other nearby tissues.
- ***Distal pancreatectomy***: The surgeon removes the body and tail of the pancreas if the tumor is in either of these parts. The surgeon also removes the *spleen*.
- ***Total pancreatectomy***: The surgeon removes the entire pancreas, part of the small intestine, a portion of the stomach, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes.

Sometimes the cancer cannot be completely removed. But if the tumor is blocking the common bile duct or duodenum, the surgeon can create a *bypass*. A bypass allows fluids to flow through the digestive tract. It can help relieve jaundice and pain resulting from a blockage.

The doctor sometimes can relieve blockage without doing bypass surgery. The doctor uses an endoscope to place a *stent* in the blocked area. A stent is a tiny plastic or metal mesh tube that helps keep the duct or duodenum open.

After surgery, some patients are fed liquids *intravenously* (by IV) and through feeding tubes placed into the abdomen. Patients slowly return to eating solid foods by mouth. A few weeks after surgery, the feeding tubes are removed.

These are some questions a person may want to ask the doctor before having surgery:

- What kind of operation will I have?
- How will I feel after the operation?
- How will you treat my pain?

- What other treatment will I need?
- How long will I be in the hospital?
- Will I need a feeding tube after surgery? Will I need a special diet?
- What are the long-term effects?
- When can I get back to my normal activities?
- How often will I need checkups?

Radiation therapy (also called radiotherapy) uses high-energy rays to kill cancer cells. A large machine directs radiation at the abdomen. Radiation therapy may be given alone, or with surgery, chemotherapy, or both.

Radiation therapy is *local therapy*. It affects cancer cells only in the treated area. For radiation therapy, patients go to the hospital or clinic, often 5 days a week for several weeks.

Doctors may use radiation to destroy cancer cells that remain in the area after surgery. They also use radiation to relieve pain and other problems caused by the cancer.

These are some questions a person may want to ask the doctor before having radiation therapy:

- Why do I need this treatment?
- When will the treatments begin? When will they end?
- How will I feel during therapy? Are there side effects?
- What can I do to take care of myself during therapy? Are there certain foods that I should eat or avoid?
- How will we know if the radiation is working?
- Will I be able to continue my normal activities during treatment?

Chemotherapy is the use of drugs to kill cancer cells. Doctors also give chemotherapy to help reduce pain and other problems caused by pancreatic cancer. It may be given alone, with radiation, or with surgery and radiation.

Chemotherapy is *systemic therapy*. The doctor usually gives the drugs by injection. Once in the bloodstream, the drugs travel throughout the body.

Usually chemotherapy is an *outpatient* treatment given at the hospital, clinic, doctor's office, or home. However, depending on which drugs are given and the patient's general health, the patient may need to stay in the hospital.

Side Effects of Treatment

Because cancer treatment may damage healthy cells and tissues, unwanted side effects are common. These side effects depend on many factors, including the type and extent of the

treatment. Side effects may not be the same for each person, and they may even change from one treatment session to the next. The health care team will explain possible side effects and how they will help the patient manage them.

The NCI provides helpful booklets about cancer treatments and coping with side effects, such as *Radiation Therapy and You*, *Chemotherapy and You*, and *Eating Hints*. See the sections called "National Cancer Institute Information Resources" and "National Cancer Institute Booklets" for other sources of information about side effects.

Surgery

Surgery for pancreatic cancer is a major operation. Patients need to stay in the hospital for several days afterward. Patients may feel weak or tired. Most need to rest at home for about a month. The length of time it takes to regain strength varies.

The side effects of surgery depend on the extent of the operation, the person's general health, and other factors. Most patients have pain for the first few days after surgery. Pain can be controlled with medicine, and patients should discuss pain relief with the doctor or nurse. The section on "Pain Control" has more information.

Removal of part or all of the pancreas may make it hard for a patient to digest foods. The health care team can suggest a diet plan and medicines to help relieve diarrhea, pain, cramping, or feelings of fullness. During the recovery from surgery, the doctor will carefully monitor the patient's diet and weight. At first, a patient may have only liquids and may receive extra nourishment intravenously or by feeding tube into the intestine. Solid foods are added to the diet gradually.

Patients may not have enough pancreatic enzymes or hormones after surgery. Those who do not have enough insulin may develop diabetes. The doctor can give the patient insulin, other hormones, and enzymes. The section "Nutrition for Cancer Patients" has more information.

Radiation Therapy

Radiation therapy may cause patients to become very tired as treatment continues. Resting is important, but doctors usually advise patients to try to stay as active as they can. In addition, when patients receive radiation therapy, the skin in the treated area may sometimes become red, dry, and tender.

Radiation therapy to the abdomen may cause nausea, vomiting, diarrhea, or other problems with digestion. The health care team can offer medicine or suggest diet changes to control these problems. For most patients, the side effects of radiation therapy go away when treatment is over.

Chemotherapy

The side effects of chemotherapy depend mainly on the drugs and the doses the patient receives as well as how the drugs are given. In addition, as with other types of treatment, side effects vary from patient to patient.

Systemic chemotherapy affects rapidly dividing cells throughout the body, including blood cells. Blood cells fight infection, help the blood to clot, and carry oxygen to all parts of the body. When anticancer drugs damage healthy blood cells, patients are more likely to get infections, may bruise or bleed easily, and may have less energy. Cells in hair roots and cells that line the digestive tract also divide rapidly. As a result, patients may lose their hair and may have other side effects such as poor appetite, nausea and vomiting, diarrhea, or mouth sores. Usually, these side effects go away gradually during the recovery periods between treatments or after treatment is over. The health care team can suggest ways to relieve side effects.

Pain Control

Pain is a common problem for people with pancreatic cancer. The tumor can cause pain by pressing against nerves and other organs.

The patient's doctor or a specialist in pain control can relieve or reduce pain in several ways:

- **Pain medicine** - Medicines often can relieve pain. (These medicines may make people drowsy and constipated, but resting and taking laxatives can help.)
- **Radiation** - High-energy rays can help relieve pain by shrinking the tumor.
- **Nerve block** - The doctor may inject alcohol into the area around certain nerves in the abdomen to block the feeling of pain.
- **Surgery** - The surgeon may cut certain nerves to block pain.

The doctor may suggest other ways to relieve or reduce pain. For example, massage, *acupuncture*, or *acupressure* may be used along with other approaches to help relieve pain. Also, the patient may learn relaxation techniques such as listening to slow music or breathing slowly and comfortably.

More information about pain control can be found in the NCI booklet *Pain Control*. The NCI's Cancer Information Service can send this booklet.

Nutrition

People with pancreatic cancer may not feel like eating, especially if they are uncomfortable or tired. Also, the side effects of treatment such as poor appetite, nausea, or vomiting can make eating difficult. Foods may taste different. Nevertheless, patients should try to get enough calories and protein to control weight loss, maintain strength, and promote healing. Also, eating well often helps people with cancer feel better and have more energy.

Careful planning and checkups are important. Cancer of the pancreas and its treatment may make it hard for patients to digest food and maintain the proper blood sugar level. The doctor will check the patient for weight loss, weakness, and lack of energy. Patients may need to take

medicines to replace the enzymes and hormones made by the pancreas. The doctor will watch the patient closely and adjust the doses of these medicines.

The doctor, dietitian, or other health care provider can advise patients about ways to maintain a healthy diet. Patients and their families may want to read the National Cancer Institute booklet *Eating Hints*, which contains many useful suggestions and recipes. The "National Cancer Institute Booklets" section tells how to get this publication.

Orthomolecular Medicine- Big Talk, Little Evidence, Real Risk

One of the most impressive-sounding labels for an unproven alternative therapy is Orthomolecular Medicine. And the origin of the term, coined by Nobel laureate Linus Pauling, gives it added gravitas. As it turns out, though, it's just a fancy way of claiming that there are medical benefits to giving high doses of vitamins above and beyond the ordinary, and quite small amounts necessary for normal health. Proponents of this concept argue that many diseases are due to undetected vitamin or mineral deficiencies, usually attributed to the unspecified evils of modern life or industrial agriculture. They also seem to follow the philosophy that if a little is good, more is better in arguing that extremely high doses of essential micronutrients can treat or prevent illness.

It is culturally difficult to argue against the benefits of vitamins, or to suggest they might cause harm. The memory of a time in which people in Western societies were routinely deficient in micronutrients, and when supplementation provided seemingly miraculous benefits, is still accessible. And there are still places in the world in which the poor not only do not have our nutrient-excess health problems but in which vitamin deficiencies are still common, and supplementation can be beneficial. Recent surveys suggest vitamins are seen as generally benign even by doctors, who commonly use them as placebo therapy.

However, the grand claims made in the 1970s by Pauling and others about the benefits of megadoses of vitamins have had a long time to prove themselves, and they have so far failed to do so. In human medicine, the loosely-organized set of theories called Orthomolecular Medicine has passed through the classic stages of CAM research:

1. An untested idea

2. An idea with support from a few random in vitro and animal model studies

3. An idea with a few supportive findings in small, poorly designed clinical studies

4. An idea clearly debunked in larger and better-designed studies but whose proponents cling to it tenaciously despite the lack of evidentiary support because they see themselves as visionaries ignored or oppressed by the unimaginative and venal mainstream medical establishment.

In veterinary medicine, as usual, not all of the stages are well-represented. The closest I have been able to find to Stage 3 are some case reports and papers from the 1970s that are long on grand theorizing and short on data by Dr. Wendell Belfield. These are balanced by a number of *in vitro* and animal model studies showing the implausibility or potential dangers megadoses of vitamins, but to my knowledge well-designed, adequately powered clinical trials have not been done to definitively prove or disprove any of the claims orthomolecular practitioners make. In my opinion, this is as it should be since the basic plausibility, the in vitro data, and the data from human medicine all argue against wasting resources on something so unlikely to prove safe and effective, but it is always nice to be able to show with solid data that likely nonsense truly is nonsense.

Since there do not appear to be definitive studies, I have put together some information of a cautionary nature about some commonly advocated vitamin therapies. This is certainly not a comprehensive literature review, nor do I claim it is the final word on megadose vitamin therapy. I have selected cautionary research to illustrate the potential risks of orthomolecular therapies and to remind everyone why the burden of proof is properly on proponents of this approach to justify their extravagant claims. It is also important to emphasize that the use of vitamins in high doses to prevent or treat disease is essentially using these compounds as drugs. They are not "nutritional" therapies when given above the recognized necessary amounts but active pharmaceuticals, and as such any possible benefits will come with associated risks and side effects.

Vitamin A

As a fat-soluble vitamin, Vitamin A can accumulate over time, making reaching dangerous levels more likely. As for most vitamins, there are clear benefits to appropriate amounts, and supplementation sometimes shows benefit for people in impoverished environments with inadequate nutrition, but the evidence does not support benefits for supplementation of healthy people with adequate diets or clear benefits for treating non-deficiency diseases.

Excessive dietary Vitamin A can worsen osteoporosis and raise the risk of hip fractures.

A nice summary of the risks of Vitamin A, including neurologic disease, birth defects, and osteoporosis.

A Cochrane Review that presents mixed evidence for the possible benefit of Vitamin A for reducing mortality in children with measles. However, another review found no benefit for non-measles pneumonia.

A Chochrane Review showing Vitamin A does not reduce transmission of HIV from mother to offspring.

A Cochrane Review that found no value in Vitamin A for preventing lower respiratory tract infections in children, and even a few studies showing and increase risk with supplementation.

Vitamin C

The original megavitamin Linus Pauling promoted obsessively in his later years. The most extensively studied claims of orthomolecular practitioners are those relating to Vitamin C, and these are the claims that have been most soundly disproven. In addition, recent evidence illustrates the real risks of large doses of Vitamin C.

Vitamin C can interfere with the effectiveness of chemotherapy.

A pair of detailed reviews and refutations of a couple of papers purporting to finally show some value to megadoses of Vitamin C . First Post Second Post

A paper showing Vitamin C not helpful, and potentially exacerbating for hypertrophic osteodystrophy in dogs.

No evidence oral Vitamin C improves immune system parameters in dogs.

Cochrane Reviews-Evidence does not support Vitamin C for prevention or treatment of the common cold and is generally absent or of unreliable quality for the use of Vitamin C in prevention or treatment of pneumonia, tetanus, and asthma.

Vitamin D

There is a great deal of interest in the potential of this vitamin to reduce cancer risk. However, the evidence so far is mixed, with some studies showing a decreased risk (e.g. colon cancer), little or no change in risk (e.g. breast, prostate, and others), and even some increase in risk (e.g. pancreatic cancer among smokers). Excessive amounts can cause kidney stones, abnormal heart rhythms, and other serious side effects. This is one substance for which I think there is justification to conducting further research.

Vitamin E

In this study, Vitamin E use increased the risk of lung cancer.

A pair of studies that showed Vitamin E had no protective benefit for prostate cancer and increased the risk of heart failure.

Multivitamins and Miscellaneous

A systematic review and meta-analysis published in the Lancet that suggests not only do antioxidants and Vitamin A and E supplements not prevent cancer, they may actually increase mortality risk.

A large study that found no benefit to multivitamin supplements for older women.

Neurologic toxicity with oral supplementation of Vitamin B6 in dogs.

Extensive research into orthomolecular claims in neurologic and psychiatric disease has found no evidence of benefit.

Orthomolecular Treatment of Cancer
By Abram Hoffer, M.D., Ph.D., FRCP(C)

Introduction

Between 1978 and March, 1999 I have seen over 1040 patients suffering from cancer who came to me for nutritional and psychiatric counseling. This is no longer a surprising combination as it was when I first started to practice psychiatry in 1952. I attended my first annual meeting of the American Psychiatric Association in Los Angeles, in 1952. I did not meet another psychiatrist there with a PhD in Biochemistry. Since then many more scientists with the double degrees have become active in this field but of these very few actively pursue this particular combination. Orthomolecular theory and practice drives these two together. I have retained my interest in the biochemistry and clinical aspects of nutrition combining this with my education in medicine and later in psychiatry. The recovery of my first patient in 1960 from terminal bronchiogenic cancer of the lung arose from this coalescence of these two disciplines.

By 1960 my research group in Saskatchewan had discovered the first biochemical substance that was clearly related to the schizophrenias. Not knowing its structure we called it the mauve factor until it was later identified as kryptopyrrole. We tested thousands of patients and found that over 75% of all schizophrenic patients excreted this substance in their urine. It was also present in about 25% of other psychiatric groups, in about 10% of severely stressed physically ill patients and in about 5% of normal people but they were mostly first order relatives of schizophrenic patients. It disappeared with recovery of the patients no matter how they were treated. I was particularly interested in the fact that out of eight patients with cancer of the lung, this factor was present in 5.

In 1960 a retired psychotic professor was admitted to our psychiatric department at University Hospital in Saskatoon. He had a bronchiogenic carcinoma of the lung and when he became psychotic it was concluded he had secondaries in his brain. He was placed on terminal care, expected to die in a month or so. Earlier he had been discharged to the care of his wife and a nurse but after several weeks had to be readmitted since they could not cope with his behavior. As soon as I discovered he

was on our ward I had his urine collected and we tested it for the factor. He excreted copious quantities which we were able to use to help us identify the substance. I then advised his resident to start him on niacin 1 gram after each meal and on ascorbic acid 1 gram after each meal. By then I knew that this combination of vitamins used in megadoses was very helpful in treating any patient with this factor in their urine no matter what they were diagnosed. Fortunately for this patient the resident accepted my advice (the patient was not under my care but I was Director of Psychiatric Research at the hospital). He was started on the two vitamins on Friday afternoon and he was mentally normal by the following Monday.

I knew this patient before he became ill as I had treated his wife. After he had recovered I advised him to remain on these two vitamins. In 1960 our research unit was the only one in Canada, and perhaps in the world, where 500 mg tablets of these vitamins were available. They were specially made for us. If smaller tablets were used in these large doses they would make our patients sick because they contained so much filler. I told him that if he would pick up a supply each month I would give it to him free. This meant he had to see me each month and this gave me the opportunity of assessing his psychiatric state. I did not expect he would recover from his cancer. He had been told of his dismal prognosis and I did not contradict that. To my surprise he kept on coming back. About 12 months later I had lunch with the Director of the Cancer Clinic which had been following his case. He told me that the tumor had become less and less visible with each X ray every three months and that it was now no longer present. He lived about 30 months after he was diagnosed terminal. I had hoped that when he died he would be autopsied at University Hospital. Unfortunately he died at another hospital and I did not hear this until several days later. He did not die from his cancer.

