THE USE OF TETRAHYDROCANNABINOL (MARINOL) IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY

by

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Thesis submitted to the Faculty of the
Virginia Polytechnic Institute and State University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

in

Human Nutrition and Foods

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July, 1988
Blacksburg, Virginia

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(ABSTRACT)

The effect of Marinol, which contains the antiemetic tetrahydrocannabinol (THC), was evaluated in five cancer patients undergoing chemotherapy. Subjects rated their nausea and vomiting, food intake, appetite and mood status three times daily. Drug therapy (THC) or no drug was administered for an average of four months during the course of their chemotherapy regimen. Subjects began taking THC the first day of chemotherapy and continued (5mg/three times a day) for an average of two weeks. Subjects reported their nausea and vomiting to be increased while receiving THC which coincided with their period of chemotherapy treatment. Subjective ratings for food intake and appetite varied in each case and did not always correlate with actual caloric intake from food. Food intake in most subjects was approximately the same, or greater with THC even though the period when THC was given coincided with chemotherapy treatment, and the use of emetigenic drugs. This resulted in weight maintenance or minor weight loss in most subjects. The absence of THC during chemotherapy treatment resulted in decreased food intake. Some

of the moods reported most frequently by subjects while receiving THC were activity, interaction and relaxation. Depression, social withdrawal and anxiety were reported less frequently and usually occurred around the time of chemotherapy. The majority of the moods reported indicated that subjects had positive feelings associated with THC therapy.

The results of this study indicated that THC benefitted cancer patients by increasing food intake during chemotherapy regimens without causing adverse behavioral changes.

To the memory of

Martin M. Sacks,

Morris H. Goldberg and

Jane E. Gruin

ACKNOWLEDGEMENTS

The author wishes to express her thanks to the following individuals for their assistance during her graduate studies:

Dr. Ryland E. Webb, major professor, for advice, encouragement and willingness to listen and share his knowledge throughout the author's graduate studies;

Julie Watts, M.S., R.N., member of the graduate committee, for her time in implementing, planning, and participating in this project and sharing her expertise about oncology;

Dr. J.R. Hutcheson, member of the graduate committee, for offering his time and patients in this project;

Dr. S.J. Ritchey and Dr. Klaus Hinklemann, members of the graduate committee, for assistance and guidance;

Dr. Vera J. Wall for encouragement with this project;

Roxane Laboratories, Inc. for donation of Marinol;

A special thanks to the cancer patients and their families for their time and participation in this study;

To my friends for proofreading and moral support;

To my mother for financial and emotional support.

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INTRODUCTION

The term "cancer cachexia" is used to describe altered host metabolism in oncology patients that usually results in generalized wasting (Harvey and Bothe, 1979; Schein et al., 1979; Theologides, 1979; Wesdorp et al., 1983). The aggressive antitumor therapy currently being used can contribute to cancer cachexia. Morrison (1976) estimated that two thirds of patients with cancer have cachexia at death. Protein-calorie malnutrition (PCM) is usually seen in cancer cachexia syndrome. A prevalent cause for PCM is anorexia. Anorexia may be due to the antitumor therapy, altered host metabolism, or possibly to an unknown cause (Dewys, 1977). Anorexia leads to decreased intake and commonly contributes to the weight loss. PCM can have an effect on the response to antitumor therapy and general well-being of cancer patients. Cancer patients who are cachectic do not tolerate vigorous antitumor therapy well (Ohnuma and Holland, 1977). These malnourished cancer patients have impaired cell-mediated immunity (Bull, 1975) and decreased resistance to microbes (Nixon et al., 1980). The early treatment of PCM in cancer patients has been associated with a decrease in their mortality rate (Harvey and Bothe, 1979).

It is important to detect PCM effectively in cancer patients so that appropriate nutritional support can be pro-

vided. Nutritional assessment of cancer patients can be performed using serial measurements. These include anthropometric, biochemical and immunocompetency measurements. Dietary analyses including calorie counts are also employed. Medical and dietary histories serve as tools to evaluate patient`s present status. The earlier that PCM is detected and treated, the better the possibility for response to therapy with enhanced quality of life for oncology patients. Increased caloric intake is important in preventing PCM and improving nutritional status. All modes of increasing appetite to promote increased food intake need to be explored. It is most preferable to use the oral route for providing optimum nutrition, therefore ways to control and alleviate the factors that contribute to anorexia and decreased appetite are important.

Tetrahydrocannabinol (THC) (Baker, 1986) has been used by researchers as an antiemetic in cancer patients receiving chemotherapy (Frytak et al., 1979; Orr et al., 1980; Sallan et al., 1975; Ungerleider et al., 1982; Sweet et al., 1981; Lucas and Lazlo, 1980). The results are conflicting, though THC has been shown to be an effective antiemetic in some cancer patients. An incidental side effect of increased appetite had been noted (Sweet et al., 1981; Hollister 1970; Sallan et al., 1980) and is suggestive that with the reduction of nausea and vomiting, and the possible stimulation of appetite, there might be an increase of food intake in can-

cer patients.

The widespread use of THC, as an antiemetic, was restricted by the availability of other regimens containing noncontrolled drugs, i.e. Metoclopramide, Dexamethasone and Diphenhydramine combinations which have proven to be highly effective in nausea suppression. Due to undesirable side effects and social pressures, the use of THC has been somewhat restricted in antiemetic preparations. An additional side effect which has been noticed, both in illicit and prescription use of THC and marijuana, was the accentuation of appetite widely regarded as "munchies" in street parlors. It appears that other potential benefits to cancer patients might be available through the use of low dose THC, as an adjunct to chemotherapy.

Marinol, the brand name of dronabinol (delta-9-tetrahydrocannabinol, THC), is the principal psychoactive substance present in Cannabis sativa L. (marijuana) (Roxane Laboratories, Inc.). The purpose of this study is to evaluate the effects of Marinol (Baker, 1988 and Roxane Laboratories, Inc.) on appetite, food intake and emesis in cancer patients receiving chemotherapy. Specifically, the effects sought would be: to achieve or to find a dose which provided no psychoactive effects but provided evidence of stimulation of appetite with improved caloric and nutritional intake for patients undergoing chemotherapy.

REVIEW OF LITERATURE

Progressive weight loss is a common finding in cancer patients (Wesdorp et al., 1983; Holroyde et al., 1975; DeWys, 1977; Theologides, 1974; Theologides, 1979; Costa, 1977 . The term "cancer cachexia" has been used to describe the continued weight loss in cancer patients, in whom adequate calories are apparently ingested to meet the body's needs (Wesdorp et al., 1983). Cancer cachexia syndrome can be the result of anorexia, causing a decrease in food consumption and subsequent weight loss. Impaired digestion and absorption of nutrients in the gastrointestinal tract may also be present. Competition for nutrients and altered host metabolism of carbohydrates, lipids and proteins are observed in cancer patients (Wesdorp et al., 1983; DeWys, 1977; Theologides, 1974; Costa, 1977; Dickerson, 1984). An increased energy expenditure in the host has also been observed (Theologides, 1979).

Food consumption has been studied in cancer patients, through evaluation of intake before and after discovery of neoplastic disease (Costa et al., 1976). These researchers demonstrated that both males and females ingested less food during neoplastic disease, when compared to normal intake, and incurred a weight loss. When weight loss developed, there was a negative balance between caloric intake and expenditure. As mentioned, anorexia leading to inadequate

intake could be a major contributor to the noted weight loss.

A relationship exists between a patient's nutritional status, the tumor growth, and the antitumor therapy used. Cancer patients experience anorexia and early satiety which can lead to progressive weight loss (Harris and Probert, 1981). The anorexia and decreased intake may eventually lead to the cachexia so often observed in cancer patients (Harris and Probert, 1981). Anorexia can also be due to psychological causes. The disease may cause depression and anxiety which could alter normal hormonal levels, and in turn affect appetite. Some researchers feel that abnormal production of substances in patients with cancer may be the reason for the anorexia (DeWys, 1982; Theologides, 1979).

Anorexia may be due to a number of causes. These include nonspecific manifestations of disease, alterations of taste and/or smell perception, production of lactate, production of ketones, hypothetical tumor toxins, direct effect on appetite center and psychological factors (Costa, 1977). Some researchers (Wesdorp et al., 1983; Lundholm et al., 1985) have hypothesized that altered neurotransmitter metabolism in cancer patients may contribute to anorexia.

When weight loss continues, protein-calorie malnutrition usually occurs. When malnutrition is present, it can be supported by the following criteria (Harris and Probert, 1981):

1) Recent weight loss of more than 5-10 percent of body weight.

2) Serum albumin level of less than 3.8-5.0 gm/dl.

3) Decreased state of immunocompetency evidenced by negative reaction to a series of skin antigen tests or delayed hypersensitivity tests.

Some researchers have shown that by reversing protein-calorie malnutrition, cancer patients are likely to have fewer side-effects related to treatment and respond better to anti-tumor therapy (Blackburn, 1977; Copeland et al., 1977).

Nutritional support needs to be provided to the cancer patient as long as useful life remains. The type of support used will depend on the specific type of antitumor treatment, extent of disease and nutritional status of the patient. It is important not to lose sight of how the therapy chosen will be of benefit to the host. Many types of cancer can be cured, whereas others may be considered to be a chronic disease.

A. Chemotherapy

Cancer chemotherapy agents are used based on selective toxicity to cancer cells, but also have an effect on all dividing cells. Host toxicity is likely to occur since the maximum tolerated dose is used in treatment and therefore may be toxic in many patients (Carter, 1981). This dosage is determined from Phase I studies and usually remains constant, unless toxicity occurs. Unfortunately, the toxic side effects associated with the anti-tumor therapy can be deleterious to a patient's nutritional status. Some of these side effects are nausea, diarrhea, vomiting, and stomatitis (Kokal, 1985; Carter, 1981). These side effects can contribute to decreased appetite, resulting in increased weight loss.

While no two chemotherapy regimens can be said to be exactly comparable in terms of appetite suppression and/or emitogenesis, certain chemotherapy combinations are well known to produce both of these effects. Specifically, chemotherapy combinations which include the drugs Adriamycin, Cis-Platinum, and high doses of Cyclophosphamide are well recognized by oncologists to be a problem resulting in appetite suppression and/or loss of appetite.

There are several different classes of antineoplastic drugs used in chemotherapy. The drugs are cytotoxic in nature and prevent cell division and therefore cell prolif-

eration, but do not directly kill tumor cells. Antimetabolites affect cellular processes by interfering with the synthesis of nucleic acids. Alkylating agents function in such a way that replication is prevented by damaging the deoxyribonucleic acid (DNA) template with cross-linking of the two strands in the double helix. Antitumor antibiotics selectively bind with DNA, which form complexes that block the formation of DNA dependent ribonucleic acid (RNA). Enzymes are used to cause depletion of endogenous sources of certain amino acids thought to be essential for malignant cells. Mitotic inhibitors are used and result in metaphase arrest by acting on the mitotic spindle apparatus. Hormones are also used in chemotherapy by affecting cancers originating from organs that are sensitive to the particular hormone. Hormones also inhibit specific pituitary secretions that are responsible for stimulating certain malignant cells (Carter, 1981).