Two years later a woman I had treated for depression several years earlier consulted me again. This time she was depressed because her 16-year-old daughter had Ewings tumor (a highly malignant sarcoma) in one arm and she was slated for surgery to amputate her arm. This was the standard treatment. I told her about the previous patient and his recovery and suggested that although there was no evidence it would help it could do no harm and might possibly be of some value. Her daughter agreed to take niacinamide 1 gram after each meal and ascorbic acid 1 gram after each meal. Her surgeon agreed to postpone surgery for a month. She recovered and the last time I heard from her family she was married and leading a normal productive life, with both arms. I concluded that vitamin B-3 was the most important component and that the vitamin C was helpful. In Saskatchewan under my direction we did the first double blind controlled therapeutic trials in Psychiatry, completing six by 1960. Therefore I was aware of the powerful influence of placebo. However when two terminal patients recovered on the vitamins it became powerful evidence that there was more than placebo at work.

I did not see any more cancer patients until 1977 after I had established my practice in Victoria, BC. In British Columbia specialists will not accept patients until they have been referred by their general practitioners. As a psychiatrist I saw patients referred

with psychiatric problems but in most cases the referring physicians would not indicate why the referral had been made and I would only discover the reason when I finally saw my patient.

A.S., an elderly woman appeared and when I asked her why she had come she replied that she had cancer of the head of the pancreas. She had developed jaundice. Her surgeon discovered she had a large tumor in the head of the pancreas which occluded her bile duct. He promptly closed, created a by-pass, and when she recovered from the anesthesia advised her that she had about 3 to 6 months to live. She worked in a book store. She had read Norman Cousins book Anatomy of an Illness and thought that if he was able to take so much vitamin C with safety she could too and she began to take 10 grams each day. The next time she consulted her doctor she told him what she was doing. He referred her to me since he was familiar with my interest in megadoses of vitamins. I reviewed her program and increased her vitamin C to 40 grams daily trying to reach the sublaxative level. I had been using multi nutrients for my schizophrenic patients for many years and since I had no idea which, if any, of these vitamins might help I reasoned that she would have a much better chance if she also were to take more than one nutrient. I then added vitamin B-3, selenium, and zinc sulfate. Six months later she called me at home in great excitement. She had just had a CT scan. No tumor was visible. The CT scan was repeated by the incredulous radiologist. Her original bile duct had reopened and now she had two. She remained alive and well until she died February 19, 1999, nearly 22 years after she was told she would die.

Rarely patients make a major contribution to medicine by their interest in a disease and their willingness to try innovative approaches. A.S's recovery changed my professional career and I believe will make a major contribution to the complementary treatment of all cancer patients. Last year at a public meeting I thanked her publicly when I discussed her case before a meeting of Cancer Victors. She added that I had changed her life as well. She has also changed the life of hundreds of cancer patients who became victors, not victims.

By telling her friends, relatives and customers about her recovery she changed the nature of my practice. That first year another five patients were referred. The second case was a man with a sarcoma of the prostate which was invading his pelvic bone. He was advised no treatment was available. His doctor referred him to me and I started him on a similar program. But he was only able to take about 10 grams of vitamin C daily. I asked his doctor if he would mind injecting him with 10 grams of vitamin C twice weekly. After six months his doctor wanted to know how much longer would he need to receive his vitamin C. He told me that the tumor was gone. He stopped the injection. He lived another 9 years and died at age 80, but not from his cancer.

More patients were referred to me each year. At first almost all of them were patient-generated and often it took remarkable persuasive powers for the patient to obtain the necessary referral. After assessing their physical and mental state I would talk to them

about the therapeutic regimen. I outlined the program in detail describing each nutrient and why I thought they might be helpful. I added that there was no guarantee that the vitamins would be helpful but gave them hope by describing the cases who had had a dramatic response. I added that the vitamin mineral program would decrease the toxicity of the xenobiotic treatment and would increase the efficacy of the xenobiotic program. If they needed surgery they would heal faster afterwards. If they needed chemotherapy the program would make it more tolerable and less painful and if they needed radiation the program would decrease the intensity of the side effects of the radiation and increase its efficacy. These comments were based on the literature which was developing rapidly. The program was designed to assist the body in controlling the cancer and was not a direct assault on the tumor. The attack on the tumor was carried out by the other physicians including their family doctor, the surgeons, the radiologist and oncologists. The diagnosis of the cancer and the xenobiotic treatment used was left entirely to the patient and their other doctors. I did not advise them whether or not they should take any other treatment. Very few did not receive xenobiotic therapy. After describing the program I would arrange to see them once more unless they were very depressed and anxious, in which case I would see them more often. A few of the patients had been under my care before they developed their cancer and I continued to see them. I then sent a consultation report to each referring physician. After the second interview they were returned to the care of their family physicians. I had not planned on doing any follow up but after several years when I had treated about 50 patients I became aware that the patients who had followed the regimen consistently for at least two months lived much longer than the patients who did not start the program or did not take it for at least two months.

About this time I went to a Festchrift for Dr. Arthur Sackler at Woods Hole, Mass. We met in 1951 when I was starting our research program. He and his brothers were practicing in mid-Manhatten. They were probably the first orthomolecular psychiatrists in the United States. They were treating schizophrenic patients by injecting them with histamine. After I returned home I repeated their studies and found that their observations were correct. Out of twelve patients I treated using their regimen 8 became normal. The treatment was difficult since they had to be given increasing amounts of subcutaneous histamine until their diastolic pressure decreased to 0. It was amazing to see how comfortable they could be with that low blood pressure. Treatments were given daily on week days until the series was completed. I did not continue this series because by this time I was using megadoses of vitamin B-3 which was much easier to administer and equally effective. The histamine flush was identical with the niacin flush. At that meeting Dr. Linus Pauling delivered a vigorous and careful critique of the Mayo Clinic's attempt to repeat the studies he had done with Dr. Ewan Cameron in Scotland. The Mayo group claimed they had exactly repeated these studies but it was clear on reading their paper that they had not. Dr. Pauling did not object to their negatives findings. He objected to their statement that their conclusions resulting from a different method of administering the vitamin C were used to condemn his and Camerons findings. In other words no scientist can claim to confirm or deny any study unless they really have repeated the original work as described by the original authors.

The next morning, after breakfast, I visited Linus Pauling who was staying in the room next to mine. When I walked in he was busy with a hand calculator. He told me he was working out the electron orbitals saying that he did not understand them unless he did the calculations himself. I told him that on the basis of my fifty patients I had concluded that he and Cameron were right, that vitamin C in large doses did improve enormously the outcome of treatment for cancer. Linus asked me if I intended to publish the data. I replied that I did not. I added that in my opinion there was little point in trying to do so since it would be impossible to gain entry into any medical journal, that they would not accept any paper that dealt favorably with megadose vitamin therapy. The New England Journal of Medicine, which had published the Mayo Clinic attack on Pauling, refused to publish his rebuttal. Linus urged me to do a complete follow up study of every patient I had treated. I was flattered and agreed that I would. He said that he would see that the material would be published. But when I returned home I decided not to do the follow up. It would have meant an enormous amount of work. I thought that Dr. Pauling was being kind to me. Two years later I received a letter from Linus in which he said bluntly "Abram where is the study". I decided that he was serious about it. By then I had seen 134 patients. I apologized and promised to start the follow up immediately. I traced every patient and determined whether they were alive, where they were, and what had happened to their lives. I contacted the patients, their families, their doctors, the cancer clinic where nearly all of them had been seen and treated. The Cancer Clinic in Victoria did a good job of investigation, diagnosis and treatment using only xenobiotic therapies.

Dr. Pauling developed an elegant method for determining the probable outcome of treatment using cohorts of patients who were or were not treated. After I had completed the follow up I sent the case histories, with identification of each patient removed, and the follow up study. We decided to use the duration of life as the only variable. This began when they first saw me and ended with the day of their death. There is increasing evidence that this hard measure of success is much more useful than trying to decide whether the tumor is slightly smaller or not. Patients have lived for a long time with slowly growing tumors. We agreed to publish as coauthors. I suggested that the first paper would be by Pauling and Hoffer. This was because it was his original idea to use megadoses of vitamin C and the work I had done was merely to test his conclusions. He was very firm that he would not consider this and insisted it would appear as Hoffer and Pauling. I think he felt that as a clinician who had done the clinical work I should be the senior author. He did not have an MD. Linus Pauling, in my opinion, was the most brilliant humanitarian scientist that ever lived. Over his life time in addition to his two Noble Prizes, he was awarded nearly 40 Honorary degrees, PHD's and DSc's. I am sorry he was never given an Honorary MD. His contribution to human health has surpassed that of most physicians. We wrote the paper using his method for analyzing the data and my clinical material. But the Proceedings of the National Academy of Sciences refused to accept the paper. One of the criticisms of our paper came from some rumor which had reached the critic that I had solicited patients to come to be seen implying I had selected only the best prognostic patients. On the contrary I had nothing to do with the selection and I included every patient who had been referred. Eventually we published in the Journal

of Orthomolecular Medicine. I am the editor and I could not refuse to accept our work. That original paper was reprinted in the book by Ewan Cameron and Linus Pauling Cancer and Vitamin C. Updated and Expanded. Camino Books Inc, P.O. Box 59026, Philadelphia, PA 19102. 1993. Appendix IX is this report.

We began to write a book. My case load was building very quickly and I published a second paper with Dr. Pauling and several more after that on my own. We finished most of the book except for much of the detailed clinical material but we could not find a publisher in the United States willing to publish it. The topic was still too controversial. I found a Canadian Publisher, Quarry Press, Kingston, ONT. A few months ago I sent him the completed manuscript. This contains all the original material Dr. Pauling had written dealing with each type of cancer and a presentation of my data based on nearly 800 patients. We concluded in our manuscript that the optimum treatment for cancer today is a combination of xenobiotic and orthomolecular therapy and that treatment must be started as soon as possible. This book will be available presently. Here are the early references.

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One Patient's Recovery From Lymphoma. *Townsend Letter for Doctors and Patients*. #160 , 50-51, 1996

A new book just arrived by Burton Goldberg, edited by W.John Diamond, W. Lee Cowden with Burton Goldberg, *Alternative Medicine Definitive Guide to Cancer*.

Future Medicine Publishing, Inc. Tiburon, California.1997. In this valuable book 37 physicians including myself, describe the alternative methods they use with clinical descriptions of some of the results they have obtained. I prefer the term complementary to alternative and expect that soon all medicine will be complementary and that physicians using only xenobiotic methods will be the exception.

Review of Previous Reports and Present Summary.

The use of large doses of nutrients for the treatment of cancer has not yet entered the mainstream of medicine, not in the Universities, nor in the medical journals, or in the wards, halls and corridors of hospitals. But it is beginning to do so, largely due to the persistence and dedication of Professor Linus Pauling. He needed forums in which to outline his views and these were provided for him by the physicians and other interested individuals. The Canadian Schizophrenia Foundation was honored to host Linus Pauling on three separate occasions, in Toronto and in Vancouver. About the same time the National Cancer Institute held a meeting in September 1990. This was not a clinical meeting. No one presented clinical data showing what nutrients might do. At this meeting Dr. Linus Pauling and two associates presented their findings. Dr. Pauling commented at that meeting "It is very interesting to be here since, for some ten years or so, you have refused every request of mine for research grants on vitamin C". The Proceedings, National Academy of Sciences (US) refused to publish any clinical papers authored by Dr. Linus Pauling. The first paper, by Hoffer and Pauling, was rejected.

During May 10-12, (1991) Jay Patrick, President, Alacer Corporation, hosted a meeting- the Second World Congress on Vitamin C and The Immune System, in San Diego, Bahia Resort Hotel. He had hosted the First World Congress on Vitamin C in 1978 in Palm Springs. That one was addressed by Dr. Szent-Gyorgyi who won the Noble Prize for his work on vitamin C and intermediary metabolism, by Dr. Linus Pauling, and by Dr. Fred Klenner, the first physician to use megadoses of vitamin C. The Second World Congress brought together a distinguished group of vitamin researchers and clinicians including Dr. E. Cheraskin, Dr. C.A.B. Clemetson, Dr. E. Ginter, Dr. J. Priestly, and others. Their papers were published in the *Journal of Orthomolecular Medicine* Volume 6, 1991. I also presented a report on the clinical procedures I was then using in treating the terminally ill cancer patients with Vitamin C. Dr. Linus Pauling presented an excellent outline of his research into vitamin C and Cancer but his presentation was not published. Dr. Pauling was an excellent speaker, very honest, and very blunt. The following quotation from his paper will convey some of the flavor of his presentations. "When Irvine Stone wrote to me in 1965, after having heard me give a talk in which I said that I would like to live 25 years longer in order to enjoy reading about the new discoveries about the nature of the world that no doubt would be made by scientists during these 25 years and said if I were to take three grams a day of Vitamin C, I would perhaps not only live the 25 years but even 50 years. And that was when I increased my uptake ot ascorbate fifty fold to 3,000 milligrams a day, then later to a hundredfold, 6000, then to two hundredfold, then to three hundredfold and I'm still not sure what the optimum intake is. There is a practical

reason why I stopped at three hundredfold at 18,000. Well, I think that's pretty important. I read a statement by physicians that they should tell their patients not to worry about being constipated. I think they should worry about being constipated, its so harmful to carry waste toxic materials around an unnecessarily long period of time. So, it was Irwin Stone that got me interested in Vitamin C and of course, it was Victor Herbert who was responsible for my having begun writing books about vitamins". So the other day I got a book published by the National Academy of Sciences on control of diseases. It mentions practically nothing about vitamins and their usefulness but it does have something about common colds. A statement that 16 control trials have been turned out, every one of which showed that Vitamin C has no value in controlling the common cold, preventing or controlling the common cold. They didn't listen, but I'm sure they're the 16 control trials that I discuss in my books, where I give the amount of decrease in illness. Every one of these shows that Vitamin C has value, not that it doesn't have value. That's perhaps a minor misrepresentation. A couple of years ago, I got two or three letters from people who sent me clippings from a magazine. One of them said he had stopped taking his Vitamin C because of the statement in this magazine. It was a quotation from the Professor of Medicine at Yale University Medical School. I had mentioned, three or four weeks ago, while speaking in Yale University Medical School, his statement that you shouldn't take as much as even one gram of Vitamin C per day because it will damage the liver. So I wrote to him and said that I read the literature on Vitamin C to the extent that I can, and there are a couple of thousand new papers published every year about Vitamin C, but I missed the meal. Would you please send me the references to the work done on the damage done to the liver. Well, he was a gentleman, which you'd expect at Yale Medical School and often when I write letters like that I don't get an answer from them. He wrote back saying oh, that was just a mistake. That was the end of that. So far as I know he didn't write to the magazine and say that was a mistake, but he did say it to me. And there are lots of mistakes of this sort about vitamins that perhaps sometimes intentionally misrepresent the facts. For some perhaps there is a reason an economic, financial reason, that there is so much opposition in the medical establishment against improving your health by taking vitamins."

This first symposium which included laboratory and medical scientists was one of the first with this mix of clinical and preclinical data. The number attending was not very large but they made up in quality for the lack of numbers. There I met Dr. Patrick Quillin, Vice President of Nutrition, Cancer Treatment Centers of America. He was thinking about organizing a conference to consider the connection between nutrition and cancer. I thought it was an excellent idea and encouraged him to do so. The first symposium was held in Tulsa, Oklahoma, November 6 to 8, 1992. The title of the meeting was Adjuvent Nutrition in Cancer Treatment. Over 300 physicians and others attended. Participating were seven Universities, more than 6 cancer institutes. The last half day of the symposium was taken up by clinical studies including my report, and a report from Prof Rudy Falk, University of Toronto Medical School. This was the first meeting were both the academic physicians and orthomolecular physicians met in an amicable and interesting exchange of information. The meeting was co- sponsored

by the Cancer Treatment Research Foundation and the American College of Nutrition, and published as a proceedings.