Toxicity from chemotherapy affects many areas in the host, a major site being the bone marrow (Carter, 1981). Metabolism of blood components are altered leading to thrombocytopenia, leukopenia, and anemia. Leukopenia is most commonly observed and frequently becomes the controlling factor for limiting dosage. Infection may result from leukopenia, compromising the patient's state further. The changes in bone marrow function may cause altered production of blood constituents resulting in deleterious effects on

the nutritional status of cancer patients.

Other side effects of chemotherapy include nausea and vomiting, which along with anorexia can lead to decreased oral intake. The chemotherapy drugs used are classified according to severity of nausea and vomiting that they cause (Carter, 1981 and Yasko, 1983). Another area affected by cytotoxic drugs is the lining of the gastrointestinal tract. Chemotherapy affects the rapid turnover of epithelial cells in the mucosa. Problems such as cheilosis, glossitis, pharyngitits, and oral ulcerations, may arise and can lead to decreased food intake resulting in dehydration and poor nutritional status. Diarrhea and malabsorption also result from chemotherapy, due to the toxic effects on the mucosa. Severe diarrhea can lead to electrolyte imbalance, dehydration and therefore contribute to compromised nutritional status resulting in malnutrition (Carter, 1981; Harris and Probert, 1981).

Toxicity can also affect the central nervous system, and result in decreased oral intake. Various drugs produce different effects, but all have the same end result of accelerating malnutrition. Cancer chemotherapeutic agents are commonly used in combinations, as they produce a more aggressive or complete effect on the cancer. When a single chemotherapeutic agent is used, it is usually administered in the maximum tolerated dose which imposes a risk to the patient, with more detrimental side effects. When several

agents are used in combination, a lower dose may be administered, usually decreasing the side effects to the patient. The duration and severity of nausea and vomiting from chemotherapy depends on the type of drugs used, the dosage and route of administration. Some patients develop "anticipatory" vomiting which is explained as a conditioned aversion to chemotherapy (Kokal, 1985).

The vomiting and nausea associated with chemotherapy is mediated through the vomiting center located in the medullary reticular formation near the dorsal nucleus of the vagus (Kokal, 1985; Pratt et al., 1984). The chemoreceptor trigger zone (CTZ), located in the fourth ventricle in the area postrema is another structure involved. These two structures comprise the neural mechanism of the vomiting process (Pratt et al., 1984).

Certain factors have been used to evaluate and predict responses to chemotherapy. Weight loss prior to chemotherapy is a poor sign for prognosis. Shorter survival and lower response rate has been shown in patients with weight loss when compared to patients without weight loss (Carter, 1981). Patients who are in poor nutritional status also seem to tolerate chemotherapy poorly. Performance status (Karnofsky's Index), which is measured by a patient's ambulatory functioning (Wynagaarden and Smith, 1982), has been used to predict the patient's ability to tolerate appropriate drug therapy and to predict response and survival rates in cancer

patients. It would seem likely then, that by improving nutritional status, an enhanced performance status would result with improved response to therapy. This has yet to be proven, as many variables are present that may alter results, but it seems promising that increased nutritional support would serve as adjuvant therapy for a patient undergoing aggressive chemotherapy.

The nutritional goals for cancer patients undergoing chemotherapy should include (Harris and Probert, 1981):

1) To achieve or maintain ideal body weight.

2) To provide sufficient nutrients (kilocalories, carbohydrates, protein, fat, vitamins and minerals) to correct or prevent nutritional deficiencies and imbalances.

3) To maintain or restore immunocompetence.

Cancer is a chronic disease and nutritional support must be provided to meet the changing needs of the cancer patient. The most preferred route for providing nutritional support is by the oral route. This may involve counseling of the patient and family along with provision of nutritious supplements. Tube feedings would be the next desirable mode of support, followed by total parenteral hyperalimentation. Each patient varies with the type of malignancy involved, side effects of therapy and level of nutritional status and therefore the nutritional support must be individualized to meet the patient's needs.

B. Nutritional Assessment of Patients Receiving Cancer Chemotherapy

The most common secondary diagnosis in cancer patients is protein-calorie malnutrition (PCM) (Harvey and Bothe, 1979). PCM can result from anorexia, altered host metabolism, compromised function of the gastrointestinal tract and certain organs, and stress of antitumor therapy (surgery, radiation and chemotherapy) (Black et al., 1983).

Serial anthropometric and biochemical data have been used to assess the nutritional status in cancer patients (Blackburn and Bothe, 1978; Ota et al., 1985; Nixon et al., 1980). The purpose is to compare values found in cancer patients to those of healthy subjects to observe what differences exist. The parameters that are used to assess nutritional status include adipose tissue stores, measurements of skeletal mass and visceral protein status.

The Diet, Nutrition and Cancer Program (DNCP) of the National Cancer Institute (NCI) developed core data that consists of anthropometric, hematologic, biochemical, immunologic and dietary information to be recorded in studies involving cancer patients (Ellison, 1980). The data obtained is evaluated and should provide consistency for measuring nutritional status of cancer patients.

The following parameters are components of the nutritional assessment process (Blackburn et al., 1977):

1) Height, weight and wrist circumference are obtained. Percentage of ideal body weight (IBW) for height is calculated using standard height, weight and frame charts (Grant and DeHoog, 1985).

2) Upper Arm Triceps Skinfold (TSF) is measured with calipers and compared to normal standards. This is an indirect estimate of calorie stores or body fatness and can be used as an index of energy reserves (Grant et al., 1981).

3) Arm Muscle Circumference (AMC) is obtained from Upper arm circumference (AC) and the TSF (AMC = AC - (0.3 X TSF X 10))3. When this value is compared to normal standards, it is expressed as a percentage of that standard. AMC is used to measure the degree of protein depletion (Blackburn et al., 1977).

4) A 24-hour creatinine excretion is used in calculating the creatinine height index (CHI). These values are compared to normal standards (for height and weight). The CHI is used to measure skeletal muscle mass (Grant et al., 1981).

5) Visceral protein status is measured by serum albumin and transferrin which are secretory proteins (Grant et al., 1981). Transferrin is calculated using total iron binding capacity (TIBC). Transferrin = (0.8 X TIBC) - 43. (Blackburn et al., 1977). Some of the plasma proteins can be used to assess response to short and long term nutritional therapy in cancer patients (Ota et al., 1985).

6) Total lymphocyte count (TLC) and skin testing with

recall antigens are used to assess immunocompetency (Grant et al., 1981). A white blood cell count (WBC) with differential is used to calculate TLC. TLC = % lymphocytes X WBC/100.

Biochemical tests are routinely performed to assess nutritional status. The results from these tests along with information on anthropometric measures is a good way to assess any changes in a patient due to therapy (Grant et al., 1981) or progression of the disease.

These parameters allow the assessment of nutritional status in cancer patients, although not all are practical or feasible. The tests are performed serially to allow for observance of any changes. The assessment used by Blackburn and Bothe (1978) is part of the recommended core data from the National Cancer Institute (Ellison, 1980). The type of study being performed will dictate which of the parameters are to be utilized. Some tests may be run solely on an experimental basis to see what differences exist, while others can be used to evaluate nutritional status in an individual.

C. Tetrahydrocannabinol

Delta-9 tetrahydrocannabinol (THC) is a psychoactive substance found in marijuana (Baker, 1986). It is synthe-

sized under the generic name of Dronabinol, and the brand name of Marinol (Roxane Laboratories, Inc.). Marinol is formulated in sesame oil and encapsulated in gelatin capsules to be administered orally (Roxane Laboratories, Inc.).

Since Marinol is the same as the active substance in marijuana, it can produce physical and psychological effects seen in marijuana use (Baker, 1986). The central nervous system can be affected by Marinol and changes in mood have been observed with the use of marijuana. These include depression, anxiety, panic, euphoria, detachment, decrements in memory and cognitive performance, and a decreased ability to control impulses and drives. Chronic use of Cannabis has been associated with decrements in cognition, judgment and motivation. There are also some systemic effects noted, such as increased heart rate and changes in blood pressure. The 11-hydroxy metabolite of Marinol is the psychoactive metabolite found in the plasma and is at maximum concentration approximately two to three hours after oral dosage. The major route of excretion is biliary. Approximately 50 per cent of the dose is recovered in the feces within 72 hours following oral ingestion. Another 10 to 15 percent is found in the urine as a metabolite or is unchanged (Baker, 1986). Refer to Appendix A for additional information on Marinol.

Marijuana is rapidly absorbed and is highly lipid-soluble. The primary active ingredient - tetrahydrocannabi-

nol (THC) has an elimination half-life of 19-20 hours. There are other metabolites formed from hepatic metabolism such as an active 11-hydroxy metabolite which has a half-life of up to 50 hours. Tolerance to THC develops rapidly, but disappears after abstinence. Mild withdrawal symptoms which could last a few days may develop with abrupt discontinuation (Dukes and Beeley, 1985).

THC has been used with some success to treat nausea and vomiting in cancer patients receiving chemotherapy. In some studies it has been found to be a superior antiemetic, but other researchers found it to be ineffective. The discrepancy in results may be due to difficulties in utilizing a double-blind research design, poor randomization of subjects and innate differences in the subjects. It is also difficult for patients to assess nausea and vomiting, since it is subjective (Dukes and Beeley, 1985).

An early study by Hollister (1970) evaluated hunger and appetite after single doses of marijuana, alcohol and dextroamphetamine. The results indicated that in more than half of the subjects, after oral administration of marijuana, there was an increase in food intake, hunger and appetite. A pilot study by Sweet et al. (1981) reported the use of delta-9 THC as an antiemetic in patients receiving cancer chemotherapy and suggested that oral administration of THC is a toxic substance that acts transiently as an effective antiemetic. Six patients out of 25 noted inciden-

tal improvement in appetite. Frytak et al. (1978) evaluated the use of delta-9 THC as compared to placebo and prochloraperazine in cancer patients receiving chemotherapy. THC was found to be a superior antiemetic over the placebo but was not better than the prochloroperazine. Subjects in this study who received THC therapy revealed a more unpleasant experience, due to central nervous system side effects. The median age of the subjects in this study was 61 years. In the study by Sallan et al. (1980), the median age of the subjects was 29.5 years. Many patients admitted to prior use of marijuana in this study. Ungerleider et al. (1982) found that approximately one-half of the patients had prior experience with marijuana. Previous use of marijuana and age of subjects could affect the results of studies utilizing THC due to acceptability and expectation of using THC as a treatment (Frytak et al., 1979).