In my presentation at the Tulsa Conference I described how I became involved in the treatment of patients with cancer. My preliminary data indicated that the addition of vitamin C in mega doses improved the outcome of treatment substantially. I described these findings to Linus Pauling. He urged me to follow up carefully every patient I had seen and offered to analyze the follow up data using the method he had developed. In our two recent studies, Hoffer and Pauling concluded that the addition of vitamin C improved the outcome of treatment for cancer significantly and substantially. In the first study 134 patients seen between August 1977 and March 1988 were followed until December 31, 1989. We concluded that orthomolecular treatment given to female related cancers had improved life expectancy about 20 times compared to our non random controls and 12 times for other cancers. In our second paper a second cohort of 170 patients seen between April 1988 to December 31, 1989 was followed to December 31, 1992. These results were about the same as those we had published earlier. We concluded that while vitamin C alone led to about 10 % excellent responders the addition of the other nutrients increased this to about 40 %.

Orthomolecular treatment improves the quality of life. It also decreases the side effects of radiation and chemotherapy. The program is palatable. The only patients who could not follow it were those who were getting chemotherapy and suffered severe nausea and vomiting or patients who could not swallow because of lesions in their throat. Orthomolecular therapy provides a step forward in the battle against cancer and must be fully explored. 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.

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Anti Cancer Nutrition

A large number of special diets ranging from fasting (water only) to juice fasts to low fat and sugar free diets are used. Every one of the special diets have proponents who think they are very helpful, and patients who have been helped by them but no one has ever conducted an experiment to compare all the diets to determine which is the

best. Perhaps there will never be a "best". Because of the individuality of people it may turn out that each person will have to determine what is their own best diet. In my book *Hoffer's Laws of Natural Nutrition* Quarry Press, P.O.Box 1061, Kingston, Ontario K7L 4Y5. Almost all the diets used by complementary therapists are lower in animal proteins, much more vegetarian, with emphasis on vegetables rich in bioflavonoids and fruits. I advise my patients to obey three rules (1) To eliminate all junk food i.e,. food containing any added simple sugars like table sugar or glucose as in corn syrup. This simple rule, comprehensible even to children, will eliminate nearly 90% of the additives commonly added to processed foods. (2) To reduce fat levels, I think that dairy products are the chief villains. Nearly every study internationally has shown that countries with lower fat intake have fewer cases of cancer, particularly breast cancer. Milk is very rich in estrogens from the cow and in phytoestrogens from the grass that they eat.(3) To eliminate all foods they know they are allergic to. These rules allow the diet to be varied, palatable and interesting.

Vitamin Supplements

No one should take any supplements until they have become familiar with their properties and how to use them. It is advisable always to work with a knowledgeable physician. But if they can not find any physician or orthomolecular nutritionist they should go ahead on their own using the information now readily available on nutrition and vitamin supplements. They should advise their doctors what they are doing and which supplements they are using. By listing the vitamins and dose ranges I am not suggesting that every person need to take them all. This is an individual matter based on discussions with their doctor. The vitamin and mineral supplements are compatible with medication and with the diet.

Vitamin C. The dose range is anywhere from 3 to 40 grams daily in three divided doses. If the dose is too high it will not be absorbed by the intestines, will stay in the bowel and act like a laxative causing loose stools and gas. It is a good laxative. The best dose does not act like a laxative. Forms of vitamin C include the pure ascorbic acid (hydrogen ascorbate), and the mineral salts such as sodium ascorbate (slightly salty in taste), calcium ascorbate (slightly bitter), and other salts often found in combinations of the mineral ascorbates, In large doses it is best used as the powder dissolved in water or one of the juices. Do not use commercial grade vitamin C crystals of powders. Use CP grades as is found in drug stores or health food stores. Contrary to false rumors issued by some hostile critics of megadose vitamin use it does not cause kidney stones, does not cause pernicious anemia, does not cause sterility. A recent suggestion in a letter, to Nature, published in England concluded that more than 500 milligrams of vitamin C daily could cause DNA damage. This was based on one of a possible 20 markers that could have been used which showed no damage and a 21st marker which is seriously questioned. Some of the key scientists in this field criticized these conclusions. My only comment is that if they were correct why do my patients who take large doses of vitamin C live so much longer.

Vitamin B-3. There are two forms. Niacin lowers cholesterol, elevates high density lipoprotein cholesterol and reduces the ravages of heart disease, but causes flushing when it is first taken. The flushing reaction dissipates in time and in most cases is gone or very minor within a matter of weeks. Niacinamide, the other form, has no effect on blood fats (lipids) but is not a vasodilator. There have been 7 international conferences on the theme niacin and cancer. This vitamin is an essential component of the enzyme systems that repair broken DNA molecules. The dose ranges from 100 milligrams three times daily to 1000 milligrams three times daily. Several studies in Detroit have found that the response rate of cancer around the head and neck was 10% on radiation alone but increased to 80% when patients were given large doses of niacinamide. Very rarely niacin will cause obstructive jaundice which clears when the niacin is stopped. For details see my book Orthomolecular Medicine for Physicians.

Vitamin E (d alpha tocopherol succinate). This water soluble form has the greatest efficacy in controlling cancer cell growth in the test tube and is the one I recommend should be used. The dose ranges from 400 to 1200 International Units daily. Vitamin E is the major fat soluble anti- oxidant in the body and plays a role by decreasing the concentration of free radicals which are thought to be involved in the creation of the cancer. It also decreases the risk of heart disease, thus confirming what was found over fifty years in Ontario by Drs. Wilfrid and Evan Shute.

The Carotenoids. Most people have heard of beta carotene but this is only one of a large number of carotenoids which are present in colored vegetables and fruits such as carrots, beets, tomatoes and greens. The evidence is very powerful that these mixed carotenoids as found in these foods will decrease the incidence of cancer but there is a question about the efficacy of the pure beta carotene. There is still a vigorous debate about this. I prefer carrot juice to the beta carotene. Generally it is better to have a large variety of these natural anti cancer factors. Beta carotene is very safe. The only question is whether it is the best form. Only a small portion is converted into vitamin A.

Folic acid. Several studies have found this important vitamin has anti cancer properties, for cancer of the cervix and of the lung in lung smokers. This does not mean it is safe to smoke. It does mean that smokers should take it and immediately start their campaign to stop smoking. Women should take ample amounts to prevent neural tube disorders such as spina bifida. The US government plans to add it to flour. Canada is still thinking about it. The dose range is from 1 to 30 milligrams daily. It can be taken only on prescription.

Coenzyme Q 10. Dr. Karl Folkers discovered this substance, also called ubiquinone; toward the end of his long and distinguished career he regretted that he had not called it a vitamin. It is an odd vitamin since young people are able to make enough from the lower numbered ubiquinones such as Q 6 or Q 8 whereas older people and anyone ill is not able to make enough. It thus becomes a vitamin later in life and when one becomes ill. A few clinical studies have shown that in large doses it has anticancer

properties especially for breast cancer. These range from 300 milligrams to 600 milligrams daily.

Mineral supplements

Selenium. The presence or absence of this trace element has the clearest relationship to the presence of cancer. People living on soils that are rich in selenium have a lower incidence. I recommend between 200 to 1000 micrograms daily. One of my patients took 2000 with no side effects.

Calcium and magnesium. These are generally very useful to take to maintain calcium levels in bones and blood. They have been found helpful in cases of bowel cancer. Women should receive 1500 milligrams of calcium daily from their food and supplements and half as much magnesium. There are several forms of these minerals available. Usually a person will absorb into their body anywhere between 25 and 50% of the calcium.

Zinc and copper. There is a reciprocal connection between these two. If blood zinc levels are too high the copper levels will be too low. Because zinc can shrink enlarged prostate glands and may be helpful in the treatment of this cancer. I have been using it routinely. Also, people in Victoria tend to be low in zinc levels because our water is soft, and dissolves copper more easily from copper plumbing.

Other Substances Found in Plants.

A large number of these preparations are being used for the treatment of cancer. They include bioflavonoids, preparations from soy bean, and from mushrooms. Vaccines are also being used. Coley's vaccine originated over 100 years ago. I will not discuss these, nor other treatments such as 714-X, Ukrain, Iscador, Cartilage, Carnivora, Amygdalin (Laetril), Essiac, and many herbs. These are described in the book by Diamond, Cowden and Goldberg.

Most of the speakers at the 26th Annual International Conference on Nutritional Medicine Today, Toronto, April 1997, discussed various topics dealing with the principle and practice of orthomolecular medicine. Dr. C. Simone spoke on "Breast Cancer: Nutritional and Lifestyle Modification to Augment Oncology Care". Dr. Simone is well known for his work in researching complementary treatment of cancer.. He is an Internist, Medical Oncologist, Immunologist and Radiation Oncologist and has published several valuable books including *Cancer and Nutrition* and *A Ten Point Plan to Reduce Your Risk of Getting Cancer*. Optimum nutrition, avoiding toxic substances in food and water, and other lifestyle changes will materially reduce the risk of developing cancer.

Here is his ten point plan (1) Nutrition: calories slightly below average to maintain a weight just below the average weight. Should be high in fiber, rich in fish, fruits, and vegetables and with vitamin and mineral supplements. Eliminate additives and salt. (2)

Avoid tobacco. (3) Avoid alcohol (one drink per week allowed). (4) Avoid radiation. Take X-ray only when necessary and avoid excessive exposure to sun. (5) Keep environment, air, water, and work place clean. (6) Avoid promiscuity, hormones and any unnecessary drugs.(7). Learn early warning signs like a lump in the breast. (8) Exercise and relax regularly. (9) Take a yearly physical. (10) Read his book for a self test of risk factors and symptoms that may indicate cancer or heart disease. See the report by Esteve,J. et all. Diet and cancers of the larynx and hypopharynx: the IARC multi-center study in southwestern Europe. In *Cancer Causes and Control* 7:240-252,1996.

These ten points should be part of every treatment program as well. The main difference is that in treatment the first point becomes even more important and the doses of supplements are much greater. The sicker a person is the more nutrients are needed in optimum doses to help the bodies reparative mechanisms. Treatment must be started as soon as the diagnosis is suspected and made, and should be concurrent with any other treatment recommended by oncologists and cancer specialists. Eventually all cancer specialists will be using these orthomolecular techniques. Supplements must be maintained while chemotherapy or radiation are being used. Studies have shown that these supplements enhance the toxic effect of the treatment on the lesion and decrease the toxic effects on the body. Patients do not suffer as much from the side effects and recover much more quickly when the treatment series is completed. They enhance the quality of life during and after treatment.

Treatment with high doses ascorbic acid either by mouth or intravenously or both carries no risk and does provide substantial advantages over chemotherapy and surgery used as the sole treatment. Between 1980 and 1995 four patients with sarcoma followed my treatment protocol (a combination of orthodox and orthomolecular treatment). The first seen in Victoria, had a prostate sarcoma invading his pelvic bones. The cancer clinic could not treat him and he was declared untreatable. He responded to the regimen and died 9 years later at age 80 clear of cancer. One is alive after ten years. One is still alive after five years. The last one, an abdominal liposarcoma died in his sixth year. Counting the first young patient I saw in 1962 who was still well several years ago, five of six responded either to the vitamin regimen alone or to the combination treatment.

There is no reason in the world why any oncologist should not allow vitamin treatment in combination with chemotherapy. This would enhance the therapeutic effect of the chemotherapy and decrease its toxicity.

Orthomolecular medicine and **Optimum nutrition** are nutritional health and medical approaches that are based upon the premise that many diseases and abnormalities result from varing biochemical and/or chemical needs specific to each individual. It holds that they can be prevented, treated, or sometimes cured by achieving optimum levels for that individual's body of various biochemicals which are natural to the body, either through diet or metabolism. It normally employs doses of vitamins, minerals, amino acids, trace elements, and essential fatty acids.[1]

Orthomolecular medicine is practiced by few conventional medical practitioners.[2][3] Orthomolecular treatments are instead more common in complementary and alternative medicine fields, increasingly being integrated into over the counter retail products, naturopathic medical textbooks and mainstream pharmaceuticals.[4][5] The controversial field of orthomolecular psychiatry deals with the use of orthomolecular medicine to treat psychiatric problems.

The orthomolecular field is based on research in biochemistry, nutrition, medicine, and pharmaceuticals, which is interpreted in the light of the clinical experience of its practitioners. Orthomolecular medicine and optimum nutrition are based on the idea of individual variation in humans, with individual nutrient requirements varying widely with health, genetic and environmental influences.[6] Aspects of orthomolecular therapy remain controversial among mainstream medical organizations and physicians, who consider many aspects to be lacking sufficient RCT based evidence. In contrast, orthomolecular proponents argue that many mainstream nutritional studies, both recent and historical, provide investigational and clinical support for their treatments and recommendations.[7] They also argue that orthomolecular therapies are intrinsically less likely to cause dangerous side-effects or harm, since they utilize only chemicals that are normally present in the body.[1][8][9]

Orthomolecular treatments typically have been experimentally or empirically introduced by physicians or researchers when conventional medical treatments offered neither solution[10][11] nor hope.[12][13] Orthomolecular psychiatry began to be developed in the early 1950s by a group of biochemists and psychiatrists who identified a number of biochemical abnormalities that they thought were associated with mental illness and treated a number of mental disorders using high dosages of certain vitamins. Orthomolecular megavitamin therapies, such as with tocopherols[14] and ascorbates,[15] date back to the 1930s.

Frederick Klenner, (1907 – 1984) was an American medical researcher and doctor in general practice in Reidsville, North Carolina. From the 1940s on he experimented with the use of vitamin C megadosage as a therapy for a wide range of illnesses, most notably polio. He authored 28 research papers during his career. He is considered one of the originators of orthomolecular medicine, but his work remains largely unacknowledged by established medicine.[16][17]

In the late 1950's, Irwin Stone stated published his belief that scurvy was not a dietary disturbance, but a potentially fatal problem that had been misunderstood by nutritionists. Ascorbate was not a trace vitamin but was required in humans in large daily amounts. He produced four papers, between 1965 and 1967, describing the human requirement for ascorbate as genetic defect which he named hypoascorbemia.[18][19][20][21]

The term "orthomolecular" was first used by Linus Pauling in 1968 to express the "*idea of the right molecules in the right amounts*" within the context of psychiatry".[22] Pauling subsequently defined "*orthomolecular medicine*" as *"the treatment of disease by the provision of the optimum molecular environment, especially the optimum concentrations of substances normally present in the human body"* or as *"the preservation of good health and the treatment*

of disease by varying the concentrations in the human body of substances that are normally present in the body and are required for health."[23]

Since 1968 the orthomolecular field has diversified, but the term is still often closely associated with Pauling's advocacy of multi-gram doses of vitamin C for optimal health. Partly for this reason, detractors of orthomolecular ideas have described them entirely in terms of megadose nutrient therapy. Cassileth, a widely quoted critic of Pauling's ideas, asserts: "In 1968, the Nobel-prize-winning scientist Linus Pauling coined the term "orthomolecular" to describe the treatment of disease with large quantities of nutrients."[2] In this way, criticism of orthomolecular medicine has, to a large extent, been confused with much older medical traditions of high-dose vitamin therapies, such as earlier "megadose" usages of retinol and ergocalciferol or synthetic pharmaceutical analogues, such as menadione.[24] [25][26] However, such definitions of orthomolecular therapy are not synonymous with Pauling's definition.

Based on investigational scientific studies, single blinded and double blinded randomized controlled trials, clinical experience, and case histories, claims have been made that therapeutic nutrition can prevent,[27] treat, or sometimes cure, acne,[28] bee sting, burns, cancer, common cold, drug addiction, drug overdose, heart diseases, acute hepatitis, herpes, influenza, mononucleosis, mushroom poisoning, neuropathy & polyneuritis (including Multiple sclerosis), osteoporosis,[29] polio, "alcoholism,[30] allergies, arthritis, autism, epilepsy, hypertension, hypoglycemia, migraine, clinical depression, learning disabilities, retardation, mental and metabolic disorders, skin problems, and hyperactivity,"[31] Raynaud's disease, heavy metal toxicity, radiation sickness, * Pyroluria, schizophrenia,[32] shock, snakebite, spider bite, tetanus toxin and viral pneumonia.[33]

Orthomolecular medicine argues that it is preferable to recognize and correct any possible anomalies in metabolism at an early stage, before they cause disease. Orthomolecular medicine posits that many typical diets are insufficient for long term health; thus, orthomolecular medical diagnoses and treatment often focus on use of nutrients such as vitamins, dietary minerals, proteins, antioxidants, amino acids, ω-3 fatty acids, ω-6 fatty acids, lipotropes, prohormones, dietary fiber and short and long chain fatty acids.