Orr et al. (1980) compared the antiemetic effects of THC with placebo and prochlorperazine in treating nausea and vomiting associated with chemotherapy. THC appeared to offer significant antiemetic control, but was more efficacious in certain chemotherapy protocols than others. Appetite stimulation was not an observed side effect of THC, but some patients reported that food intake was possible at an earlier time following chemotherapy.

The study by Sallan et al. (1980) with delta-9 THC and prochlorperazine revealed more complete antiemetic responses

to THC therapy than to prochlorperazine. THC therapy was associated with increased food intake and was also accompanied by the presence of a "high". A high was characterized as a mood change that consisted of elation, heightened awareness, tendency to laugh, mild aberrations of fine motor coordination or minimal distortion of interactions and activities with others.

Ungerleider et al. (1982) evaluated the use of delta-9 THC and prochloroperazine as antiemetics and found both to be equally effective. Food intake and changes in appetite were also evaluated, and showed no change with respect to the drug given. There were noted mood changes with THC usage (less ability to concentrate, less social interaction and less activity).

Lucas and Laszlo (1980) treated cancer patients who had experienced severe nausea and refractory vomiting, while receiving chemotherapy, with delta-9 THC. Seventy-two percent of the patients had at least a 50 percent reduction in nausea and vomiting, some even experienced complete antiemetic effect. Some patients did not report an appreciable reduction in nausea and vomiting.

It is important to realize that all of the previously mentioned studies used a variety of cancer patients, various criteria for dosage levels and different research designs. All of these variables will alter the results reported. This can help to explain the discrepancies noted in the

results. Since THC is a psychoactive drug it is important to evaluate mood changes, and verify if relationships exist between altered mood status and antiemetic effect. None of the researchers looked specifically at the effect of THC on appetite, although some conflicting incidental data on the effect on appetite and food intake has been presented. These data suggest that there may be a relationship between THC and appetite that is dependent on many variables (dose, type and stage of cancer, and type of chemotherapy).

METHODS AND MATERIALS

Subjects

Eight subjects, who were adult cancer out-patients being treated for one of a series of diagnoses at the Cancer Center of Southwest Virginia in Roanoke, were studied. Subjects who were selected were undergoing chemotherapy regimens which included one of the following combinations of drugs:

1) Cytoxan, Adriamycin and 5-Fluorouracil (5-FU) for carcinoma of the breast;

2) Cytoxan, Adriamycin and Etoposide (VP-16) for small cell carcinoma of the lung;

3) Cis-Platinum, Adriamycin, 5-Flourouracil or Cis-Platinum, Adriamycin for carcinoma of the ovary;

4) Other patients with similar drug regimens for less common tumors.

Of the original eight subjects entered into the study, only four were evaluated. Of the four subjects who were not evaluated, three died early in the study due to disease progression. All subjective data on the remaining subject was lost by the postal service. Relevant information used in evaluating this subject was reported verbally by the subject and retrieved from medical records. Because the population was small and varied according to tumor type and stage, the data from each subject was treated as a case study.

Subjects received a thorough explanation of the purpose and intent of the study from the physician in charge. All subjects signed a written consent form prior to participation.

Collection of medical information

Current oncologic status was obtained from each subject's medical record. Tumor, Node and Metastases (TNM) (Appendix B) staging of the cancer and Karnofsky's Index on Performance status (Appendix C, Wynagaarden and Smith, 1982) were used to assess subjects. All subjects were at or above 60 percent on Karnofsky's Index. Subjects were also categorized according to the emetigenic potential of the chemotherapy drugs used (Appendix D, Yasko, 1983) . Chemotherapy was given by standard infusions or orally. Antiemetics were provided in an equivalent matched manner for all subjects and were usually administered during chemotherapy and for only 24 - 48 hours following the initial chemotherapy.

Design

The effect of Marinol (Baker, 1986; Roxane Laboratories, Inc.), which contains the antiemetic tetrahydrocannabinol (THC), was evaluated in cancer patients undergoing chemotherapy. Specifically, the effects of the drug on nausea, vomiting, food intake, appetite, mood status and various biochemical parameters were assessed. Subjects received

drug therapy (THC) or no drug for an average of four months during the course of their chemotherapy regimen. Subjects therefore knew they were receiving THC as no placebos were used. Subjects were allocated THC and began taking the drug on the day that chemotherapy began and continued daily for an average of two weeks during their cycle. A cycle is defined as the amount and type of chemotherapy drugs given over a period of time. Different cancers have specific drugs which are used to treat patients. These drugs may be given as infusions and/or orally.

Subjects rated their nausea, vomiting, appetite, food intake, and occurrence of mood changes three times daily; at morning, midday and evening on the appropriate form (Appendix E). Subjects also recorded their weight daily on this form, if a scale was available at home. Subjects were also evaluated for mood status by someone who resided with them on the appropriate form (Appendix F). This offered a second perspective of mood changes.

The study was conducted through the Community Clinical Oncology Program (CCOP) at the Cancer Center of Roanoke Memorial Hospitals. Approval was received for the use of THC from the Investigational Review Board.

Nutritional status

Nutritional status was assessed through anthropometric biochemical, and dietary intake measurements. The study was

broken down into cycles, corresponding with treatment periods lasting ten days to two weeks and non-treatment periods of approximately two weeks. Subjects received THC during the treatment periods. The anthropometric data included the subjects' height and weight. Wrist circumference was measured to estimate the appropriate frame size which was used in determining desirable body weight (Grant et al., 1981). The weight at the midpoint of the frame category in the 1983 Metropolitan Height and Weight tables that corresponded to each subject's height was used as the desirable body weight. The percent of desirable body weight on entry into the study was calculated.

The nutritional assessment of subjects in this study was based on the core data from the Diet, Nutrition and Cancer Program (Appendix G, Ellison, 1980) and from parameters evaluated by Carter et al. (1983) (Appendix H). Normal values from the laboratory at Roanoke Memorial Hospitals were used to make comparisons (Appendix I).

A dietary history was obtained by the investigator for each subject prior to the start of the study. The information was recorded on an initial assessment form which was based on a form used at Memorial Sloan Kettering Cancer Center (Appendix J, Shils, 1981). A medical history was recorded and a physical examination was performed by J.R. Hutcheson Jr., M.D., or the attending physician, before entry into the study. Information obtained included a medi-

cal history, drug/therapy history and pertinent information derived from a physical examination. At the time of the physical examination, the performance status of each subject was assessed by the physician using Karnofsky's Index (Wynagaarden and Smith, 1982). The chemotherapy drugs and schedule used were obtained from the medical records and these drugs were classified according to emetigenic potential. Data on current oncologic status, using the Tumor, Node and Metastases Staging Guide (Beahrs and Myers, 1983) was obtained from subjects' medical records, when available. The information for the medical history was recorded on the appropriate form (Appendix K).

Biochemical analysis

The biochemical tests included a sequential multiple analysis profile (SMA) 12, hemoglobin, white blood cell (WBC) and platelet. These biochemical tests were done on entry into the study and were conducted when subjects came for chemotherapy and thus avoided additional trips to the cancer center for blood testing. The normal ranges for these tests are included in Appendix I.

Nutrient analysis

Dietary intakes were recorded on two consecutive days each week throughout the study (Appendix L). The days were staggered in order to obtain a representative sample of dietary intakes. The days chosen represented different times throughout the study and were used to confirm any changes in weight, nausea, vomiting, and appetite. The following days' were used for subjects to record their dietary intake:

	DAY						
WEEK	Sun	Mon	Tue	Wed	Thur	Fri	Sat
1		x	x				
2				x	x		
3						x	x
4	x	x					
5			x	x			
6					x	x	
7	x						x
8		x	x				
9				x	x		
10						x	x
11	x	x					
12			x	x			
13					x	x	
14	x						x
15		x	x				
16				x	x		

Subjects received a calendar with the dates indicated for recording dietary intake (Appendix M). The information obtained from dietary intakes was analyzed using the Nutritionist III, which is produced by N-Squared Computing in Silverton, Oregon. Dietary intakes were analyzed for total kilocalories, protein, carbohydrate, fat, alcohol, and percent of total kilocalories contributed by each nutrient.

Drug protocol and schedule

Roxane Laboratories provided THC in the form of Marinol in 5.0 mg capsules. Subjects were treated with standard doses (5.0 mg three times a day), which was the dosage level recommended by Roxane Laboratories. Subjects were requested to abstain from the use of alcohol and other psychoactive drugs during the course of the study.

Statistical Analysis

The different treatments (with or without THC and chemotherapy) were analyzed for each subject. Biochemical data was reported as means, standard deviations and observed ranges. The appropriate means were compared to normal limits from Roanoke Memorial Hospitals. The data on nutrient analysis was broken down into total kilocalories, protein, carbohydrate, fat, and alcohol intake expressed as means and standard deviations. The percent that each nutrient contrib-

uted to the total kilocalories was computed. The effect of THC on dietary intake was examined with and without chemotherapy and was evaluated independent of chemotherapy.

Average ratings for nausea and vomiting (Orr et al., 1980), food intake (Sallan et al., 1980) and appetite (Ungerleider et al., 1982) were analyzed utilizing different scales, ranging from 0 - 3, for each criteria. Subjects selected responses in each category which described how they felt at one particular time of the day. The average frequency rating was computed by adding all frequency scores together and dividing by the total possible responses. The average value corresponded to the values in the scale used to identify particular criteria. The following are the scales used by subjects to describe how they felt.

Nausea and vomiting was rated on a scale of 0-3:

0 - No vomiting

1 - Nausea present, but not disabling

2 - Nausea impairing normal activities

3 - Vomiting

Food intake was rated on a scale of 0-3:

0 - No food intake

1 - Less than usual

2 - Average

3 - More than usual

Appetite was rated on a scale of 0-3:

0 - None

1 - Decreased

2 - Same

3 - Increased

The percent of occurrence for each mood (Ungerleider et al., 1982) was calculated by adding all responses for each mood and dividing by the total responses for all moods. This value represented the percent of time each mood was selected based on total number of responses recorded. Each mood was identified by a number and the subject circled the appropriate numbers describing how they felt at one particular time of the day. Subjects were given definitions of the following moods (Appendix N).

1 - Depression

2 - Inactivity

3 - Anxiety

4 - Social Withdrawal

5 - Distractibility

6 - Elevated Mood

7 - Activity

8 - Relaxation

9 - Interaction

10 - Concentration

RESULTS AND DISCUSSION

Demographic, medical, dietary, anthropometric and biochemical information was obtained for each subject. Subjects were evaluated on nausea and vomiting, appetite, food intake and mood status with or without Marinol, referred to hereafter as THC (tetrahydrocannabinol). Data on each subject is presented beginning with a medical and dietary history followed by anthropometric and biochemical information. The results of the nutrient analysis and ratings for nausea and vomiting, appetite, food intake and mood status are then examined.

Demographic Information

Three female and two male subjects comprised the sample population. Information including age, sex, and tumor type and stage is presented for each patient. Ages of subjects ranged from 29 to 60 yr. with a mean ± SD age of 46 ± 13 yr. All subjects were Caucasian and from southwest Virginia or West Virginia. Three subjects worked throughout the study, while two did not.

CASE #1

Medical and dietary history

This subject is a 60 year old male with a diagnosis of Hodgkins' disease-mixed cellular type, stage 1. Diagnosis was based on a CT (computed tomagraphy) scan which showed a retroperitoneal mass and subsequent biopsy of this mass in 10/87. He had a prior 4-5 week history of increasing chills, aches, shortness of breath, anorexia, and weight loss. His chemotherapy consisted of Mustard until 11/30/87 at which time it was replaced with Cytoxan. He also received Vincristine, Prednisone and Procarbazine. He received radiation following the chemotherapy for five weeks. His emetigenic potential was rated as SEVERE. Performance status was rated at 90 % on entry into the study at 11/6/87.

Diet history revealed a usual body weight of 230 pounds and a height of 5 feet 7 1/2 inches. Frame size was estimated to be small with a desirable body weight range of 146 - 158 pounds. On entry into the study the subject was 139 % of his desirable body weight. A prior five week weight loss of approximately 20 pounds was noted. Problems related to eating included changes in taste, food aversions, lack of appetite and an uncomfortable feeling when eating.

Anthropometric and biochemical data

The subject weighed 211.5 pounds on entry into the study and after six months in the study weighed 210 pounds. All biochemical levels, reported as means, were within normal limits with the exception of slightly lower values for creatinine and hemoglobin. The lower hemoglobin values observed were most likely due to the effect of chemotherapy on bone marrow. The normal range, mean ± SD and observed range for the biochemical tests are presented in Table 1.

Nutrient Analysis

When not receiving chemotherapy, this subject consumed almost one third of his calories in the form of alcohol. His particular chemotherapy prohibited the use of alcohol, therefore he rarely drank any alcohol while he received chemotherapy. The dietary intakes were analyzed for total kilocalories (kcal) as well as the contribution of kcal from protein, carbohydrate, fat and alcohol to the total. The comparison for caloric intake for different treatments was based on kilocalories contributed by food, excluding alcoholic beverages, since the consumption of the latter was dependent on whether or not chemotherapy was given.

Daily caloric intake and the percent of total kilocalories (kcal) from various nutrients either with or without THC and chemotherapy are presented in Table 2. Of the total kilocalories consumed with THC and without chemotherapy, 237

Table 1. Case # 1: Results of SMA[a] 12, hemoglobin, white blood cell and platelet

TEST	NORMAL LIMITS[b]	MEAN ± SD AND RANGE n = 9			
Total Protein	6.0-8.5	6.66	±	0.28	6.3-7.0
Albumin	2.6-5.2	3.74	±	0.25	3.2-4.0
Calcium	8.5-10.5	8.98	±	0.28	8.5-9.2
Phosphorous	2.5-4.5	3.52	±	0.37	3.0-4.1
Cholesterol	140-270	181.67	±	22.16	151-218
Glucose	72-128	101.44	±	5.44	90-109
Uric Acid	2.2-9.0	5.79	±	0.99	4.6-6.3
Creatinine	0.7-1.4	0.6	±	0.12	0.4-0.8
Total Bilirubin	0.2-1.2	0.34	±	0.12	0.2-0.6
Alk. Phos.	30-115	83.89	±	8.85	70-97
LDH	100-225	155.78	±	27.78	112-209
SGOT	7-40	21.67	±	3.92	17-29
WBC (X 10^3)	7.8±3.0	7.67	±	1.63	5.4-9.8
Hemoglobin	16±2	13.19	±	0.58	12.4-14.4
Platelet (X 10^3)	140-440	239.11	±	62.91	169-392

[a]SMA = sequential multiple analysis profile

[b]Normal limits were obtained from Roanoke Memorial Hospitals

Table 2. Case # 1: Distribution of total caloric intake with or without THC[a] and chemotherapy

TREATMENT			CALORIC INTAKE FROM					
THC	CHEMOTHERAPY	n[b]	Protein	Carbohydrate	Fat	Alcohol	Total Caloric Intake	Food[c] kcal
+	-	7	237 ± 64[d] (8.8%)[e]	1010 ± 249 (37.3%)	638 ± 236 (23.6%)	822 ± 337 (30.4%)	2707 ± 746	1355 ± 376
+	+	17	228 ± 51 (15.7%)	588 ± 130 (40.5%)	615 ± 96 (42.3%)	22 ± 88 (1.5%)	1453 ± 249	1418 ± 202
-	-	20	307 ± 118 (10.7%)	1040 ± 272 (36.2%)	682 ± 263 (23.7%)	847 ± 328 (29.4%)	2876 ± 882	1512 ± 461
-	+	4	125 ± 41 (16.3%)	413 ± 157 (54.1%)	226 ± 110 (29.6%)	0 (0%)	764 ± 273	764 ± 273

[a]THC = tetrahydrocannabinol

[b]n = number of daily intakes that were recorded

[c]caloric intake from food excluding all calories from alcoholic beverages (i.e. alcohol, protein and carbohydrate kilocalories)

[d]Mean ± SD

[e]percent of total kilocalories

were from protein, 1010 were from carbohydrate, 638 were from fat, and 822 were from alcohol. The distribution of total kilocalories was 8.8% from protein, 37.3% from carbohydrate, 23.6% from fat, and 30.4% from alcohol. Average daily caloric intake from food was 1355 kcal.

Of the total kilocalories ingested with THC and with chemotherapy, 228 were from protein, 588 were from carbohydrate, 615 were from fat, and 22 were from alcohol. The distribution of total kilocalories was 15.7% from protein, 40.5% from carbohydrate and 42.3% from fat. Despite instruction not to drink alcoholic beverages during chemotherapy, the subject did take in 1.5% of his total caloric intake from alcohol. Average caloric intake from food was 1418 kcal.

Of the total kilocalories consumed without THC and chemotherapy, 307 were from protein, 1040 were from carbohydrate, 682 were from fat, and 847 were from alcohol. The distribution of total kilocalories was 10.7% from protein, 36.2% from carbohydrate, 23.7% from fat and 29.4% from alcohol. Average caloric intake from food was 1512 kcal.

Of the total kilocalories consumed without THC and with chemotherapy, 125 were from protein, 413 were from carbohydrate, and 226 were from fat. The distribution of kilocalories was 16.3% from protein, 54.1% from carbohydrate, and 29.6% from fat. Average caloric intake was 764 kcal. Alcohol did not contribute to the caloric intake, thus the aver-

age caloric intake from food equals total kilocalories.

Table 3 compares the effect of THC therapy on the distribution of total caloric intake independent of chemotherapy. Protein kilocalories and percent of total intake were 230 and 12.7% with THC and 297 and 11.7% without THC. Carbohydrate kilocalories and percent of total intake were 711 and 39.1% with THC and 935 and 36.8% without THC. Fat kilocalories and percent of total intake were 622 and 34.2% with THC and 606 and 23.8% without THC. Average alcohol kilocalories and percent of total intake were 255 and 14.0% with THC and 705 and 27.7% without THC. Average caloric intake from food was 1399 kcal with THC and 1387 kcal without THC.

Consumption of food calories (nonalcoholic) was approximately the same regardless of receiving THC. This is interesting since out of 24 dietary intakes without THC, only 4 were days when chemotherapy was given. On the remaining 20 days no chemotherapy was given. One would expect the caloric intake from food to be greater when no chemotherapy was given. When THC was given, 17 of 24 days were days when chemotherapy was given, with the remaining 7 days with no chemotherapy. Instead of seeing a reduction in caloric intake, an observed maintenance of food caloric intake is seen, despite the high number of treatment days. The percent of protein composition remained relatively constant in with or without THC, whereas carbohydrate kcal were higher during THC treatment. The percent fat kcal was lower without

Table 3. Case # 1: Distribution of total caloric intake with or without THC[a] independent of chemotherapy

TREATMENT		CALORIC INTAKE FROM					
THC	n[b]	Protein	Carbohydrate	Fat	Alcohol	Total Caloric Intake	Food[c] kcal
+	24	230 ± 55[d] (12.7%)[e]	711 ± 259 (39.1%)	622 ± 151 (34.2%)	255 ± 413 (14.0%)	1819 ± 714	1399 ± 267
-	24	297 ± 125 (11.7%)	935 ± 347 (36.8%)	606 ± 298 (23.8%)	705 ± 435 (27.7%)	2543 ± 1132	1387 ± 516

[a]THC = tetrahydrocannabinol

[b] = number of daily intakes that were recorded

[c]caloric intake from food excluding all calories from alcoholic beverages (i.e. alcohol, protein and carbohydrate kilocalories)

[d]Mean ± SD

[e]percent of total calories

THC as compared to with THC. It does appear that THC stimulated appetite during chemotherapy, resulting in consistent caloric intake.

Average ratings for nausea and vomiting, food intake and appetite

Prior to receiving THC, this subject reported nausea and vomiting with chemotherapy. Average ratings for nausea and vomiting, appetite and food intake are presented in Table 4. The subject's average rating for nausea and vomiting with THC was 0.63 and without THC was 0.27. He experienced some nausea, but did not vomit due to chemotherapy while on THC. His average rating for food intake was 2.05 with THC and 2.18 without THC. His average rating for appetite with THC was 1.73 and 1.98 without THC. His ratings stayed about the same on or off THC, even though he was receiving a highly emetic chemotherapy regimen most of the time while receiving THC.

During the five days that he received chemotherapy without THC, the average ratings for nausea and vomiting were much higher, reported at 1.13 and lower for food intake and appetite at 1.07 and 0.47, respectively. This indicated that he subjectively felt that nausea and vomiting was worse, and therefore his appetite and food intake were adversely affected.

Table 4. Case # 1: The effect of THC* on average ratings for nausea and vomiting, food intake and appetite

	THC	
	+	-
	n = 273	n = 189
NAUSEA & VOMITING	0.63	0.27
0 - No vomiting		
1 - Nausea present, but not disabling		
2 - Nausea impairing normal activities		
3 - Vomiting		
FOOD INTAKE	2.05	2.18
0 - No food intake		
1 - Less than usual		
2 - Average		
3 - More than usual		
APPETITE	1.73	1.98
0 - None		
1 - Decreased		
2 - Same		
3 - Increased		

*THC = tetrahydrocannabinol

Frequency ratings for mood status

Frequency ratings for mood status expressed as percent of total responses with or without THC are presented in Table 5. The most common moods with THC were interaction (34.5%), followed by activity (26.2%) and inactivity (18.1%). The same moods were also most common without THC, interaction (34.9%), inactivity (23.4%) and activity (22.9%). This subject continued to work full-time throughout his chemotherapy and was active during the day. In the evening, he usually felt tired and therefore was relatively inactive. This explains why two opposite moods were seen with about the same frequency, as moods were rated three times a day. The ratings for moods suggest that the subject felt more active while receiving THC, even though he was on chemotherapy the majority of these days. The moods reported by the other person residing with the subject support the values that the subject reported.