Orthomolecular therapy attempts to provide what are seen as optimal amounts of these nutrients. Most often, "optimal" has been a matter of the clinical judgment of the orthomolecular practitioner, who gives nutrients in accord with the clinical symptoms of the patient and their judgement of what is appropriate, rather than the published dietary reference intakes of these nutrients. The modern orthomolecular practitioner also uses a wide range of laboratory analyses, including those for amino acids, organic acids, vitamins and minerals, functional vitamin status, hormones, immunology, microbiology, and gastrointestinal function. However, many of these tests have not been accepted by mainstream medicine for common diagnostic use.

In the early days of orthomolecular medicine, supplementation usually meant high-dose, single-agent nutrient therapy.[34] Most often today, the orthomolecular practitioner uses many substances: amino acids, enzymes, hormones, vitamins, minerals, or derivate substances in an effort to supply what they see as optimum levels of these substances.[35]

Frequently supplementation with relatively large doses of vitamins is given, and the name megavitamin therapy is popularly associated with the area. Megavitamin therapy is the administration of large amounts of vitamins, often many times greater than the recommended dietary allowance (RDA). The nominal ratio of dose to RDA to qualify for the term "megavitamin therapy" has been a matter of minor semantic debate.

Administration of short-chain fatty acids in orthomolecular practice is usually done by increasing the level of dietary fiber.[36][37] The fatty acids are produced by fermentation of the fiber in the colon, then absorbed into the body. Attempts are also made to aid this process by a combination of probiotics, prebiotics and "glyconutrients". Long chain fatty acids, such as the omega-3 fatty acids alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), may also be given directly, in food or in capsules.

A survey released in May 2004 by the National Center for Complementary and Alternative Medicine focused on who used complementary and alternative medicine (CAM), what was used, and why it was used in the United States by adults age 18 years and over during 2002. The survey reported uses in the previous 12 months that include orthomolecular related uses: Nonvitamin, nonmineral, natural products 18.9%, Diet-based therapies 3.5%, Megavitamin therapy 2.8%.[38] The survey did not include other popular related categories such as juicing, supplemental antioxidants, essential fatty acids, amino acids, enzymes and others.

Another recent CAM survey reported 12% of liver disease patients using the antioxidant silymarin, more than 6% used megavitamins among others, and "In all, 74% of patients reported using CAM in addition to the medications prescribed by their physician, but 26% did not inform their physician of their CAM use."[39]

Orthomolecular medicine claims an evolving nutritional pharmacology that overlaps between natural medicine and mainstream medicine. The International Society for Orthomolecular Medicine has conventionally-trained doctors among its members and authors. However, the leading orthomolecular medicine website, Orthomolecular Medicine Online,[40] run by the Journal of Orthomolecular Medicine, discusses differences between orthomolecular medicine and mainstream medicine,[35] which the website refers to as allopathic medicine.[3]

Amongst the differences, mainstream medicine attaches great importance to evidence-based medicine,[41] particularly to rigorous double-blind randomized controlled trials that test if a treatment is effective and exclude the placebo effect.[42] Orthomolecular medicine proponents, on the other hand, believe that such studies overemphasize certainty and underemphasise patient choice.[43] Mainstream medicine also avoids the use of new treatments whose effects are unknown, instead favoring extensively tested, clinically proven drugs. They point out that, even with extensive testing, up to 20% of drugs may subsequently have unrecognized, serious adverse reactions, requiring the later addition of the "black box warning", or withdrawal from market.[44] Orthomolecular medicine holds that their approach may be useful in treating new or incurable diseases, before conventional medical treatments are available.

The skepticism about orthomolecular medicine comes in part because some of its proponents make claims more broad than those supported by scientific research, particularly claims that

contradict clinical trials [2][45] and instead consider observational studies, clinical and anecdotal experience, single blinded controlled tests, and case histories. Proponents of orthomolecular medicine argue that, despite the extensive testing of pharmaceuticals, some medications are withdrawn after approval, due to serious adverse events, and the FDA regulatory methodology and relationship with the pharmaceutical industry has been criticized.[46]

The conventional view amongst mainstream medical physicians is that most orthomolecular therapies are insufficiently proven for clinical use, that the scientific foundations are weak, and that the studies that have been performed are too few and too open to disputed interpretation. Some mainstream medical practitioners dismiss orthomolecular medicine. For example, an adviser on alternative medicine to the National Institutes of Health, once stated that "Scientific research has found no benefit from orthomolecular therapy for any disease"[2] Proponents of orthomolecular medicine counter that vitamins are used in conventional medicine as treatments for a few diseases, such niacin for dyslipidemias (1955).[47][48]

Nutritional supplements, such as those used in orthomolecular medicine, are less regulated than pharmaceuticals in the United States. Furthermore, a recent meta-analysis in JAMA has suggested that supplementation with combinations of beta carotene, vitamin A, and vitamin E may increase mortality, and this risk may be particularly high in smokers.[49] An essential regulatory difference is that pharmaceuticals must be proven safe and effective to the satisfaction of the FDA before they can be marketed, whereas supplements must be proven *unsafe* before regulatory action can be taken.[50] A number of orthomolecular US supplements are available in pharmaceutical versions that are sometimes quite similar in strength and general content, or in other countries are pharmaceuticals. The US regulations also have provisions to recognize a general level of safety for established nutrients that can forgo new drug safety tests. Proponents of nutritional supplement use have argued that the lower level of regulation results in cost savings for American consumers, pointing to higher supplement prices in Europe, where some supplements are more tightly regulated or even unavailable.[51]

Supporters claim that some aspects of orthomolecular medicine, and in particular the optimal nutrition subset, have support in mainstream scientific research in a variety of areas:

- Greater than the RDA of selenium[52][53][54] may reduce the overall incidence of cancers; this effect is strongest in people who had low selenium levels before treatment.[55][56]

- Greater than the RDA of vitamin D may reduce the risk of cancer in post-menopausal women.[57] It may also increase the immune response to a wide range of viruses, fungi and bacteria. [58] [59]

- Greater than the RDA of "A, B_6, C and E plus zinc",[60] folic acid[61] and selenium[52][53][54] reduce the incidence of specific cancers

- Studies finding that supplementation of long-chain omega-3 essential fatty acids[62] reduced the incidence of cardiac mortality in secondary prevention trials[63][64][65]

- Early studies finding that vitamin E alone[66] and vitamin C & E together[66] reduce coronary disease mortality

- Studies finding that niacin[67], selenium[52], zinc[68], vitamin C[69] alone and vitamin E[66] alone and vitamin C & E together[66] reduce overall mortality rates

- Bruce Ames's studies on the effects of vitamins on genetic diseases and biochemical aging processes[70][71][72][73]

- The advocacy of daily multivitamins in cancer prevention by Bruce Ames[74][75] and by others in a JAMA review article for "chronic disease prevention in adults"[76][77]

Some of these findings have been reported as not consistent with other studies. For example, *(see Vitamin E controversy below)*, a subsequent meta-analysis failed to find benefit to single isomeric alpha tocopheryl ester forms of vitamin E supplementation.[78] Indeed, alpha tocopheryl ester supplementation might increase the risk for congestive heart failure.[79] The Shutes decades earlier did specifically caution about tocopherol dosage and slow buildup rates for CHF patients and those with pre-existing rheumatic heart problems; modern orthomolecular medicine has different specific nutrient recommendations for CHF patients.[80] Reconciling and confirming the conclusions of individual nutritional studies is a subject of ongoing research.

These studies all come from mainstream medical sources that do not claim to support orthomolecular doctrine, and in at least some cases, explicitly reject claims of orthomolecular proponents that nutritional supplements are desirable.[81] Ames supports daily USRDA multivitamin supplements as a public-policy solution to the lack of vegetables in United States diets, but has not endorsed global use of megavitamin therapy propounded by orthomolecular medicine.[74][75]

Orthomolecular proponents, such as Robert Cathcart, who predicts that 120+ grams per day intravenous vitamin C should cure SARS[82] and has used up to 250 grams IV vitamin C per day, have been criticised for not having any conventional medical trials of such intravenous vitamin C treatments.[83]

The orthomolecular field remains controversial among mainstream medical organizations, including the American Cancer Society, the American Psychiatric Association, the National Institute of Mental Health, the American Academy of Pediatrics, CHAMPUS, and the Canadian Paediatric Society. A number of individuals and organizations contest the claims, benefits, degree of evidence and toxicity.[2][84][85] Based on testing with dosages well below orthomolecular recommendations, Linus Pauling has been criticized for making overbroad claims[86] for the efficacy of vitamin C but Paulings' claims have received some support from tests closer to the orthomolecular recommendations during the last few years.[87][88]

The relationship of mainstream medicine to orthomolecular proponents has often been adversarial; orthomolecular proponents argue that mainstream medical claimants confuse orthomolecular medicine with other, less science based modalities.[35] The American Academy of Pediatrics labelled orthomolecular medicine a "cult" in 1976, in response to claims that

orthomolecular medicine could cure childhood psychoses and learning disorders.[89] Conventional health professionals see orthomolecular medicine as encouraging individuals to dose themselves with large amounts of vitamins and other nutritients without conventional supervision, which they worry might be damaging to health. Rare risks[90] of *non-orthomolecular* "mega" dosages of vitamin relatives, which frequently involved pharmaceutical analogues such as synthetic menadione, unsupervised misuse, deliberate abuse and earlier medical treatments, may include increased risk of coronary heart disease[91], hypertension, thrombophlebitis, peripheral neuropathy, ataxia, neurological effects, liver toxicity, congenital abnormalities, spontaneous abortion, gouty arthritis, jaundice, kidney stones, and diarrhea.[92] [93][94][95] Megavitamin proponents point[96] to an almost zero level of deaths caused by vitamins, even with large overdoses, compared to the significant numbers from pharmaceuticals, including a number of over-the-counter items.[97]

The accumulated evidence of randomized clinical trials with conventional, chemically-modified alpha tocopheryl esters, containing only one kind of natural vitamin E (of eight vitamers) in the stabilized (chemically inactivated) ester form[98] (usually acetate) have been controverted. Initial hopes for alpha tocopheryl esters (usually acetate) were based on suppositional grounds and epidemiological data that often involved the natural, full spectrum dietary forms of vitamin E (mixed R, R,R tocopher**ols** - alpha- beta- gamma-, delta-isomers).[99][100] Meta analysis of several randomized clinical trials of manufactured antioxidants, including alpha tocopheryl esters (acetate, succinate) not in an antioxidant form, have not shown any benefit to alpha tocopheryl ester supplementation for preventing coronary heart disease.[101] Orthomolecular recommendations for the full vitamin E complex typically include an additional 25% to 200% w/w of beta-, gamma-, and delta-tocopher*ol*s.[102] Recent scientific and medical research shows gamma-tocopherol, the most common vitamer of natural vitamin E, has unique beneficial functions and "gamma tocopherol is considered an integral component of the nutrient-based recommendations in many EU member countries."[103]

A controversial meta-analysis[104] published in 2005 claimed that "high dose" alpha tocopheryl esters (>=400 units/day) were associated with an all-cause mortality risk difference of 39 per 10,000 persons[105]. Furthermore, a significant relationship was claimed between dose and all-cause mortality, with increased risk with doses exceeding 150 I.U. per day. This meta-analysis, however, was criticized on a number of grounds.[106] One of several criticisms which the authors did not rebut was that the mortality effect was a confounder resulting entirely from excess mortality in a few studies of combined alpha-tocopheryl ester and synthetic beta carotene in heavy smokers. Known for decades,[107] that "[t]he antagonisms that exist between...carotene and vitamin E are complicated",[108] this supplement and smoking exposure combination once had some academic support[109] but synthetic "beta carotene...has previously been shown to be harmful"[110] in smokers, a subpopulation with high oxidative stress.[111] Long commercialized, multiple antioxidant megavitamin combinations, such as "ACES", that also include antioxidants vitamin C[112] and selenium[113] to recycle the first two antioxidants and aid liver peroxide detoxification, were not tested or measured.[104]

The orthomolecularly-preferred "vitamin E", mixed (natural) R, R,R tocopherols,[104] available for two-thirds of a century, remain to be authoritatively evaluated in tests controlled for bile, pancreatic function, certain specific heart problems and risk factors, blood levels and cofactors

(vitamins C, D_3, K_1, K_2, [114] selenium, co-enzyme Q10, etc.) in the common orthomolecular range, 600 - 3200 IU alpha tocopherol *plus* 25%-200% by weight of other R, R,R tocopherols. With the exception of controlling for standard comorbidities such as heart disease, controlling for pancreatic function, various vitamin cofactors, etc. has not been felt by conventional medicine to be clinically relevant nor routinely done in clinical trials. However, naturopathic medicine texts [115] and naturopathic physicians routinely recommend such laboratory tests[116] of biliary and pancreatic functions in their orthomolecular-related modalities.

Conventional physicians express concern that megavitamin and orthomolecular therapies used solely as alternative treatments by other practitioners, if not successful, may create dangerous delays in obtaining conventional treatments, such as radiation and chemotherapy for cancer. For example, in a highly publicized Canadian case, the chemotherapy and orthomolecular treatments of a 13-year-old cancer patient, Tyrell Dueck, were delayed, possibly fatally, due to his parents' religious beliefs, interest in alternative treatments, and lengthy legal battles. [117] Orthomolecular medical practitioners and orthomolecular oriented naturopaths have long expressed similar concerns about conventional medicine, particularly with gut related and chronic diseases as well as viral diseases.[118][119][120][121]: The use of conventional medical treatments, if not successful, may create dangerous delays in people obtaining orthomolecular treatments.[*citation needed*] It is usually possible, however, to combine orthomolecular and conventional treatments.

Several orthomolecular related AIDS approaches such as multivitamins[122], selenium and amino acids[123] are used with reported improvements in patients. High dose vitamin C treatments have long been used clinically by some orthomolecular practitioners to treat AIDS patients[124]; a minor 1994 *in vitro* laboratory study raised questions that sustained megadoses of vitamin C might inhibit some immune cells.[125] In these situations, mainstream medical criticism arises when orthomolecular approaches are advocated as *substitutes for*, rather than complements to, current medical treatments.

Some orthomolecular proponents claim partisan politics, pharmaceutical industry influence, and competitive considerations to be significant factors. Some prominent orthomolecular proponents sell lines of orthomolecular products and accept some tests questioned about their benefit that vary by medical affiliation.[*citation needed*] The Linus Pauling Institute's funding comes mostly from National Institutes of Health[126]. Several orthomolecular therapies have been officially sanctioned within Europe[127] and Japan[128] [129][130].

The Journal of Orthomolecular Medicine, founded in 1967 as the Journal of Schizophrenia, is the main publication of those involved in Orthomolecular Medicine. Abram Hoffer has written that "*We had to create our own journals because it was impossible to obtain entry into the official journals of psychiatry and medicine. Before 1967 I had not found it difficult to publish reports in these journals, and by then I had about 150 articles and several books in the establishment press.*"[131]

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- Health freedom movement
- Life extension
- List of life extension related topics
- Metabolomics
- Megavitamin therapy
- Orthomolecular psychiatry

Vitamin C Slows Cancer Down
And, Doctors Say, Can Reverse It as Well

(OMNS, October 31, 2008) The BBC recently reported (1) that "Vitamin C 'slows cancer growth.' An injection of a high dose of vitamin C may be able to hold back the advance of cancers, US scientists claim. The vitamin may start a destructive chain reaction within the cancer cell." The injection "halved the size" of tumors, and was reported in the Proceedings of the National Academy of Sciences.

The study authors themselves said that daily, high-dose vitamin C treatment "significantly decreased growth rates" of ovarian, pancreatic, and malignant brain tumors in mice. Such high, cancer-stopping levels of vitamin C can be "readily achieved in humans given ascorbate intravenously." (2)

"Readily achieved"? Then this is important, absolutely vital news for millions fighting or fearing cancer.

So what do major cancer organizations have to say? Not much. That is disappointing, but hardly surprising. Both the American Cancer Society and Cancer Research UK have

downplayed or flatly ignored decades of physician reports and controlled clinical studies indicating that vitamin C stops cancer. What's worse, each of these supposedly comprehensive cancer research and education organizations continues to actively discourage people from using vitamin C against cancer.