Table 5. Case # 1: The effect of THC[a] on frequency ratings for mood status expressed as percent of total responses

	THC	
	+	-
	self / other[b]	self / other
	n=568 n=564	n=410 n=413
1 - Depression	0.7 / 0.7	3.4 / 4.4
2 - Inactivity	18.1 / 18.8	23.4 / 22.8
3 - Anxiety	1.4 / 1.4	6.3 / 8.2
4 - Social withdrawal	1.2 / 1.1	1.5 / 1.2
5 - Distractibility	0 / 0.7	0 / 0
6 - Elevated Mood	0.5 / 1.1	0 / 0.2
7 - Activity	26.2 / 25.1	22.9 / 22.3
8 - Relaxation	17.3 / 17.2	7.6 / 8.2
9 - Interaction	34.5 / 33.3	34.9 / 32.7
10 - Concentration	0 / 0.5	0 / 0
	99.9% / 99.9%	100% / 100%

[a]THC = tetrahydrocannabinol

[b]"self" represents responses made by subject and "other" represents responses made by the person residing with subject

CASE #2

Medical and dietary history

This subject is a 29 year old female who was diagnosed with carcinoma of the right breast, having 10 of 20 lymph nodes positive. In 8/87 a right axillary dissection was performed followed by radiation therapy. She was positive for estrogen and progesterone receptors. She received radiation in 10/87. She was on Methotrexate, Cytoxan, 5-Flourouracil and Tamoxifen from 9/87 until 10/87. Her chemotherapy was then changed to Cytoxan, Adriamycin, 5-Flourouracil and Tamoxifen. The emetigenic potential was rated as SEVERE. TNM staging was T2NOMO. Performance status was rated at 80% on entry into the study.

Diet history revealed a usual body weight of 140 pounds and a height of 5 feet 6 inches. Frame size was estimated to be small with a desirable body weight range 123-136 pounds. On entry into the study this subject was 108 % of her desirable body weight. A prior two month weight gain of six pounds was reported. Problems related to eating included food aversions (fish), nausea, vomiting and constipation. Severe nausea and vomiting generally occurred with chemotherapy, sometimes lasting up to 36 hours after treatments.

Anthropometric and biochemical data

This subject demonstrated a minor weight loss during her participation in the study, dropping from 140.5 pounds to 137 pounds in three months. All biochemical levels, reported as means, were within normal limits with the exception of slightly lower values for hemoglobin, WBC and cholesterol. The lower hemoglobin values are most likely due to the effect of chemotherapy on the bone marrow. The normal range, mean ± SD and observed range for the biochemical tests are presented in Table 6.

Nutrient Analysis

Daily caloric intake and the percent of total kilocalories (kcal) from various nutrients with or without THC and without chemotherapy are presented in Table 7. Unfortunately no dietary intakes were recorded on days that chemotherapy was given, as no days were chosen that coincided with chemotherapy treatment using the calendar given to subjects to record intakes.

Of the total kilocalories consumed with THC, 322 were from protein, 764 were from carbohydrate and 720 were from fat. Average total caloric intake was 1806 kcal. The distribution of total kilocalories was 17.8% from protein, 42.3% from carbohydrates and 39.9% from fat.

Of the total kilocalories ingested without THC, 262 were from protein, 575 were from carbohydrate and 568 were from

Table 6. Case # 2: Results of SMA[a] 12, hemoglobin, white blood cell and platelet

TEST	NORMAL LIMITS[b]	MEAN ± SD AND RANGE n = 2			
Total Protein	6.0-8.5	7.20	±	0.50	6.7-7.7
Albumin	2.6-5.2	4.10	±	0.40	3.7-4.5
Calcium	8.5-10.5	9.80	±	0	9.8
Phosphorous	2.5-4.5	3.35	±	0.45	2.9-3.8
Cholesterol	140-270	131.50	±	12.50	119-144
Glucose	72-128	97.50	±	12.50	85-110
Uric Acid	2.2-9.0	4.40	±	0.80	3.6-5.2
Creatinine	0.7-1.4	0.70	±	0	0.7
Total Bilirubin	0.2-1.2	0.35	±	.06	0.29-0.4
Alk. Phos.	30-115	43.00	±	5.00	38-48
LDH	100-225	173.50	±	28.50	145-202
SGOT	7-40	33.00	±	5.00	28-38
WBC (X 10^3)	7.8±3.0	5.35	±	0.95	4.4-6.3
Hemoglobin	14±2	12.20	±	0	12.2
Platelet (X 10^3)	140-440	203.50	±	15.50	188-219

[a]SMA = sequential multiple analysis profile

[b]Normal limits were obtained from Roanoke Memorial Hospitals

Table 7. Case # 2: Distribution of total caloric intake with or without THC[a] and without chemotherapy

TREATMENT		CALORIC INTAKE FROM				Total Caloric Intake
THC	n[b]	Protein	Carbohydrate	Fat	Alcohol	
+	10	322 ± 60[c] (17.8%)[d]	764 ± 265 (42.3%)	720 ± 112 (39.9%)	0 (0%)	1806 ± 372
-	14	262 ± 92 (18.6%)	575 ± 119 (40.9%)	568 ± 181 (40.4%)	0 (0%)	1405 ± 326

[a]THC = tetrahydrocannabinol

[b] = number of daily intakes that were recorded

[c]Mean ± SD

[d]percent of total calories

fat. Average total caloric intake was 1405 kcal. The distribution of total kilocalories was 18.6% from protein, 40.9% from carbohydrates and 40.4% from fat.

This subject averaged about 400 more calories a day more when she received THC. The percent contributed by each nutrient was approximately the same in both groups, although the total amount of each nutrient was higher. Prior to entry into the study this subject had severe nausea and vomiting and was unable to resume normal eating for a few days following chemotherapy. The times when she received THC were during her chemotherapy cycle and included days where her intake was previously reported to be lower. Food intake was increased during the time she received THC, even though these periods corresponded to chemotherapy cycles.

Average ratings for nausea and vomiting, food intake and appetite

Average ratings for nausea and vomiting, food intake and appetite are presented in Table 8. Prior to receiving THC, the subject reported severe nausea and vomiting lasting for up to 36 hours with chemotherapy. She still experienced nausea and some vomiting, but it usually did not last as long as before receiving THC. Her average rating for nausea and vomiting was 0.27 with THC and 0.02 without THC. Her average food intake was rated as 1.43 on THC and 1.35 without THC. Average appetite rating was 1.51 on THC and 1.32

Table 8. Case # 2: The effect of THC[a] on average ratings for nausea and vomiting, food intake and appetite

	THC	
	+	-
	n = 122	n = 108
NAUSEA & VOMITING	0.27	0.02
0 - No vomiting		
1 - Nausea present, but not disabling		
2 - Nausea impairing normal activities		
3 - Vomiting		
FOOD INTAKE	1.43	1.35
0 - No food intake		
1 - Less than usual		
2 - Average		
3 - More than usual		
APPETITE	1.51	1.32
0 - None		
1 - Decreased		
2 - Same		
3 - Increased		

[a]THC = tetrahydrocannabinol

without THC. She seemed to feel better after her chemotherapy treatments and felt her appetite and food intake were greater while receiving THC. This permitted food intake at an earlier time after chemotherapy treatment than without THC. This is supported by the previously noted increase in caloric consumption.

Frequency ratings for mood status

Frequency ratings for mood status expressed as percent of total responses with or without THC are presented in Table 9. The most common moods reported with THC were distractibility (22.4%), activity (20.0%), relaxation (14.8%) and elevated mood (12.4%). The most common moods reported without THC were activity (23.4%), elevated mood (15.1%), relaxation (14.6%) and interaction (13.0%). The moods reported were similar regardless of THC. The main difference was the increase in distractibility while receiving THC. Elevated mood was rated higher while not on THC. This subject was apprehensive about taking THC which may have caused her anxiety during the study, even when not receiving the drug. The moods reported by the other person are similar to those reported by the subject.

This subject stated that she noticed a big improvement while on the THC during her treatments, but was experiencing moods which she attributed to THC, though these same moods were also found to occur without THC. This subject with-

Table 9. Case # 2: The effect of THC[a] on frequency ratings for mood status expressed as percent of total responses

	THC	
	+	-
	self / other[b]	self / other
	n=210 n=188	n=192 n=149
1 - Depression	5.7 / 4.8	4.2 / 0.7
2 - Inactivity	6.2 / 4.8	5.7 / 4.7
3 - Anxiety	3.8 / 2.7	2.1 / 1.3
4 - Social withdrawal	4.8 / 2.7	1.6 / 5.4
5 - Distractibility	22.4 / 23.9	11.5 / 10.7
6 - Elevated Mood	12.4 / 13.3	15.1 / 14.8
7 - Activity	20.0 / 24.5	23.4 / 27.5
8 - Relaxation	14.8 / 11.7	14.6 / 18.8
9 - Interaction	7.6 / 10.1	13.0 / 14.1
10 - Concentration	2.4 / 1.6	8.9 / 2.0
	100.1% / 100.1%	100.1% / 100%

[a]THC = tetrahydrocannabinol

[b]"self" represents responses made by subject and "other" represents responses made by person residing with the subject

drew from the study in April, 1988 , stating that she felt "paranoid" while on the THC.

CASE #3

Medical and dietary history

This subject is a 58 year old female diagnosed in 1983 with adenocarcinoma, infiltrative, ductal cell type, metastatic, with 5 out of 18 nodes positive. Her estrogen receptors were negative. At that time she was treated with surgery (radical mastectomy) and adjuvant chemotherapy. She received radiation in 1985 and 1986. In 12/86 a tumor mass was present which showed incomplete regression in the supraclavicular area. In 1/87, the right anterior chest wall showed some progression. A bone scan in 8/87 was indicative of metastatic bone disease from the primary breast carcinoma. She also has had persistent lymphedema since 1/86. TNM staging was TXN2M0. She was treated with Etoposide(VP-16) and Methotrexate which have a MODERATE emetigenic potential. Performance status was rated at 60% on entry into the study.

Diet history revealed a usual body weight of 140 pounds and a height of 5 feet 2 inches. Frame size was estimated to be medium with a desirable body weight range of 121-135 pounds. On entry into the study this subject was 88% of her desirable body weight. A prior five month weight loss of approximately 30 pounds was noted. Current appetite was rated as being worse than normal. Problems related to eating included difficulty in swallowing, choking, changes in

taste, food aversions and lack of appetite.

Anthropometric and biochemical data

This subject demonstrated minor weight loss during her participation in the study, going from 113 to 108 pounds in three months. All biochemical levels, reported as means, (means) were within normal limits with the exception of slightly lower values for total protein, calcium, hemoglobin, WBC and cholesterol. These values were probably due to the combined effect of chemotherapy and compromised nutritional status, evidenced by the previous weight loss. The normal range, mean ± SD and observed range for the biochemical tests are presented in Table 10.

Nutrient Analysis

Daily caloric intake and the percent of total kilocalories (kcal) from various nutrients either with or without THC and chemotherapy is presented in Table 11. Of the total kilocalories consumed with THC and without chemotherapy, 175 were from protein, 571 were from carbohydrate and 383 were from fat. Average daily caloric intake was 1129 kcal. The distribution of total calories was 15.5% from protein, 50.5% from carbohydrates and 33.9% from fat.

Of the total kilocalories consumed with THC and with chemotherapy, 149 were from protein, 352 were from carbohydrate and 306 were from fat. Average daily caloric intake

Table 10. Case #3: Results of SMA[a] 12, hemoglobin, white blood cell and platelet

TEST	NORMAL LIMITS[b]	MEAN ± SD AND n = 3	RANGE
Total Protein	6.0-8.5	5.33 ± 0.13	5.2-5.5
Albumin	2.6-5.2	3.37 ± 0.13	3.2-3.5
Calcium	8.5-10.5	8.37 ± 0.05	8.3-8.4
Phosphorous	2.5-4.5	3.97 ± 0.21	3.7-4.2
Cholesterol	140-270	130.67 ± 5.25	126-138
Glucose	72-128	93.33 ± 4.19	89-99
Uric Acid	2.2-9.0	3.9 ± 0.22	3.7-4.2
Creatinine	0.7-1.4	0.83 ± 0.05	0.8-0.9
Total Bilirubin	0.2-1.2	0.43 ± 0.04	0.4-0.48
Alk. Phos.	30-115	98.67 ± 14.52	86-119
LDH	100-225	177.00 ± 3.56	174-182
SGOT	7-40	31.33 ± 3.30	29-36
WBC (X 10^3)	7.8±3.0	4.10 ± 1.56	2.8-6.3
Hemoglobin	14±2	10.66 ± 0.76	9.9-11.7
Platelet (X 10^3)	140-440	134.33 ± 21.64	104-153

[a]SMA=sequential multiple analysis profile

[b]Normal limits were obtained from Roanoke Memorial Hospitals

Table 11. Case # 3: Distribution of total caloric intake with or without THC[a] and chemotherapy

TREATMENT			CALORIC INTAKE FROM				
THC	CHEMOTHERAPY	n[b]	Protein	Carbohydrate	Fat	Alcohol	Total Caloric Intake
+	-	14	175 ± 66[c] (15.5%)[d]	571 ± 178 (50.5%)	383 ± 155 (33.9%)	0 (0%)	1129 ± 349
+	+	1	149 (18.4%)	352 (43.6%)	306 (38.0%)	0 (0%)	807
-	-	17	161 ± 57 (14.9%)	539 ± 180 (49.9%)	381 ± 151 (35.3%)	0 (0%)	1081 ± 341
-	+	1	93 (13.6%)	451 (65.8%)	141 (20.6%)	0 (0%)	685

[a]THC = tetrahydrocannabinol

[b]n = number of daily intakes that were recorded

[c]Mean ± SD

[d]percent of total kilocalories

was 807 kcal. The distribution of total calories was 18.4% from protein, 43.6% from carbohydrates and 38.0% from fat.

Of the total kilocalories consumed without THC and chemotherapy, 161 were from protein, 539 were from carbohydrate and 381 were from fat. Average daily caloric intake was 1081 kcal. The distribution of total calories was 14.9% from protein, 49.9% from carbohydrates and 35.3% from fat.

Of the total kilocalories consumed without THC and with chemotherapy, 93 were from protein, 451 were from carbohydrate and 141 were from fat. Average daily caloric intake was 685 kcal. The distribution of total calories was 13.6% from protein, 65.8% from carbohydrates and 20.6% from fat.

Total caloric intake was greater with THC when chemotherapy was given than without THC. Caloric intake during her chemotherapy cycle with THC was approximately the same as non-treatment periods without THC. This subject was able to maintain her caloric intake during the treatment period, which reduced the rapid weight loss she previously experienced from inadequate intake during this time.

Table 12 compares the effect of THC therapy on the distribution of total caloric intake independent of chemotherapy. Protein kilocalories and percent of total intake were 174 and 15.7% with THC and 157 and 14.8% without THC. Carbohydrate kilocalories and percent of total intake were 556 and with THC 50.2% and 534 and 50.4% without THC. Fat kilocalories and percent of total intake were 378 and 34.1% with

Table 12. Case # 3: Distribution of total caloric intake with or without THC[a] independent of chemotherapy

TREATMENT		CALORIC INTAKE FROM				Total Caloric Intake
THC	n[b]	Protein	Carbohydrate	Fat	Alcohol	
+	15	174 ± 64[c]	556 ± 180	378 ± 150	0	1108 ± 347
		(15.7%)[d]	(50.2%)	(34.1%)	(0%)	
-	18	157 ± 58	534 ± 176	368 ± 158	0	1059 ± 342
		(14.8%)	(50.4%)	(34.8%)	(0%)	

[a]THC = tetrahydrocannabinol

[b] = number of daily intakes that were recorded

[c]Mean ± SD

[d]percent of total calories

THC and 368 and 34.8% without THC. Average caloric intake from food was 1108 kcal with THC and 1059 without THC.

This subject consumed approximately the same number of calories and composition of nutrients regardless of being on THC. Prior to receiving THC, the subject reported that intake was lower for a few days following chemotherapy. Only 2 days were reviewed when the patient received chemotherapy, and the caloric intake was much lower for both days.

Average ratings for nausea and vomiting, food intake and appetite

This subject began taking THC on 11/7/87, however, it was discontinued on 11/11/87 due to nausea and vomiting. THC therapy was restarted on 11/24/87, as the physician felt that the nausea and vomiting observed was due to the chemotherapy treatment received on 11/6/87. She continued to receive THC since that time, usually for two weeks a month during her chemotherapy cycle. Prior to THC she reported nausea and vomiting with chemotherapy, which sometimes lasted 24 - 48 hours. Since being on THC she experienced either mild nausea or no nausea from her treatment.

Average ratings for nausea and vomiting, food intake and appetite are presented in Table 13. She subjectively reported an average rating of 0.10 with THC and 0.14 without THC for nausea and vomiting. The average ratings for her

Table 13. Case # 3: The effect of THC* on average ratings for nausea and vomiting, food intake and appetite

	THC	
	+	-
	n = 147	n = 159
NAUSEA & VOMITING	0.10	0.14
0 - No vomiting		
1 - Nausea present, but not disabling		
2 - Nausea impairing normal activities		
3 - Vomiting		
FOOD INTAKE	1.80	2.02
0 - No food intake		
1 - Less than usual		
2 - Average		
3 - More than usual		
APPETITE	1.85	2.04
0 - None		
1 - Decreased		
2 - Same		
3 - Increased		

*THC = tetrahydrocannabinol

food intake were 1.80 with THC and 2.02 without THC. Her average appetite ratings were 1.85 with THC and 2.04 without THC. This data indicates that she had only a slight decrease in food intake and appetite while on THC, even though this also occurred during her chemotherapy cycle. Despite these ratings, her caloric intake was approximately the same regardless of THC. She seemed to tolerate her chemotherapy well on THC, with much less nausea and no vomiting. She also was able to eat sooner following her chemotherapy while receiving THC. At times she suffered from a sore mouth due to chemotherapy which affected her food intake. Her husband stated that her food intake and appetite improved while receiving THC.

Frequency ratings for mood status

Frequency ratings for mood status expressed as percent of total responses with or without THC are presented in Table 14. The moods reported by the subject to be the most common with THC were activity (68.3%) and relaxation (22.0%). The same moods were reported without THC with activity (83.2%) slightly higher and relaxation (12.6%) a little lower. This showed that she was able to remain active and even felt more relaxed during her chemotherapy cycle, with little disruption in her lifestyle. The moods reported by her husband indicate that she was less active, but more relaxed. Her husband felt that in spite of

Table 14. Case # 3: The effect of THC[a] on frequency ratings for mood status expressed as percent of total responses

	THC	
	+	-
	self / other[b]	self / other
	n=186 n=217	n=190 n=255
1 - Depression	1.6 / 0.9	0.5 / 0.4
2 - Inactivity	8.1 / 14.8	2.6 / 4.7
3 - Anxiety	0 / 0.5	1.1 / 0.8
4 - Social withdrawal	0 / 0	0 / 0
5 - Distractibility	0 / 0	0 / 0
6 - Elevated Mood	0 / 0	0 / 0
7 - Activity	68.3 / 47.8	83.2 / 63.5
8 - Relaxation	22.0 / 36.0	12.6 / 30.6
9 - Interaction	0 / 0	0 / 0
10 - Concentration	0 / 0	0 / 0
	100% / 100.1%	100% / 100%

[a]THC = tetrahydrocannabinol

[b]"self" represents responses made by subject and "other" represents responses made by the person residing with subject

her progressive disease, she maintained a very good attitude over the last few months on THC and remained relatively active. The subject died on 5/23/88 due to the progression of her disease.

CASE #4

Medical and dietary history

This subject is a 51 year old male with a diagnosis of adenocarcinoma of the body and tail of the pancreas, metastatic to the liver which was diagnosed in 7/87. At that time he reported weighing 178 1/2 pounds, down from a normal body weight of 195 pounds in 4/87. He had complications of gastrointestinal bleeding in 9/87 which required surgical intervention. At the time of surgery his diagnosis included duodenal ulcer with GI bleeding X3, deep venous thrombosis in right leg (right iliac vein) in addition to the pancreatic cancer. A port-a-cath was placed for chemotherapy treatment. TNM staging was TXNXM1. Chemotherapy was begun on 8/1/87 in the form of a continuous infusion (30 days on - 30 days off) of 5-Fluorouracil (300mg/day). The emetigenic potential was rated as MODERATE. Performance status was rated at 70% on entry into the study.

Diet history revealed a usual body weight of 195 pounds and a height of 6 feet 2 inches. Frame size was estimated as small with a desirable body weight range of 158 - 172 pounds. On entry into the study this subject was 79% of his desirable body weight. A prior eight month weight loss of approximately 65 pounds was noted. The subject stated that his appetite was worse than usual, due to feeling sick while on chemotherapy and that usual food did not taste right.

Other problems related to eating were food aversions, nausea, vomiting, diarrhea, constipation and changes in salivation. Major food aversions (particularly meats) caused him to eat only soup, milk, juice, oatmeal and eggs.

Anthropometric and biochemical data

This subject demonstrated a weight loss in the last part of the study which coincided with the progression of his disease. On entry into the study, he weighed 129.5 pounds which he maintained for one month. Weight loss occurred after that point and three months later he weighed 111 pounds. Many biochemical levels, reported as means, were not within normal limits. This was expected since at the time of diagnosis, metastases was noted in the liver and other organs. The normal range, mean ± SD and observed range for the biochemical tests are presented in Table 15.