Look for yourself and see. The American Cancer Society's vitamin C webpage (3) specifically states: "Although high does of vitamin C have been suggested as a cancer treatment, the available evidence from clinical trials has not shown any benefit." And Cancer Research UK states that "There is currently no evidence from clinical trials in humans that injecting or consuming vitamin C is an effective way to treat cancer." (1)

"No benefit," they say. "No evidence," they say.

Both organizations are wrong. Neither statement is true.

In 2008, Korean doctors reported that intravenous vitamin C "plays a crucial role in the suppression of proliferation of several types of cancer," notably melanoma. (4)

In 2006, Canadian doctors reported on the effectiveness of intravenous vitamin C in treating cancer. (5)

In 2004, doctors in America and Puerto Rico published clinical cases of vitamin C successes against cancer. (6)

In 1990, American doctors published their results successfully using vitamin C to treat kidney cancer (7). In 1995 and 1996, other cancers. (8) Using 30,000 mg of intravenous vitamin C twice per week, they found that "metastatic lesions in the lung and liver of a man with a primary renal cell carcinoma disappeared in a matter of weeks. . . We subsequently reported a case of resolution of bone metastases in a patient with primary breast cancer [1A] using infusions of 100 grams, once or twice per week." (9)

In 1982, Japanese doctors showed that vitamin C greatly prolonged the lives of terminal cancer patients. (10)

And as early as 1976, over two decades ago, physicians in Scotland showed that intravenous vitamin C improved quality and length of life in terminal cancer patients. (11)

Why are ACS and Cancer Research UK oblivious to the weight of evidence? All these previous clinical reports were published in peer-reviewed medical journals. One may bear in mind that both ACS and Cancer UK made their restrictive statements August 2008. Yes, 2008. In spite of increasingly compelling evidence for 22 years, both the American Cancer Society and Cancer Research UK are dragging their feet. Foot-dragging costs lives. Hundreds of thousands of people have died from cancer that could have been helped with ascorbate therapy. But for decades, their three advocated cancer treatments have been "cut, zap, and drug": surgery, radiation and chemotherapy. The use of high doses of vitamins has been thoroughly excluded.

Indeed, ACS still says: "If a supplement is taken, the best choice for most people is a balanced multivitamin/mineral supplement that contains no more than 100% of the 'Daily Value' of most nutrients." (3) That is harmful advice. Many well designed clinical studies show that large doses of vitamin C and other nutrients improve both quality and length of life for cancer patients. The key is the use of sufficiently high quantities, appropriately administered. More orange juice just won't do it.

Cancer Research UK even maintains (1) that vitamin C "can make cancer treatment less effective, reducing the benefits of radiotherapy and chemotherapy." That statement is untrue. (12,13) Oncologists routinely administer antioxidant drugs along with chemotherapy with no diminution of effect. (14)

ACS and Cancer Research UK say that there is "no evidence from clinical trials" that vitamin C is any good against cancer. They should start reading the medical literature. They are way behind the times. And they are wrong. Dead wrong

Vitamin C confirmed to kill cancer cells

Vitamin C is a powerful antioxidant effective against cancer. Cancer cells metabolize anaerobically (without oxygen) and so produce no antioxidant enzymes. This makes them unable to metabolize the antioxidant activities of vitamin C thus suffocating their means of energy production.
High dose IV vitamin C selectively targets cancer cells while providing healthy cells protection against oxidative stress.
Vitamin C also increases intracellular production of hydrogen peroxide which selectively destroys cancer cells due to their relative deficiency of the enzyme catalase. Catalase metabolizes Hydrogen peroxide into water and free oxygen in healthy cells but is absent in cancer cells.

1) Tumor cells are more susceptible to the effects of high-dose, ascorbate-induced peroxidation products because of a relative catalase deficiency.

2) Concentrations of ascorbate high enough to kill tumor cells likely can be achieved in humans.

Researchers found that diets high in vitamin C significantly reduce the risk of mouth, throat, stomach, and pancreas cancers. They have also been found to reduce breast, cervix, and rectum cancers. Research shows that a combination of both vitamin C and beta-carotene are important factors in reducing your risk for cancer. It is best to eat foods high in Vitamin C whenever possible, and only take supplements when in need or due to travel.

Foods rich in Vitamin C are:

- Broccoli
- Brussels Sprouts
- Cabbage

- Cantaloupe
- Cauliflower
- Greens (collard, mustard, or turnip)
- Kale
- Kiwi
- Mango
- Papaya
- Peppers, sweet green or red
- Potato, white or sweet
- Strawberries
- Tomato's and Tomato Juice

High Dose Intravenous Vitamin C and Long Time Survival of a Patient With Cancer of Head of the Pancreas

Share

(Excerpted from *Journal of Orthomolecular Medicine*)

A 68-year old white male was a self-referral to the Center in December 1993. Two months previously, he was seen at another medical facility for painless jaundice (bilirubin was 14 mg/dL), "black urine," pain in the stomach and a rapid weight loss of 21 pounds. A CT scan and abdominalangiogram suggested a blocked bile duct and a pancreatic mass. An operation was performed and because of it's location, all of the tumor could not be removed. An area of the tumor (4 cm x 2 cm x 4 cm) was removed. The gallbladder, head of the pancreas, distal stomach, and duodenum were also removed and a complete "Whipple" procedure performed. The pathology report showed a grade I adenocarcinoma of the pancreas with metastasis to 1 of 7 regional lymph nodes (T3, N1, Mo). A month after the operation the patient developed hyperglycemia. He was placed on the ADA diet with blood glucose monitoring twice a day. After a short period, the blood glucose returned to, and remained, normal. Three months prior to the Whipple procedure, he had a transurethral resection for an enlarged prostate which proved to be benign.

After discussing treatment options with an Oncologist, the patient decided not to take conventional chemotherapy and radiation. At the Center, a complete physical, psychological and biochemical examination was done on the patient. He was an alert, pleasant, 68-year old male who weighed 140 pounds and was 70 inches tall. Significant laboratory data included blood DHEA 39.7 ng/dL(normal, 200 to 335), beta carotene 2.4 ug/dL (normal 10 to 85), and vitamins A, C and E in the non-supplementing normal range. Urine vitamin C was 10 mg/dL (our normal is 20 to 40), and the RBC essential fatty acid profile showed low gamma linolenic, palmitoleic fatty acids and a low stearic/oleicratio. His fructosamine was 313 umol/L (175 to 272 normal) and blood glucose 326 mg/dL. Hair tissue analysis showed calcium, magnesium and sodium to be low.

A blood analysis for G6PD, a BUN, creatinine and urinalysis was done before I.V. vitamin C was started. All were normal. Appropriate supplements were started for those identified as low or sub-optimal by the laboratory results.

The patient initially received a small dose of vitamin C in Ringer's Lactate during a one hour infusion to screen for toxic reactions. The next infusion of 115 g was given in 1000 mL of Ringer's Lactate over a 8 h period. One hour into the infusion, the plasma C level was 3.7 mg/dL and at 5 h was 19 mg/dL. During the fourth 8-h infusion (8 days later), the 1 h plasma C level was 158 mg/dL and 5 h was 185 mg/dL. Both values are well above the concentration required to kill 100% of human pancreatic tumor cells as found in our research laboratory. 1 The low plasma levels of C in this patient during the first infusion compared to the fourth infusion, shows the value of measuring the plasma level to see that adequate levels are achieved during therapy. The patient received 39 of the 8-h infusions in doses ranging from 57.5 to 115 g over a 13-week period, the length of the treatment protocol with high dose I.V. vitamin C.

A CT scan of the abdomen six months after the surgery failed to detect any progression of the tumor. A recurrence of the tumor occurred after the amount and frequency of I. V. vitamin C was significantly reduced so the patient could travel in his motor-home (family reunions, etc). The patient lived for 12 months after the initial diagnosis of cancer of the head of the pancreas. He received no chemotherapy or radiation treatment and enjoyed a good quality of life until the time of his death.

Altogether, six patients have been infused intravenously with similar doses of vitamin C over 8-h periods with no reported side- effects. In all cases, the patients had either been given no further therapeutic options by their oncologists, had refused conventional treatment or requested I.V. vitamin C in conjunction with standard chemotherapy.

Clinical Trial of Pancreatic Enzymes: One View

Tag it:

?

Saturday, 12 September 2009

I am leaving shortly for another tour of German and Swiss complementary cancer clinics. I hope to report on my findings when I get home in a few weeks. In the meantime, I wanted to share with you an excellent blog from H. Kenneth Schueler. Ken discusses an important article on a trial of pancreatic enzymes that was recently published in the *Journal of Clinical Oncology*.

"Why we need Integrative Cancer Care: A Necessary Remedy to the "them" against "us" schism between CAM (Complementary & Alternative Medicine) and Conventional Oncology"

by H. Kenneth Schueler (reprinted with permission).

OK, it's August 17th and I'm reading my latest issue of the *Journal of Clinical Oncology*, and there it is, an article I never expected to see published: "Pancreatic Proteolytic Enzyme Therapy Compared With Gemcitabine-Based Chemotherapy for the Treatment of Pancreatic Cancer."

My friend Ralph Moss, PhD, one of the keenest observers of alternative cancer treatments, has previously described the unfortunate political acrimony which haunted this clinical trial. See Dr. Moss's very insightful Newsletter of June 21,2008, "A Great Opportunity Lost" at:

http://www.cancerdecisions.com/content/view/122/2/lang,english/

This Phase III trial was to be the showcase study for Dr. Nicholas Gonzalez's regimen for pancreatic cancer which included "proteolytic (digestive) enzymes, nutritional supplements, detoxification (coffee enemas), organic diet (70% raw or minimally cooked); skin brushing and cleansing; salt and soda baths, liver flush, clean sweep, etc." 32 patients chose Dr. Gonzalez's Enzyme regimen and were managed by him; 23 patients chose conventional chemotherapy and most of them were managed at Columbia University-19 of those 23 received Gemcitabine(Gemzar), Capecitabine (Xeloda) and Docetaxel (Taxotere).

Pancreatic cancer is considered one of the most lethal cancers with a survival of 4-6 months for metastatic disease and an overall 5-year survival < 4 percent. The results of the above trial were as follows: "Those who chose gemcitabine-based chemotherapy survived more than three times as long (14.0 months) vs 4.3 months median survival for those on the enzyme protocol. The chemo patients also had a better quality of life than those who chose proteolytic enzyme treatment."

The above trial results were not a surprise to me. It is almost impossible to put the brakes on an extremely aggressive metastatic cancer without employing chemotherapy to disrupt tumor cell division by targeting DNA within the nucleus. Molecularly targeted therapies can be invaluable in simultaneously inhibiting cell cycle signaling from growth factors (e.g. VEGF, EGFR, PDGFR,etc.), proteins, genes, signal transduction molecules, oncogene products ,etc. Examples of some targeted therapies include: Tarceva, Erbitux, Avastin, Sutent, Sorafenib, Vatalanib, etc. Surprisingly, Tarceva (inhibits EGFR) was recently approved (in combination with Gemzar) for pancreatic cancer even though it only extended survival by two weeks: median survival 6.24 months v 5.91 months. (*J Clin Oncol*. 2007 May 20;25:1960-

1966.)

It could be noted that the chemo patients were receiving hospital-based supportive care at Columbia (e.g., pain medication, noninvasive biliary stents, etc.) so their quality of life reports may have been superior to the enzyme patients treated at Dr. Gonzalez's office. But much more likely, it was the Gemcitabine which improved the symptoms in the Columbia Group. Several compelling studies have demonstrated that even though Gemcitabine did not produce objective responses (radiographically confirmed reductions in tumor size), there was a measureable "clinical benefit" defined as an improvement in pain, performance status or weight without a deterioration in any other factor-although the objective response rate for patients with measurable disease was only 11 percent, a clinical benefit was observed in 27 percent. ["A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer." *(Ann Oncol.* 1996;7:347-353.) "Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial." *(J Clin Oncol.* 1997;15:2403-2413.)

SO WHAT'S IMPORTANT ABOUT THIS COLUMBIA STUDY? It's this conclusion by the Columbia authors: "This report may be among the first controlled, clinical studies to compare allopathic treatment to an alternative medicine program for a survival end point." They go on to reference another study in which vitamin E and beta carotene are cited as having no effect in reducing the incidence of lung cancer among male smokers, and raise the possibility they may actually have harmful as well as beneficial effects (*N Engl J Med.* 1994;330:1029-1035). Bottom line message: Standard of Care conventional oncology trumps CAM! Not only was the trial poorly constructed and executed, but the above Conclusion demonstrates the same "Us Against Them" attitude which has so fragmented not just oncology but all of healthcare.

Several of my physician friends have told me two lessons they learned during medical school: never say anything publicly that is so far outside the box you could be labeled a "quack". Secondly, you will rarely get a research grant for a non-patentable drug-pharmaceutical companies have no interest in testing any drug they can't obtain exclusive rights to. So basically, that would have eliminated Ignaz Simmelweis's radical idea in 1847 of washing hands with chlorinated lime solutions before obstetrical deliveries to reduce the 10-35% infant mortality caused by Puerperal fever. It also would have prevented the bold discovery by Dr Barry J. Marshall and Dr J. Robin Warren of Australia of H. Pylori bacteria as the cause for duodenal and gastric ulcers and stomach cancer, and it's eventual treatment with antibiotics. When Marshall and Warren first presented their research 25 years ago, they were ridiculed by colleagues. But they were proven correct and in 2005 they jointly received the Nobel Prize.

Conventional Oncologists have regrettably dismissed many valuable alternative

therapies as either confounding influences in their clinical trials of monotherapies or doublets[often funded by pharmaceutical companies], or as interfering with treatment [they lump together all botanicals, when only a few may have contraindications due to anti-oxidative effects with radiation or chemo, or competing for Cytochrome P-450 liver enzymes, or increasing coagulation times).

There is a growing consensus amongst Integrative Oncologists that for patients with metastatic cancer, the most effective approach to substantially increase survival is a cocktail regimen incorporating a group of therapeutic agents which simultaneously and synergistically target multiple tumor cell mechanisms.

Chemotherapy Doesn't Work, So Blame Vitamin C

(OMNS, October 7, 2008) When Memorial Sloan-Kettering Cancer Center announces that vitamin C may interfere with chemotherapy, the news media trumpet it far and wide. But before cancer patients throw away their vitamin C supplements, they need to know rest of the story.

Most of the media dutifully reported the researchers' claim that the equivalent of 2,000 mg of vitamin C "blunted the effectiveness of the chemotherapy drugs." But only some of the media included a study author's incredible statement that "If you take an oral dose even as low as 100 milligrams a day" even "that could be harmful" during chemotherapy (1)

100 mg "could be harmful"? That's the amount of vitamin C in a few glasses of orange juice. Something is very wrong here.

First of all, this research involved mice with implanted cancerous tumors; it was not a trial on cancer patients. A mouse study is a long way from a human clinical trial. This obvious difference was conceded by the study authors. However, there is a more subtle, and probably much more important factor they did not consider: all mice make their own vitamin C. Indeed, mice make quite a lot. Adjusted for body weight, mice synthesize the human body weight equivalent of approximately 10,000 milligrams of vitamin C each day. (2) Incredibly, sick mice make even more. Mice given transplanted tumors become sick mice.

Secondly, previous research has demonstrated that mice with cancer respond well to high-dose vitamin C therapy. One study found, "With an increase in the amount of ascorbic acid there is a highly significant decrease in the first-order rate constant for appearance of the first spontaneous mammary tumor. . . Striking differences were observed between the 0.076% ascorbic acid and the control groups, which synthesize the vitamin." (3) Another study concluded that: "A pronounced effect of vitamin C in decreasing the incidence and delaying the onset of malignant lesions was observed with high statistical significance. By 20 weeks, approximately five times as many mice had developed serious lesions in the zero-ascorbate as in the high-ascorbate group." (4) Interestingly enough, when this research was first publicized,

the media discounted these findings saying that mouse studies were not particularly applicable to people.

Thirdly, a mouse's ability to make vitamin C, and a great deal of it, is an overlooked confounding factor that may well render the entire experiment invalid. If the Sloan-Kettering team had tried their experiment on Guinea pigs, their results might have been very different. Guinea pigs are more like human beings in that they cannot make their own vitamin C. As controls for comparison, the researchers also treated "no-added-vitamin C" mouse cancers with chemotherapy. Chemo worked just fine on those mice, by the researchers own admission. And each of those mice was internally synthesizing a body weight equivalent of 10,000 mg/day of vitamin C, even though given none supplementally.

So how come 10,000 mg of vitamin C does not interfere with chemo treatment, and 2,000 mg - or even 100 mg - supposedly does?

A sweeping recommendation warning cancer patients to not take supplemental vitamin C, not even 100 mg, is irresponsible. It is impossible to justify caution about taking 100 mg of vitamin C daily when your animal subjects made the equivalent of one hundred times that amount, and chemotherapy in them was still reported as effective. You cannot have it both ways. If a synthesized 10,000 mg of C does not interfere, there can be no real "interference" or "blunting" from a supplemental 2,000 mg. And most certainly not from 100 mg.

The study did report tumor shrinkage, in both groups of mice receiving chemo. That is not surprising. Chemotherapy's claimed success is based on tumor shrinkage. But tumor shrinkage, encouraging though it is, is not a reliable indicator of long-term cancer survival. As cancer research critic Philip Day puts it, many patients are "cured but dead" after five years, hardly a long-term survival. Day, noting that this is not because oncologists are not trying, explains the chemotherapy quandary: "You can be insincere, or you can be sincerely wrong." (5)

The Sloan-Kettering study team seems to have missed the essential point that vitamin C is not just an antioxidant. Inside cancer tumors, it also acts as a prooxidant, killing malignant cells. Comments Dr. Steve Hickey, of Manchester, UK: "Essentially, the paper seems to be rather misguided and shows a lack of understanding of the dual nature of vitamin C in tumors. Chemotherapy has been shown by over 40 years of clinical trials not to work in the majority of tumors, and its use is counterproductive."

Chemotherapy drugs have come and gone; the five year survival rate for cancer treated with chemo has remained virtually unchanged for decades. Unfortunately, just over 2% of all cancers respond to chemotherapy. Specifically, one scientific review concluded, "The overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1% in the USA . . . chemotherapy only makes a minor contribution to cancer survival. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required." (6)

Perhaps this new, very well-publicized study results from an ever-growing realization that chemotherapy is largely ineffective, and the search is on for the reason why. Vitamin C should not be made the scapegoat.

Vitamin C, in doses well over 100 mg/day, is known to help prevent cancer. (7) Nearly 30 years ago, a review concluded that "Many factors involved in host resistance to neoplasia are significantly dependent upon the availability of ascorbate." (8) Beginning in the 1970s, many well-designed studies show that very large doses of vitamin C improve both quality and length of life for cancer patients since they invariably are "significantly depleted of ascorbic acid." When given intravenous vitamin C, "The mean survival time is more than 4.2 times as great for the ascorbate subjects . . . This simple and safe form of medication is of definite value in the treatment of patients with advanced cancer." (9) Additional clinical trials have confirmed this over the past several decades. (10)

Even more importantly, recent research indicates that in high doses, vitamin C is selectively toxic to cancer cells. That means vitamin C can function very much like chemotherapy is supposed to, but without the severe side effects of chemotherapy. "A regimen of daily pharmacologic ascorbate treatment significantly decreased growth rates of ovarian, pancreatic, and glioblastoma tumors established in mice. Similar pharmacologic concentrations were readily achieved in humans given ascorbate intravenously." (11)

"Cautioning" the public to avoid taking any supplemental amount of vitamin C will decrease host resistance to cancer, increase the incidence of this dreaded disease, and shorten survival times. A cynic might say it will also create a larger market for chemotherapy.

Is vitamin C a commercial competitor for chemo? To answer this, one needs to consider what appears to be serious conflict of interest at Sloan-Kettering. Bristol-Myers-Squibb makes chemotherapeutic drugs. According to a DEF 14A SEC filing of March 22, 2006, the Chairman of the Board of Bristol-Myers-Squibb is also a director of the Coca-Cola Company, and Honorary Chairman of Memorial Sloan-Kettering Cancer Center. (http://sec.edgar-online.com/2006/03/22/0001193125-06-060566/Section8.asp). A previous Bristol-Myers-Squibb Chairman of the Board was a director of the New York Times Company. He was also Vice Chairman of the Board of Overseers and the Board of Managers of Memorial Sloan-Kettering Cancer Center and Chairman of the Board of Managers of Sloan-Kettering Institute for Cancer Research. (http://www.secinfo.com/dsvrt.bC7.htm) Some sources say that there are even more Bristol-Myers-Squibb directors who have or held positions on the board at Memorial Sloan-Kettering Cancer Center. (12)

Positive endorsements for vitamin C as a cancer fighter are not in the interests of any pharmaceutical company. Scaring the public away from vitamin C might be profitable. It appears that Sloan-Kettering is biased. So are media reports that attack vitamins.

If the Sloan-Kettering study authors' recommendations to not take 2,000 mg, or even 100 mg, of vitamin C are followed, there will definitely be an increase in the number of people that need chemotherapy.

Ascorbic Acid in the Prevention and Treatment of Cancer

Categories
Health through Nutrition

Here is more background to the post: "VITAMIN C AND CANCER: NEW DEVELOPMENTS" and other uses of vitamin C. Reading these one can see how the medical Mafia has kiboshed THE most potential non toxic, immune enhancing treatments. With so much information in the literature, I wish people should start do demand the use of nutrient therapies under the treat of malpractice and or negligence. Reasoning with these self serving professionals is simply not going to cut it...

..."since it appears to improve quality of life and extend survival time, it should be considered as part of a treatment protocol for all patients with cancer, whether they have chosen a primarily orthodox, alternative medical, or complementary approach."

HEAVEN FORBID WE JUST CAN'T ALLOW THAT, THEY SHRIEK, just in case it actually cures the cancer!

To late, as this is precisely how Dr. Hoffer ended up curing cancer in his patients

Also see:

Conquering Cancer Through Vitamin C & Other Antioxidants

Cancer & Vitamin C for more details.

The Negative Impact of Sugar on Vitamin C

Chris Gupta

Ascorbic Acid in the Prevention and Treatment of Cancer

by Kathleen A. Head, N.D.

Abstract

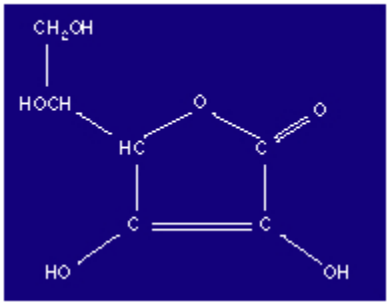
Proposed mechanisms of action for ascorbic acid (ascorbate, vitamin C) in the prevention and treatment of cancer include enhancement of the immune system, stimulation of collagen formation necessary for "walling off" tumors, inhibition of hyaluronidase which keeps the ground substance around the tumor intact and prevents metastasis, prevention of oncogenic viruses, correction of an ascorbate deficiency often seen in cancer patients, expedition of wound healing after cancer surgery, enhancement of the effect of certain chemotherapy drugs, reduction of the toxicity of other chemotherapeutic agents such as Adriamycin, prevention of free radical damage, and neutralization of carcinogenic substances. Scottish as well as Japanese studies have pointed to the potential benefit of high dose vitamin C for the treatment of "terminal" cancer. Mayo Clinic studies, however, have contradicted the Scottish and Japanese

findings, resulting in accusations of methodological flaws from both sides. Numerous epidemiological studies have pointed to the importance of dietary and supplemental ascorbate in the prevention of various types of cancer including bladder, breast, cervical, colorectal, esophageal, lung, pancreatic, prostate, salivary gland, stomach, leukemia, and non-Hodgkin's lymphoma. (Altern Med Rev 1998;3(3):174-186)

Introduction

In the mid-18th century, James Lind first demonstrated that the juice of fresh citrus cures scurvy. The active agent, the enolic form of 3-keto-L-gulofurnlactone, or ascorbic acid, was isolated in the late 1920s by Albert Szent-Gyorgyi.

Figure 1. Structure of Ascorbic Acid.



By the mid-1930s, methods had been devised to synthesize ascorbic acid, making it widely available at low cost. In the 1990s, it is the most commonly used single supplement in the U.S.1

In 1954, W.J. McCormick, a Canadian physician, formulated the hypothesis that cancer is a collagen disease, secondary to a vitamin C deficiency.2 While alternative cancer treatments, such as The Gerson therapy, have been incorporating diets high in vitamin C for many years, the use of vitamin C supplementation in large doses for the prevention and treatment of cancer was further advanced in 1971 by Linus Pauling, PhD, and Ewan Cameron, MD. A discussion of their use of high-dose vitamin C for treatment of patients with advanced cancer can be found below. Since 1971, considerable attention has been paid to vitamin C and cancer, particularly in the area of prevention. However, there has been a paucity of human studies using vitamin C to treat already existing cancer.

Biochemistry of Ascorbic Acid

Ascorbic acid is widely distributed in plants, its concentration varying from 0.01 percent in apples to about 1 percent in rose hips and citrus. It is one of the most important reducing agents occurring in living tissue. While most animals synthesize their own vitamin C, humans and a few other animals, such as non-human primates, guinea pigs, and fruit bats do not. Ascorbate accelerates hydroxylation reactions, in part by donating electrons to metal ion cofactors of hydroxylase enzymes. Hydroxylation reactions are important in collagen synthesis, conversion of lysine to carnitine, conversion of dopamine to norepinephrine, and in tyrosine metabolism.

Ascorbate is also utilized to catalyze other enzymatic reactions, such as amidation necessary for maximum activity of the hormones oxytocin, vasopressin, cholecystokinin, and alpha-melanotropin.3

Ascorbic acid is a water-soluble, chain-breaking antioxidant which reacts directly with singlet oxygen, hydroxyl, and superoxide radicals. It also may react with tocopheroxy radicals to regenerate vitamin E.1 Conversely, ascorbyl radicals are quenched by vitamin E.

Mechanisms of Action

Proposed mechanisms of vitamin C activity in the prevention and treatment of cancer include: (1) enhancement of the immune system by increased lymphocyte production; (2) stimulation of collagen formation, necessary for "walling off" tumors; (3) inhibition of hyaluronidase, keeping the ground substance around the tumor intact and preventing metastasis;4 (4) inhibition of oncogenic viruses; (5) correction of an ascorbate deficiency, often seen in cancer patients; (6) expedition of wound healing after cancer surgery;5 (7) enhancement of the effect of certain chemotherapy drugs, such as tamoxifen, cisplatin, DTIC and others;6-8 (8) reduction of the toxicity of other chemotherapeutic agents, such as Adriamycin;9 (9) prevention of cellular free radical damage;10 and (10) neutralization of carcinogenic substances.11

Taking a closer look at the phenomenon of hyaluronidase inhibition Cameron, Pauling and Leibovitz wrote in "Ascorbic Acid and Cancer: A Review": ..."the dangerous features of neoplastic cell behavior (invasiveness, selective nutrition, and perhaps growth) are caused by microenvironmental depolymerization. In turn, this matrix destabilization is brought about by constant exposure to lysosomal glycosidases continually released by the neoplastic cells. Finally, ascorbate is involved in the natural restraint of this degradative enzyme activity."12

Proper collagen formation is an important factor in the encapsulation of tumors or the slowing of metastasis via the development of an almost impermeable barrier (known as the schirrus response). Ascorbic acid plays an important role in collagen synthesis and stability. A lack of ascorbate significantly reduces hydroxylation of proline and lysine to hydroxyproline and hydroxylysine, respectively, jeopardizing proper collagen cross-linking. This leads to instability of the triple helix of collagen which, in turn, results in increased collagen catabolism. In vitro, vitamin C also has been found to increase collagen synthesis by fibroblasts.12

Cancer patients tend to be immuno-compromised, demonstrating low lymphocyte ascorbate levels. The immune surveillance system is important, both in inhibiting the initiation phase of cancerous growth, and also in the prevention of spread. Ascorbate supplementation increases the number and effectiveness of lymphocytes and enhances phagocytosis.12

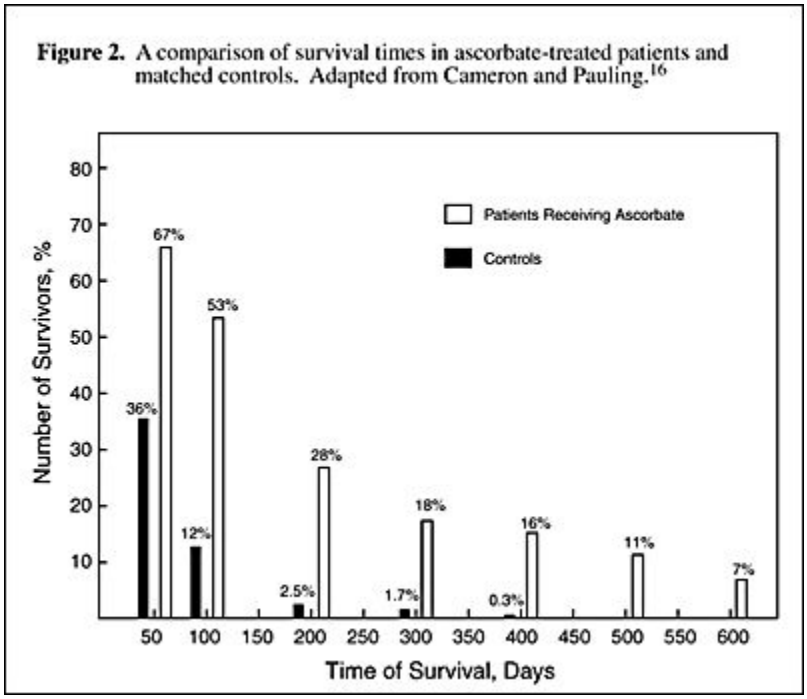
Vitamin C in the Treatment of Cancer

The Vale of Leven Studies: Most of the studies on vitamin C and cancer relate to its protective effect, rather than use of the vitamin for the treatment of active cancer. The Vale of Leven

studies conducted by Ewan Cameron, MD and his associates, (later including Linus Pauling, PhD), at his hospital in Loch Lomondside, Scotland, are among the few exceptions. In preliminary studies which began in November 1971, a small group of patients with advanced cancer were given 10 grams of sodium ascorbate daily. The initial testing was an uncontrolled study, conducted on 50 patients. Seventeen of these patients exhibited seemingly no response, 10 a minimal response, 11 retardation of the tumor growth, 3 ceasing of the tumor growth, 5 regression of tumor growth with long-term survival, and 6 experienced hemorrhage and necrosis of the tumors, which destroyed the tumors but killed the patients in the process.13 An evaluation of the life expectancy of these first 50 "terminally ill" patients treated with ascorbate yielded promising results. Based on data from previous similar groups of patients, it was expected that 90 percent of the group would be dead within three months of being labeled "terminal." When 10 g ascorbate was prescribed daily (beginning at the time the patient was labeled "terminal"), by the 100th day of treatment the mortality rate was only 50 percent. Of the remaining 25 patients, 20 died between days 110 and 659, with an average survival time of 261 days; and five had an average survival time of greater than 610 days.14

Subsequently, a controlled retrospective study was conducted, comparing survival times of 100 terminally ill cancer patients at Vale of Leven Hospital with 1,000 matched controls from the same hospital. The patients were randomly selected from the database of those terminal cancer patients who had received ascorbate. Each ascorbate-treated patient was matched with 10 controls from the same hospital of the same age, sex, and type and stage of cancer who had not been prescribed vitamin C. In 90 percent of the cases, the ascorbate-treated group lived three times longer than the control group. For the other 10 percent, long-term survival made it impossible to assess survival time with certainty, but at the time of publication of the study, the ascorbate group exhibited greater than 20 times the survival rate of the control group.15

Figure 2. A comparison of survival times in ascorbate-treated patients and matched controls. Adapted from Cameron and Pauling.[16]



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Having been criticized by some investigators for not assuring the subjects were randomly chosen from the same representative subpopulations in the treated and control groups, a second retrospective evaluation at the Vale of Leven hospital was undertaken in 1978 again with 100 patients receiving ascorbic acid compared to 1,000 matched controls without vitamin C.17 Most of the ascorbate-treated group and about half the controls were the same subjects as in the initial study. This time, since there are different mean survival times for different types of cancer, the groups were further divided according to types of cancer, and controls carefully matched (see Table 1). In addition, the groups passed several "randomness" tests. In each of the nine types of cancer the ascorbate group had a considerably longer survival time than their matched controls. At the time of evaluation, eight patients in the vitamin C group were still living, while no one was alive in the control group; this resulted in 321+ days longer lifespan for the vitamin C treated group. Factoring out those in the ascorbate group who were still living at the time of evaluation, the vitamin C group lived an average of 251 days longer than the control group.