Nutrient Analysis

Daily caloric intake and the percent of total kilocalories from various nutrients either with or without THC and chemotherapy are presented in Table 16. Of the total kilocalories consumed with THC and without chemotherapy, 235 were from protein, 684 were from carbohydrate and 558 were from fat. Average caloric intake was 1477 kcal. The distribution of total kilocalories was 15.9% from protein, 46.3% from carbohydrate and 37.8% from fat.

Table 15. Case # 4: Results of SMA 12[a], hemoglobin, white blood cell and platelet

TEST	NORMAL LIMITS[a]	MEAN ± SD AND n = 3	RANGE
Total Protein	6.0-8.5	5.63 ± 0.33	5.2-6.0
Albumin	2.6-5.2	2.93 ± 0.09	2.8-3.0
Calcium	8.5-10.5	8.80 ± 0.43	8.2-9.2
Phosphorous	2.5-4.5	3.53 ± 0.40	3.2-4.1
Cholesterol	140-270	235.33 ± 8.73	226-247
Glucose	72-128	194.00 ± 37.21	147-238
Uric Acid	2.2-9.0	4.47 ± 0.76	3.4-5.1
Creatinine	0.7-1.4	0.83 ± 0.05	0.8-0.9
Total Bilirubin	0.2-1.2	0.18 ± 0.10	.08-.32
Alk. Phos.	30-115	158.00 ± 9.63	148-171
LDH	100-225	263.33 ± 113.29	172-423
SGOT	7-40	51.67 ± 10.78	40-66
WBC (X 10^3)	7.8±3.0	6.73 ± 1.59	4.5-8.1
Hemoglobin	14±2	10.50 ± .73	9.5-11.2
Platelet (X 10^3)	140-440	205 ± 42.36	147-247

[a]SMA = sequential multiple analysis profile

[b]Normal limits were obtained from Roanoke Memorial Hospitals

Table 16. Case # 4: Distribution of total caloric intake with or without THC[a] and chemotherapy

TREATMENT			CALORIC INTAKE FROM				
THC	CHEMOTHERAPY	n[b]	Protein	Carbohydrate	Fat	Alcohol	Total Caloric Intake
+	-	2	235 ± 18[c] (15.9%)[d]	684 ± 39 (46.3%)	558 ± 61 (37.8%)	0 (0%)	1477 ± 37
+	+	10	193 ± 65 (20.7%)	379 ± 116 (40.6%)	362 ± 104 (38.8%)	0 (0%)	934 ± 326
-	-	6	203 ± 46 (16.8%)	467 ± 148 (38.6%)	539 ± 176 (44.6%)	0 (0%)	1209 ± 359
-	+	3	266 ± 43 (15.3%)	767 ± 133 (44.0%)	710 ± 130 (40.7%)	0 (0%)	1743 ± 289

[a]THC = tetrahydrocannabinol

[b]n = number of daily intakes that were recorded

[c]Mean ± SD

[d]percent of total kilocalories

Of the total kilocalories consumed with THC and chemotherapy, 193 were from protein, 379 were from carbohydrate and 362 were from fat. Average caloric intake was 934. The distribution of total kilocalories was 20.7% from protein, 40.6% from carbohydrate and 38.8% from fat.

Of the total kilocalories consumed without THC and chemotherapy, 203 were from protein, 467 were from carbohydrate and 539 were from fat. Average caloric intake was 1209 kcal. The distribution of total kilocalories was 16.8% from protein, 38.6% from carbohydrate and 44.6% from fat.

Of the total kilocalories consumed without THC and with chemotherapy, 266 were from protein, 767 were from carbohydrate and 710 were from fat. Average caloric intake was 1743 kcal. The distribution of total kilocalories was 15.3% from protein, 44.0% from carbohydrate and 40.7% from fat.

Table 17 compares the effect of THC therapy on the distribution of total caloric intake independent of chemotherapy. Protein calories and percent of total intake were 200 and 19.5% with THC and 213 and 15.5% without THC. Carbohydrate calories and percent of total intake were 430 and 42.0% with THC and 567 and 41.2% without THC. Fat calories and percent of total intake were 394 and 38.5% with THC and 596 and 43.3% without THC. The carbohydrate and fat calories were higher without THC, whereas protein calories remained constant. This indicated that the increase in caloric consumption without THC was in the form of carbohydrate and

Table 17. Case # 4: Distribution of total caloric intake with or without THC[a] independent of chemotherapy

TREATMENT		CALORIC INTAKE FROM				Total Caloric Intake
THC	n[b]	Protein	Carbohydrate	Fat	Alcohol	
+	12	200 ± 62[c] (19.5%)[d]	430 ± 156 (42.0%)	394 ± 123 (38.5%)	0 (0%)	1024 ± 356
-	9	213 ± 46 (15.5%)	567 ± 201 (41.2%)	596 ± 181 (43.3%)	0 (0%)	1376 ± 413

[a]THC = tetrahydrocannabinol

[b] = number of daily intakes that were recorded

[c]Mean ± SD

[d]percent of total calories

fat, not protein.

This subject took in less calories when THC was given. The reduction of caloric intake coincided with the progression of his disease. The higher caloric intake without THC corresponded to dietary intakes taken at the beginning of the study, when his intake was greater. During the time he received THC, his disease progressed and his caloric intake became less. He was taken off THC after his chemotherapy ended and found that he had to force himself to eat, and therefore received THC again. He remained on THC for the remainder of the study, which included dietary intakes from the latter part of his disease. He maintained a higher percent protein intake when he was on THC, which is surprising, since he had an aversion to all meats on entry into the study. Even though his intake became less as his disease progressed, he was still able to eat during chemotherapy. This was important since he received chemotherapy for 30 days at a time. Prior to THC therapy, he had difficulty eating during his chemotherapy.

Average ratings for nausea and vomiting, food intake and appetite

Average ratings for nausea and vomiting, food intake and appetite are presented in Table 18. He subjectively reported an average rating of 0.16 with THC and 0.15 without THC for nausea and vomiting. The average ratings for his

Table 18. Case # 4: The effect of THC[a] on average ratings for nausea and vomiting, food intake and appetite

	THC	
	+	-
	n = 140	n = 54
NAUSEA & VOMITING	0.16	0.15
0 - No vomiting		
1 - Nausea present, but not disabling		
2 - Nausea impairing normal activities		
3 - Vomiting		
FOOD INTAKE	1.94	1.74
0 - No food intake		
1 - Less than usual		
2 - Average		
3 - More than usual		
APPETITE	1.96	1.70
0 - None		
1 - Decreased		
2 - Same		
3 - Increased		

[a]THC = tetrahydrocannabinol

food intake were 1.94 with THC and 1.74 without THC. His average appetite was rated at 1.96 with THC and 1.70 without THC. Prior to the THC, he had severe nausea and vomiting with chemotherapy. The ratings indicated that he subjectively felt that his appetite and food intake were better while receiving THC. He was taken off THC in January after his chemotherapy ended, and noticed a decrease in appetite. He stated that "the food just didn't taste the same". He was then restarted on THC and received it continuously for almost three months, without any observable behavioral changes.

Frequency ratings for mood status

Frequency ratings for mood status expressed as percent of total responses with or without THC are presented in Table 19. The most common moods reported with THC were inactivity (56.4%) and relaxation (31.3%). These same moods were reported to be the most common without THC with inactivity (46.6%) slightly lower and relaxation (35.6%) a little higher. On entry into the study, this subject was compromised nutritionally, evidenced by the previous weight loss. He was weak and remained relatively inactive most of the time. The lower inactivity and higher relaxation percentages were recorded when no THC was given and coincided with the beginning of the study when the subject felt better. While on THC, his disease progressed and he became more

Table 19. Case # 4: The effect of THC[a] on frequency ratings for mood status expressed as percent of total responses

	THC	
	+	-
	self / other[b]	self / other
	n=195 n=218	n=73 n=70
1 - Depression	2.1 / 2.3	1.4 / 1.4
2 - Inactivity	56.4 / 56.4	46.6 / 60.0
3 - Anxiety	5.6 / 5.5	5.5 / 4.3
4 - Social withdrawal	0 / 0	0 / 1.4
5 - Distractibility	0 / 0.5	0 / 0
6 - Elevated Mood	0.5 / 0.5	2.7 / 0
7 - Activity	2.1 / 2.8	4.1 / 4.3
8 - Relaxation	31.3 / 31.2	35.6 / 22.9
9 - Interaction	1.5 / 0.5	4.1 / 4.3
10 - Concentration	0.5 / 0.5	0 / 1.4
	100% / 100.2%	100% / 100%

[a]THC = tetrahydrocannabinol

[b]"self" represents responses made by subject and "other" represents responses made by the person residing with subject

inactive. The moods reported by his wife indicated that he was more inactive and less relaxed. His wife felt that he was less nervous while receiving THC. He had been receiving medication to help him relax and found he did not need it while receiving THC. He remained on the THC until his death in April, 1988.

CASE # 5

Medical and dietary history

This subject is a 32 year old female diagnosed in 7/87 with comedocarcinoma of the left breast, with 8 of 26 lymph nodes positive. At that time she underwent a left modified radical mastectomy. Her estrogen and progesterone receptors were negative. Her chemotherapy included 5-Fluorouracil, Adriamycin, and Cytoxan and was rated as having a SEVERE emetigenic potential. TNM stage was T2N1M0. Performance status was rated at 90% on entry into the study on 9/18/87.

Dietary history revealed a usual body weight of 125 - 130 pounds and height of 5 feet 4 inches. Frame size was estimated to be small with a desirable body weight range of 117 - 130 pounds. On entry into the study the subject was 102% of her desirable body weight. A prior five week weight loss of 11 pounds was noted. Other changes in weight during the seven months prior to diagnosis were due to the subject being pregnant in January, 1987 with subsequent miscarriage in April, 1987. Prior to entry into the study the subject experienced nausea and vomiting during her chemotherapy with reduced appetite the following week.

Anthropometric and biochemical data

The subject weighed 126 pounds on entry into the study and after four months weighed 137 pounds. All biochemical levels (means) were within normal limits. The normal range, mean ± SD and observed range for the biochemical tests are presented in Table 20.

Assessment of THC therapy

Unfortunately all data for this subject had been lost by the postal service. However the subject did state that she remained active during her chemotherapy treatments, while receiving THC, and had a high energy level. She discontinued THC after four months, and found that she became sick after chemotherapy, and sometimes remained sick for five days. She found it easier to eat and maintain a good appetite with THC and felt better. She requested to be placed back on THC for the remainder of her chemotherapy.