Cameron and Pauling later evaluated the first 500 "terminal" cancer patients to receive ascorbate. In most cases, subjective improvement increased feeling of well-being, more energy, more alertness, decrease or elimination of pain, better appetite were noted by the ascorbate patients. Cameron reported a quite dramatic relief of bone pain from metastases in four out of five patients. Objective improvements included a decrease in malignant ascites and pleural effusion, relief from hematuria, some reversal of hepatomegaly and jaundice, and decreases in erythrocyte SED rate and serum seromucoid levels, all accepted indicators of a decrease in malignant activity.14 Furthermore, patients who had been on large doses of narcotics, such as morphine, for pain relief, showed none of the typical withdrawal symptoms.

Based on the above cited studies the researchers concluded: "**It is our conclusion that this simple and safe treatment, the ingestion of large amounts of vitamin C, is of definite value in the treatment of patients with advanced cancer. Although the evidence is as yet not so strong, we believe that vitamin C has even greater value for the treatment of cancer patients with the disease in earlier stages and also for the *prevention of cancer*."18**

The Vale of Leven protocol called for a ten-day course via intravenous (IV), continuous slow-drip infusion of sodium ascorbate in half-strength Ringer's Lactate Solution. After the IV treatment, assuming the patient was able to take medication by mouth, an oral dose of vitamin C was begun at a dose of 2.5 grams every 6 hours for a total of 10 grams in 24 hours. The dosage varied somewhat, ranging from 10-30 grams daily, and was continued indefinitely. The goal was to maintain plasma ascorbate levels of at least 3 mg/dl. The researchers reported generally a subjective improvement in well-being, vigor, pain relief, and appetite was apparent within 5-7 days. Increased energy was believed to be a result of improved carnitine synthesis with a resulting increase in triglyceride transport into cell mitochondria.19

Japanese Studies: Uncontrolled trials conducted at two different hospitals in Japan during the 1970s also confirmed the increase in survival time of terminal cancer patients supplemented with ascorbate. At the Fukuoka Torikai Hospital, the average survival time after being labeled "terminal" was 43 days for 44 patients supplemented with low levels of ascorbate (less than 4 grams daily), and 246 days for 55 patients supplemented with higher dosages of ascorbate

(greater than 5 grams daily - averaging 29 grams daily) and starting at the time of "terminal" diagnosis.20 The researchers found no differences in survival times between the groups receiving 5-9 grams daily and those receiving 10-29 grams daily. A decline in effect was noted in those receiving 30-60 grams daily. They found the best results with uterine cancer, and the smallest increases in survival time with lung and stomach cancer.

Effectiveness of ascorbate was also observed at the Kamioka Kozan Hospital where 19 terminally-ill **control patients survived an average of 48 days compared to six patients on high levels of vitamin C who lived an average of 115 days, or 2.4 times longer than the control group.21 These researchers also reported the improved quality of life observed in the Scottish studies.**

Mayo Clinic Studies: In an attempt to either duplicate or refute the Cameron and Pauling results, the Mayo Clinic initiated a test on 150 patients.22 Subjects were randomly divided into two groups, one group of 60 received 10 grams of ascorbic acid daily in four divided doses while the control group of 63 received an equal number of placebo capsules. After randomization, 27 patients elected not to participate and comprised a third "no treatment" group. Treatment was continued until death or until the patient was no longer able to take medication orally. The two groups were evenly balanced with regard to age, sex, tumor site, initial performance status, and previous treatment. Fifty-eight percent of those receiving placebo and 63 percent of those receiving ascorbate reported subjective improvement in symptoms during the treatment period. The researchers reported no significant difference between the vitamin C and placebo groups in regard to survival time; however, the 27 patients who received no treatment experienced a significantly lower survival time, living an average of 25 days compared to an average of 51 days for the vitamin C or placebo groups. All but nine of the 123 subjects had received prior chemotherapy, radiation, or both.

Based on other researchers' complaints that the Mayo study had not addressed the effect of vitamin C on cancer patients who had not received prior chemotherapy or radiation, a second trial was initiated by the same researchers.23 In this study, only patients with advanced colorectal cancer were included. At the time of administration of vitamin C, the researchers deemed them all inappropriate candidates for chemotherapy. One hundred patients were randomly assigned to receive either 10 grams ascorbic acid or placebo daily. Patients continued on the treatment for as long as they were able to take oral medications or until there was evidence of tumor progression. At this point, over half of the subjects received subsequent chemotherapy. The researchers did not report survival times as they did not continue the patients on vitamin C until they died. Instead, they reported that after one year 49 percent of the vitamin C group and 47 percent of the placebo group were still living. They reported that for both groups survival time was comparable to the Cameron and Pauling untreated group. When they selected patients with a bias toward those with a more favorable prognosis, they found results in both groups similar to the Cameron and Pauling vitamin C treated groups, implying bias selection on the part of Cameron and Pauling. Because of the differences in study design, it is impossible to compare the results of these trials.

The Controversy: It is impossible to have a discussion about vitamin C and cancer without discussing the controversy stirred by the Vale of Leven and Mayo studies. Both sides accused

the other of serious study flaws. The Mayo researchers claimed that, because the Vale of Leven studies were retrospective instead of prospective, and since the subjects were not randomly assigned to groups ahead of time but chosen after the fact, that selection bias occurred, with the researchers consciously or subconsciously selecting the ascorbate- treated patients who had the best prognosis and outcomes to be part of the study group. The Mayo researchers made this statement:

"Uncontrolled or historically controlled studies have a necessary purpose in the evaluation of any therapeutic method, since they serve to develop a hypothesis of therapeutic effectiveness. Such studies, however, rarely prove such effectiveness, which in most circumstances should be established by prospective randomized study. Whether one is dealing with the treatment of the common cold or of cancer, and whether one is dealing with a benign vitamin or a highly toxic chemotherapy program, it would seem to serve the interest of the patient best for public advocacy of a proposed treatment to be withheld until that treatment had been proved effective by definitive studies of sound scientific design."23

The initial Mayo study was criticized by Pauling and Cameron as they felt the two groups were not comparable. In the initial Cameron study, only 4 of the 100 patients had received prior chemotherapy or radiation, while in the first Mayo study the majority of patients had received prior chemotherapy. As previously mentioned, the Mayo Clinic conducted a second study with patients who had not received prior chemotherapy or radiation.

Regarding the second study, in a personal interview with Dr. Pauling, he told this author:24

"I have formulated three criteria for validity of a clinical trial. The Mayo Clinic paper fails on all three." When asked what the three criteria were, this is what he said: "Well, first if you want to test something with a cohort of patients, every patient should be treated the same way as the other patients and the same way over the period of the trial. In the Mayo Clinic study, there were perhaps four separate periods. There was a period when the vitamin C patients received vitamin C every day. So that would be like Cameron's patients. They received vitamin C every day. Then there was a period when they didn't receive vitamin C and that would be a trial of patients during a period after they receive vitamin C for awhile and then stop it. Then there was a period when they were being given chemotherapy. This was a rather short period, maybe a month or two. Then there was a period when they didn't receive anything after they'd been given chemotherapy. So, there were four periods. The first period lasted a median time of 2.5 months and nobody died. None of the vitamin C or control patients died. Since none of the vitamin C patients died you don't have any mortality data similar to Cameron's, of patients who received vitamin C every day until their death. So, it just doesn't have any relation to Cameron's work. Then there is the period after the vitamin C or placebo was stopped. None of the placebo patients died for some strange reason. During this period, after stopping the vitamin C, the vitamin C and placebo patients died off at about the same rate. That's perhaps what you would expect, not expect the vitamin C given the year before to be [effective]. Then there's no information about what happened when they started giving chemotherapy to the patients, but about 58 out of 100 got chemotherapy

and they began dying faster than when they weren't getting chemotherapy. So, that may be significant. Well, that's the first criteria.

"The second criteria is if you plot the logarithm of the fraction surviving against time, you either get a straight line or it can be bending up, it can't bend down unless you do something that causes them to die. Well, theirs bent down because they started giving them chemotherapy.

"Thirdly, for a well-conducted study, the death line, surviving line extrapolates back to the origin. They had a period of 90 days when only one patient died out of 100. They should have had about 30 dying in that first 90 days according to the rate at which they died afterward. So, there's something fishy about that."

In a personal interview with Dr. Ewan Cameron, he said of the Mayo study:25

"They give a drug in tolerable doses for a particular period of time and then suddenly stop it. If they don't see significant results they go to the next drug and so on. That's not how to test vitamin C. We're talking about a totally different therapy. We're talking about something that supports the patient for the rest of his life, not for ten weeks, which was what the Mayo clinic did. Then they stopped it abruptly and gave them 5FU."

Vitamin C in the Prevention of Cancer: Epidemiological Evidence

There is considerable epidemiological evidence pointing to the benefits of vitamin C in the prevention of a number of types of cancer. Unfortunately, epidemiological evidence is often difficult to assess since general dietary factors are difficult to pinpoint. For instance, is high fruit consumption indicative of a high vitamin C intake or is it the fiber that is the key? In addition, frequently the studies report the effects of a number of antioxidants without separating the results for each. The following examines epidemiological evidence according to site of primary tumor.

Bladder: Interest in vitamin C and cancer of the lower urinary tract, including the bladder, stems in part from the discovery that dye-workers exposed to certain carcinogens in the workplace (which oxidize to endogenous orthohydroxy and hydroxylamine derivatives) were more likely to develop bladder cancer. It was hypothesized by at least one group of researchers that higher levels of ascorbate in the urine might prevent the oxidation of these carcinogens. They found that a dosage of 300 mg vitamin C in the form of 3 glasses of orange juice daily raised urinary ascorbate to a level capable of preventing, at least to some degree, the oxidation (or activation) of these carcinogens.26 The most important known risk factor for the development of bladder cancer is cigarette smoking.27 It is interesting to note that cigarette smokers tend to be lower in serum ascorbate than non-smokers.

An epidemiological study in Hawaii comparing 195 males and 66 females with cancer of the lower urinary tract with two matched controls each found a decreasing risk of cancer with increasing levels of vitamin C consumption for women but not for men.28 Another group of

researchers noted low serum ascorbate levels in the majority of 35 patients with bladder cancer.29

Breast Cancer: Plasma levels of ascorbate were significantly lower while platelet levels were higher in a group of recently diagnosed breast cancer patients when compared to a matched group of controls.30 Epidemiological studies appear to point to ascorbate as a possible chemopreventive for breast cancer. In the Iowa Women's Health Study, women who reported consuming at least 500 mg vitamin C daily had a relative risk of developing breast cancer of 0.79 (not statistically significant), compared with women who did not supplement with vitamin C.31 Rohan et al reported a small, statistically insignificant decrease in risks with vitamin C consumption (as assessed by dietary reporting).32 In a Spanish study comparing vitamin C intake among breast cancer patients and matched controls, the patients reported significantly lower intakes of dietary vitamin C than controls.33

A meta-analysis of 12 studies and a number of different nutrients and their relationship to breast cancer found "vitamin C intake had the most consistent and statistically significant inverse association with breast cancer risk."34 Verhoeven et al found no significant association between vitamin C supplementation and decreased breast cancer risk. To make the claim as they did, however, that supplementation with vitamin C does not confer protection from breast cancer, is erroneous since their "higher doses" were an average of 165.3 mg daily. (The group was divided according to supplemental intake as reported on a questionnaire into quintiles with the average reported intake of vitamin C daily ranged from 58.6 mg in the lowest quintile to 165.3 mg in the highest).35

A study to compare the 5-year survival rates of women diagnosed in the early stages of breast cancer who were supplemented with 3 grams daily ascorbate, with a similar group who was not supplemented, found similar 5-year survival rates in both groups.36 Since the prognosis for women with breast cancer which is detected early is quite good in general, this is not surprising, as you would expect a good prognosis, with or without ascorbate supplementation.

In an animal study, the effect of selenium in the form of sodium selinite on protection from mammary tumorigenesis was interfered with by high doses of vitamin C, while the effect of seleno-DL-methionine was not affected by vitamin C.37

Cervical Cancer: A Latin American study compared nutrient intake and dietary patterns of 748 cervical cancer patients with 1,411 controls.38 The results supported a protective affect of vitamin C against invasive cervical cancer. Other researchers have found a similar inverse relationship between cervical neoplasia and dietary vitamin C.39,40 A review article examining a number of studies concluded that in many, but not all studies, an inverse relationship between vitamin C status and risk for cervical dysplasia was observed.41

Colorectal Cancer: 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.42 Other researchers have used antioxidants to prevent recurrence of polyps in patients who had

undergone surgical removal of their polyps. Patients were divided into three groups receiving either lactulose, a combination of vitamins A, C, and E, or nothing. Among 209 patients, polyps recurred in 5.7 percent of those given the vitamins, in 14.7 percent of those receiving lactulose, and in 35.9 percent of the untreated controls.43

An Australian study examining dietary habits and incidence of colorectal cancer found vitamin C but not A to be protective.44 A similar study on patients of a major health plan in Los Angeles found a weak inverse relationship between supplemental and dietary vitamin C and incidence of colorectal cancer.45

Esophageal Cancer: Esophageal cancer is among the more common types found in Lin-Xian County in northern China. Higher levels of nitrosamines have been detected in the gastric juices and urine of people in this area compared to those from a low-risk area of China. A positive correlation was found between esophageal lesions and nitrosamine levels. Intake of moderate doses of ascorbic acid by Lin-Xian subjects was found to decrease urinary nitrosamines to the level detected in the low-risk area.46

The relationships of dietary and supplemental factors with esophageal cancer were examined in 147 males with esophageal cancer and 264 males with other diagnoses at Roswell Park Memorial Institute. Vitamins C, A, and intakes of fruits and vegetables were associated with decreased risks of esophageal cancer.47

Leukemia: An in vitro examination of bone marrow cells taken from patients with acute nonlymphocytic leukemia was conducted. The cells were allowed to colonize on agar culture. In seven of 28 patients, the numbers of leukemic cell colonies were reduced to 21 percent of that of controls by the addition of ascorbate to the culture medium. Neither glutathione (similar oxidation-reduction potential as ascorbate) or HCl (added to cause a comparable pH reduction to ascorbic acid) resulted in a decrease in colonization. It was the researchers opinion that ..."suppression was a specific effect of L-ascorbic acid and was not due to its oxidation-reduction potential or pH change. Leukemic cells were selectively affected at an L-ascorbic acid concentration attainable in vivo while normal hemopoietic cells were not suppressed."48

Lung Cancer: Blood samples from 139 lung cancer patients were examined for both plasma and buffy coat ascorbate levels. Most samples showed hypovitaminosis C below the levels for clinical scurvy.49 Other researchers found hypovitaminosis C in the majority of 24 lung cancer patients.29 The First National Health and Nutrition Examination Survey related dietary habits with lung cancer risk. An estimate of dietary vitamin C intake by 24-hour recall was used. The amount of vitamin C in vitamins was estimated (i.e., guessed to be 60 mg in a multiple and 500 mg if taken as a sole supplement). The researchers found a protective effect of vitamin C (as well as vitamin E and carotenes) from dietary sources of these vitamins but reported no added benefit from vitamin supplementation.50

Non-Hodgkin's Lymphoma: An epidemiological study of factors contributing to non-Hodgkin's lymphoma (NHL) in men and women in Nebraska found a statistically significant inverse relationship between intakes of vitamin C, carotenes, green leafy vegetables and citrus fruits, and incidence of NHL.51

Pancreatic Cancer: A review of the epidemiological evidence of a dietary link to pancreatic cancer reported consistent inverse relationships between vitamin C and fiber, and the incidence of pancreatic cancer.52

Reticulum Cell Sarcoma: Cameron et al reported on a case of disseminated reticulum cell sarcoma successfully treated with high dose ascorbate. Within 10 days of beginning treatment the patient felt subjectively much better and subsequent chest x-rays indicated he had gone into remission. When ascorbic acid was discontinued, reactivation of the disease coincided. A second but slower complete remission occurred when vitamin C was reinstated.53

Salivary Cancer: A case-control study conducted in the San Francisco area examined dietary effects on incidence of salivary gland cancer. When 141 patients with salivary gland cancer were compared to 271 controls, it was determined that vitamin C intake of greater than 200 mg daily compared to 100 mg daily or less resulted in a 60 percent decrease in incidence of salivary gland cancer.54

Stomach/Gastrointestinal Cancer: There are normally high levels of ascorbic acid in the gastric mucosa and gastric juices, suggesting that vitamin C might play an important metabolic role in the stomach.55 Helicobacter pylori has been implicated as a risk factor for gastric cancer. In a group of 88 dyspeptic patients, 58 tested positive for H. pylori. Gastric juice vitamin C levels were examined in these patients as well as in the H. pylori-negative patients. Gastric ascorbate levels were significantly lower in the H. pylori-positive group when compared both with the negative group and to themselves after eradication of the bacteria.56

Cohen and associates examined epidemiological studies and found 9 of 10 case-control studies and 10 of 11 non-controlled studies yielded a significant inverse relationship between ascorbic acid intake and stomach cancer risk.57 Administration of vitamin C to patients with asymptomatic peptic ulcer disease resulted in a decrease in DNA damage in 28 of 43 subjects.58

Safety of Vitamin C

Due to the popularity of vitamin C as a nutritional supplement, a rash of potentially harmful side-effects have been reported, including: calcium oxalate kidney stones, B-12 destruction, iron overload, and elevated urinary uric acid. Although reports have been contradictory, an extensive literature search yielded a lack of support for these effects in healthy individuals.59 Ingestion of large amounts of vitamin C results in only small increases in urinary oxalates60 or urates.61 Until more information is available it is probably prudent to avoid high doses of ascorbate in calcium oxalate stone formers, with patients on dialysis or with serious kidney disease,1 and possibly in patients with hemochromatosis and other iron overload diseases.3

Cameron and Campbell reported on the catastrophic effect of vitamin C in a certain sub-population of terminal cancer patients. These patients suffered from widely disseminated metastasis and the administration of high doses of ascorbate provoked tumor hemorrhage and necrosis, resulting in the destruction of the tumor but the concomitant death of the patient.13

Recently, a team of researchers in England reported in a one-page scientific correspondence to the journal, Nature, that higher dosages of vitamin C (500 mg daily) could actually have a pro-oxidant, rather than an antioxidant effect by reacting with metal ions in DNA. They found that while the blood samples from patients supplemented with vitamin C showed antioxidant effects on guanine, the oxidation of another purine, adenine, seemed to be increased.62 They concluded that vitamin C can be dangerous. Certainly vitamin C has the potential to produce free radicals in the form of ascorbyl radicals in the same way that vitamin E forms tocopheryl radicals. A symbiotic relationship occurs with each quenching the other's radicals. Thus, **administration of high doses of vitamin C may best be accompanied by vitamin E.** In addition, the fact that adenine was oxidized may have nothing to do with the ascorbic acid and everything to do with the test procedures. Jenner et al, reported frequent artifactual oxidation of DNA bases unless specific precautions are taken.63

Conclusions

Vitamin C in high dosages appears to be safe for the majority of individuals. Extensive epidemiological evidence points to the capacity of ascorbic acid to prevent cancer at a number of sites. In addition, some of the limited studies which have been conducted on the use of high dose ascorbate in the treatment of cancer have yielded promising results. While vitamin C alone may not be enough of an intervention in the treatment of most active cancers, since it appears to improve quality of life and extend survival time, it should be considered as part of a treatment protocol for all patients with cancer, whether they have chosen a primarily orthodox, alternative medical, or complementary approach.

The pH Miracle of Vitamin D3

A clinical observation published in April 2000 in the Archives of Internal Medicine caught my attention. Dr. Anu Prabhala and his colleagues reported on the treatment of five patients confined to wheelchairs with severe weakness and fatigue. Blood tests revealed that all suffered from severe vitamin D deficiency. The patients received 50,000 IU vitamin D per week and all became mobile within six weeks.1

Dr. Prabhala's research sparked my interest and led to a search for current information on vitamin D, how it works, how much we really need and how we get it. The following is a small part of the important information that I found. Read more...

Ayurstate for Prostate Care

Current treatment of pancreatic cancer is generally associated with poor prognosis, even if diagnosed early, owing to its aggressive rate of metastasis and non-responsiveness to chemotherapy and radiotherapy. Matrix metalloproteinases (MMPs) have received much attention in recent years for their role in various malignancies, and have been implicated in tumor invasion, metastasis, and angiogenesis.

A Special Message for Cancer Patients Seeking "Alternative" Treatments

Don't let desperation lead you to try things just because someone advises you to do so. Read the information on this web site thoroughly. We strongly recommend that you avoid any "alternative" cancer treatment discussed on Quackwatch. If you or someone you know investigate or pursue any such treatment, please share your experience with us. Your name and report will remain confidential.

An Overview of "Alternative" Methods
These explain how promoters of dubious treatments manipulate the emotions of desperate cancer patients and their families.

- Be Wary of "Alternative" Health Methods
- How Quackery Sells
- How Quackery Harms Cancer Patients
- 25 Ways to Spot Quackery
- "Health Freedom" How It Harms Cancer Patients
- More Ploys That May Fool You
- Why Strong Laws Are Needed to Protect Us

Myths vs. Facts

- Cancer "Clusters"
- Do Power Lines Cause Cancer?
- Most Cancer Death Rates are Not Increasing

"Alternative" Methods: Investigative Reports

- Questionable Cancer Therapies LONG ARTICLE - READ THIS FIRST
- Is There a Conspiracy to Suppress Cancer Cures?
- General Advice from the National Cancer Institute
- Can Any Cancer Treatment Strengthen the Immune System?
- "Miraculous Results" that Weren't
- Be Wary of Fee-Based Advice That Includes "Alternative" Treatment Options
- OTA Report: Unconventional Cancer Treatments (a 300-page book)
- ACS List of Unproven Methods (1971)
- Reports of the Swiss Study Group for Complementary and Alternative Methods in Cancer
- Book Review: American Cancer Society's Guide to Complementary and Alternative Cancer Methods

Questionable Tests

- Cancer Detector LEC-03
- Electrodermal Screening
- OncoDiagnosticator

Dubious Treatments

Topics with posting dates or links to other sites are detailed reports. Items without posting dates are linked to a brief report or a longer OTA passage on Quackwatch.

- AM-2
- Amyloxine
- Antimalignocyt (CH-23)
- Antineoplastons (Stanislaw Burzynski, MD)
- Anvirzel (FDA warning letter)
- Aveloz
- Bemer 3000
- Bio-Ionic System (Evans Rapsomanikis)
- Biotech Cell Information
- BioResonance Tumor Therapy
- Bioterrain Management System
- Bryomixol
- CanCell (also called Cantron, Entelev, and Protocel)
- Canova Method
- Cansema System
- Carnivora
- Cat's Claw (link to another site)
- Cellular Health™ (Matthias Rath)
- Cellular Therapy
- Cesium chloride
- Chaparral
- Controlled Amino Acid Therapy
- Coral calcium
- "Cure for All Cancers" (Hulda Clark)
- CWAT-Treatment: Bioresonance therapy (link to FTC complaint)
- Davidson Cancer Clinic/Monterrey Wellness Cancer
- Devices: General comments
- Devitalisation
- Di Bella therapy
- Dimethyl sulfoxide (DMSO)
- Electron replacement therapy
- Elixir Vitae
- Escharotic Salves
- Essiac
- Fasting

- Forticel tea (link FDA warning letter)
- Fractional chemotherapy
- Galavit
- Galvanotherapy
- Gc-MAF (also called GcMAF)
- Gerson Method
- Gonzalez (Kelley) Metabolic Therapy
- Grape cure
- Greek Cancer Cure (Alivazatos) (posted 8/31/98)
- GS Drops
- Hallelujah Diet
- Hamer's "New Medicine" (also called German New Medicine)
- HANSI™
- Health Restoration Program (Lorraine Day, MD)
- Holt microwave treatment
- Hoxsey Treatment
- Hydrazine Sulfate
- Hyperthermia, whole body
- Immuno-Augmentative Therapy
- ImmunoPower
- Immunostim
- ImmuStim (Gregory E. Caplinger)
- Induced Remission Therapy (Sam Chachoua)
- Induced Hypoglycemic Treatment (IHT, also called Hypoglycemic Adjuvant Therapy)
- Instinctotherapy (raw food diet)
- Insulin Potentiation Therapy (IPT)
- Intra-Cellular Hyperthermia Therapy (ICHT)
- Issels' Whole Body Therapy
- Jason Winters tea
- Jomol
- Krebiozen
- Laetrile
    - The Rise and Fall of Laetrile
    - Laetrile Spammers Facing $631,585 Penalty
    - "Christian Brothers" Ordered to Shut Down
- Livingston-Wheeler Regimen
- Macrobiotic diet
- MGN-3
- Metabolic therapy
    - Manner Metabolic Therapy
    - Questionable Practices at Mexican Border Clinics (link to American Cancer Society)
- MICOM
- Mistletoe/Iscador
- Moerman diet
- Mucorhicin

- Multi Wave Oscillator
- Naltrexone
- Nieper Therapy
- NeyTumerin
- Oncolyn
- "Oxygenation therapies")
- Pap Ion Magnetic Inductor
- Pau D'arco
- PC-SPES (link to ACS article)
- Polyatomic Oxygen Therapy
- Polydox or polyMVA link to ACS article)
- Pulsating Energy Resonance Therapy (PERTH)
- Psychic surgery
- Psychologic methods
- R-A therapy
- RANA System
- Recancostat
- Resan Antitumor Vaccine
- Revici Cancer Control
- Rife Frequency Generator
- RM-10
- Seasilver
- 714X
- Shark Cartilage
- Sodium bicarbonate injections (Dr. T. Simoncini)
- Stockholm Protocol
- Sundance Nachez Mineral Water (see MICOM)
- Tahitian Noni
- Thymus therapy
- Tian Xian Liquid
- Tumorex
- T-Up
- Two Feathers Healing Formula
- Ukrain
- Ultraviolet blood irradiation
- VG-1000
- "Vitamin B-17" Tablets
- Vitamin C
- Wheat grass
- Zoetron therapy (Cell Specific Cancer Therapy)

Other Questionable Activities

- Genetic Services Management (dubious "clinical trial")

Quackery Victim Reports

- The Death of Debbie Benson
- Ruth Conrad (burned by an escharotic)
- Lucillle Craven
- Lori Hoeksema
- An Experience with Robert H. Dowling
- Some Thoughts about the Klinik St. George

Legal and Regulatory Actions

- American Metabolic Institute (link to another site)
- Cancer Treatment Centers of America (1996)
- Century Wellness Clinic
- Court Rules Doctor Not Required to Tell Patients about "Alternative" Therapies
- Issels Medical Center
- Laetrile Spammers (Christian Brothers) Facing $631,585 Penalty
- Limits Placed on Burzynski's Cancer Treatment (1998)
- Phony Doctor Sentenced for Cancer Drug Scam (LK-200)

Nonrecommended Information Sources

- Amber's Alliance Foundation
- Arlin J. Brown Information Center
- Bioimmune Inc (formerly CancerOption.com) (link to Casewatch)
- Canadian Cancer Research Group (CCRG)
- Cancer Control Society
- Cancer Cure Foundation / Cure Research Foundation
- Cancer Information and Support Society
- Cancer Information Center
- Cancer Tutor
- CancerSource complementary & integrative therapies
- CANHELP (founded by Patrick M. McGrady, Jr.)
    - General Comments
    - A Case Report
- Center for Advancement in Cancer Education
- Center for Alternative Cancer Research (Project Cure)
- Committee for Freedom of Choice in Medicine
- Commonweal
- Foundation for Advancement in Cancr Therapy, Ltd (FACT), formerly called Foundation for Alternative Cancer Therapy, Ltd.
- International Association of Cancer Victors and Friends
- International Cancer Association Network (Australia)
- International Council for Health Freedom
- National Cancer Research Foundation (New York City)
- National Foundation for Alternative Medicine

- National Health Federation
- Orthomolecular Oncology
- People Against Cancer
- Prostate Health Resources (Larry Clapp)
- Ralph Moss on Cancer
- Syracuse Cancer Research Institute

Recommended Information Sources

- About Herbs, Botanicals, & Other Products: Memorial Sloan-Kettering Cancer Center database
- American Cancer Society: A few articles on "complementary and alternative therapies" are too bland.
- American Society of Clinical Oncology
- CancerNet: The National Cancer Institute's comprehensive resource for both doctors and patients. The information on standard treatment is excellent, but the information on "complementary and alternative medicine" is skimpy and not very useful.
- Cancer News on the Net
- CancerTrack: Index to relaible cancer information on the Internet.
- Clinical Trials
    - Index of National Cancer Institute Information
    - Taking Part: What Cancer Patients Need to Know
- Dictionary of Cancer Terms
- FDA Oncology Tools
- National Alliance of Breast Cancer Organizations
- National Comprehensive Cancer Network
- National Guidelines Clearinghouse: Index to guidelines for detection and management of many types of cancer.
- Oncolink: University of Pennsylvania's Cancer database
- Pancreatica.org: All about cancer of the pancreas

Patient Support

- Helping People Cope: A Guide for Families Facing Cancer (1988). Published by the Pennsylvania Department of Health
- Oncology Mailing Lists: Active discussions with searchable archives on the general topic of cancer and for more than 20 specific types of cancer. These offer an opportunity to share ideas and experiences with other cancer patients. Messages promoting quack methods are sometimes posted. When that happens, they are usually debunked.
- Guide for Cancer Supporters: Appropriate strategies for dealing with cancer. **Warning**: The "mental welfare" section of Part 2 contains unsubstantiated statements and should be ignored.

Nonrecommended Books

- Beating Cancer with Nutrition (Michael Quillin, PhD, Rd, 1994)
- Cancer: Why We're Still Dying to Know the Truth (Phillip Day, 2001)
- Cancer and Common Sense (Douglas Brodie, MD)
- Cancer and Its Nutritional Therapies (Richard Passwater, 1978, 1983)
- Cancer & Nutrition (Charles B. Simone, MD, 1983)
- Cancer: One Disease, One Cause, One Cure (Mike Thompson, DC)
- Cancer: Treating Cancer with Insulin Potentiation Therapy (Ross Hauder, MD, Marion A. Hauser, MS, RD, 2002)
- Cancer: Why We're Still Dying to Know the Truth (Philip Day, 2000)
- The Cancer Industry (Ralph W. Moss.1980, 1989).
- Cancer Therapy (Ralph W. Moss, 1992)
- Choices in Healing (Michael Lerner, 1994)
- Comprehensive Cancer Care (James S. Gordon, MD, and Sharon Curtin, 2000)
- Cure for All Cancers (Hulda Clark, 1993)
- Definitive Guide to Cancer (W. John Diamond, MD, W. Lee Cowden, MD, and Burton Goldberg, 1997)
- Getting Well Again (O. Carl Simonton, MD, Stephanie Matthews-Simonton, James L. Creighton, 1978)
- Living Well Naturally (Anthony J. Sattilaro, MD, 1984)
- B17: Metabolic Therapy in the prevention and control of cancer, a technical manual (Philip Day, 2002)
- Nutrition: The Cancer Answer II (Maureen Salaman, 1995)
- Options: The Alternative Cancer Therapy Book (Richard Walters, 1993)
- Prostate Health in 90 Days (Larry Clapp, 1997-2002)
- Recalled by Life (Anthony J. Sattilaro, MD, 1982)
- Sharks Don't Get Cancer (I. William Lane, PhD, 1992)
- Thee Cancer Cure That Worked! (Barry Lynes)
- Third Opinion (John M. Fink, 1988, 1992, 1997)
- Ultimate Cancer Breakthroughs (Marco Wutzer)
- When Healing Becomes a Crime (Kenny Ausubel, 2000)
- World without Cancer (G. Edward Griffin, 1974, 1997)