Table 20. Case #5: Results of SMA[a] 12, hemoglobin, white blood cell and platelet

TEST	NORMAL LIMITS[a]	MEAN ± SD n = 3	OBSERVED RANGE
Total Protein	6.0-8.5	6.47 ± 0.31	6.2-6.9
Albumin	2.6-5.2	3.80 ± 0.22	3.6-4.1
Calcium	8.5-10.5	8.80 ± 0.08	8.7-8.9
Phosphorous	2.5-4.5	3.30 ± 0.37	2.9-3.8
Cholesterol	140-270	194.67 ± 15.84	182-217
Glucose	72-128	85.67 ± 2.62	82-88
Uric Acid	2.2-9.0	3.77 ± 0.66	3.0-4.6
Creatinine	0.7-1.4	0.80 ± 0.14	0.7-1.0
Total Bilirubin	0.2-1.2	0.29 ± 0.13	0.1-0.4
Alk. Phos.	30-115	110.67 ± 11.56	103-127
LDH	100-225	159 ± 29.06	136-200
SGOT	7-40	26.67 ± 9.84	14-38
WBC (X 10^3)	7.8±3.0	6.57 ± 1.28	4.8-7.8
Hemoglobin	14±2	12.87 ± 0.97	11.5-13.7
Platelet (X 10^3)	140-440	273.33 ± 25.95	237-296

[a]SMA=sequential multiple analysis profile

[b]Normal limits were obtained from Roanoke Memorial Hospitals

SUMMARY AND CONCLUSIONS

The intent of this study was to evaluate the use of Marinol (tetrahydrocannabinol) in cancer patients undergoing chemotherapy. Food intake was approximately the same, or greater with THC in most subjects even though the period when THC was given coincided with chemotherapy treatments. The absence of THC during chemotherapy treatment resulted in a decreased food intake. This indicated that subjects were able to maintain caloric intake, while on THC, even though they were receiving emetigenic drugs. The results of maintaining caloric intake led to a reduction in weight loss and even a weight gain was observed in one subject. The subjects who demonstrated large amounts of weight loss prior to entry into the study experienced less weight loss while receiving THC.

The average ratings for nausea and vomiting, food intake and appetite, and the actual caloric intake from food are presented in Table 21. These ratings were subjectively reported by each subject and varied in each case. Some subjects' ratings for appetite and food intake correlated with what was actually consumed, whereas other ratings did not. Even though the category of nausea and vomiting was almost always higher with THC, subjects were able to maintain caloric intake. Three of four subjects consumed more calories while receiving THC, even though this period corresponded to

Table 21. The average ratings for nausea and vomiting, food intake, and appetite, and the average caloric intake from food with and without THC[a]

		AVERAGE RATING			
Case #	THC	Nausea and Vomiting	Food Intake	Appetite	Average Food Kilocalories
1	+	0.63[b]	2.05[c]	1.73[c]	1399
	-	0.27[b]	2.18[c]	1.98[c]	1387
2	+	0.27[b]	1.43[d]	1.51[e]	1806
	-	0.02[b]	1.35[d]	1.32[e]	1405
3	+	0.10[b]	1.80[d]	2.02[f]	1108
	-	0.14[b]	1.85[d]	2.04[f]	1059
4	+	0.16[b]	1.94[d]	1.96[e]	1024
	-	0.15[b]	1.74[d]	1.70[e]	1376

[a]THC=tetrahydrocannabinol

[b]Average values reported indicate subjects had rated themselves between having no vomiting (0) and nausea present, but not disabling (1)

[c]Average values reported indicate subjects had rated themselves between having average (2) to more than usual (3) food intake

[d]Average values reported indicate subjects had rated themselves between having less than average (1) and average (2) food intake

[e]Average values reported indicate subjects had rated themselves between decreased (1) and same (2) appetite

[f]Average values reported indicate subjects had rated themselves between having same (2) and increased (3) appetite

chemotherapy cycles, when one would expect intake to be less. This demonstrated maintenance of food intake. The status of the subject with lower food intake while receiving THC is reflective of his disease progression with accompanying decreased consumption. The effects of disease progression (involvement of organs) and chemotherapy were reflected in some of the biochemical parameters, although most levels were within normal limits.

The moods reported most frequently by subjects while receiving THC were activity, interaction and relaxation. The subject who was most compromised on entry into the study chose inactivity more frequently. One subject, who was apprehensive on entry into the study because of the psychoactive effect of THC, chose distractibility and elevated mood more frequently with and without THC than the other subjects. Depression, social withdrawal and anxiety were chosen less frequently and usually were found to occur around the time of chemotherapy administration. The moods reported by the "other" person were very close to the average ratings reported by the subject. The majority of the moods selected indicated that subjects had positive feelings associated with THC therapy and that the selected dosage did not cause undesirable effects.

Cancer patients undergoing chemotherapy treatments usually have decreased food intake due to the emetigenic effect of the drugs used. This research indicates that appetite

can be stimulated during chemotherapy cycles, resulting in increased food intake. Since chemotherapy regimens may last for long periods of time, it is important to find ways that cancer patients can maintain adequate intake and avoid compromised nutritional status.

More research needs to be done in the area of regulation of appetite to understand the internal mechanisms which are affected in cancer patients. To do this, studies need to be developed that would minimize variables and utilize a larger homogeneous population. These variables include tumor type and stage and chemotherapy regimen used. The design should be a double-blind randomized crossover where subjects would receive either placebo or drug and act as their own controls. Subjects knew they were receiving THC, and could have expected results which altered their responses. The duration of the study should be longer in order to gather more data about what happens to patients during chemotherapy. Dietary intake records should be kept daily to closely monitor subjects during all treatment arms.

The results of this study indicated that THC benefitted cancer patients by increasing food intake during chemotherapy cycles without causing adverse behavioral changes.

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APPENDIX A

INFORMATION ON MARINOL FROM ROXANE LABORATORIES, INC.

Roxane Laboratories Announces...

a new antiemetic option for patients refractory to conventional therapies

MARINOL® capsules (dronabinol) 2.5 mg, 5 mg, 10 mg

(Warning: May be habit forming)

A new treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic agents

First reported effective in 1975...

Since then, confirmed effective in a wide range of therapeutic trials

- Confirmed effective in patients unresponsive to conventional treatment[1,2,5,6,7,8,11,13,16,17,18]
- Confirmed effective in placebo control studies[1,2,4,7,12]
- Confirmed effective in prochlorperazine comparison trials[3,4,5,7,11,12,13]

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CANCER PAIN MANAGEMENT PRODUCTS AND EDUCATION

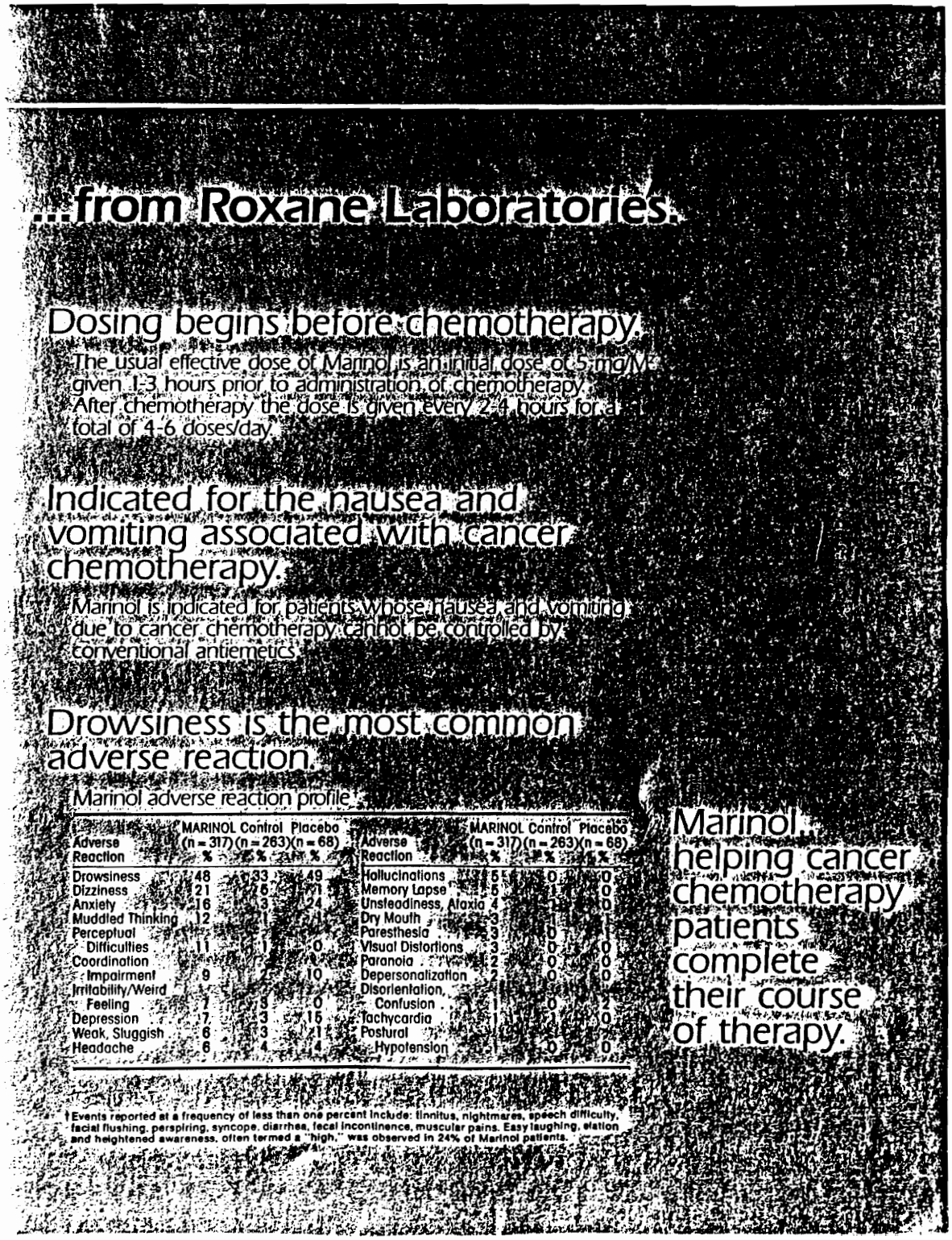
Laboratories, Inc.
Columbus, Ohio 43216

APPENDIX A

INFORMATION ON MARINOL FROM ROXANE LABORATORIES, INC.

APPENDIX A

INFORMATION ON MARINOL FROM ROXANE LABORATORIES, INC.



...from Roxane Laboratories.

Dosing begins before chemotherapy.

The usual effective dose of Marinol is an initial dose of 5 mg/M² given 1-3 hours prior to administration of chemotherapy. After chemotherapy the dose is given every 2-4 hours for a total of 4-6 doses/day.

Indicated for the nausea and vomiting associated with cancer chemotherapy.

Marinol is indicated for patients whose nausea and vomiting due to cancer chemotherapy cannot be controlled by conventional antiemetics.

Drowsiness is the most common adverse reaction.

Marinol adverse reaction profile

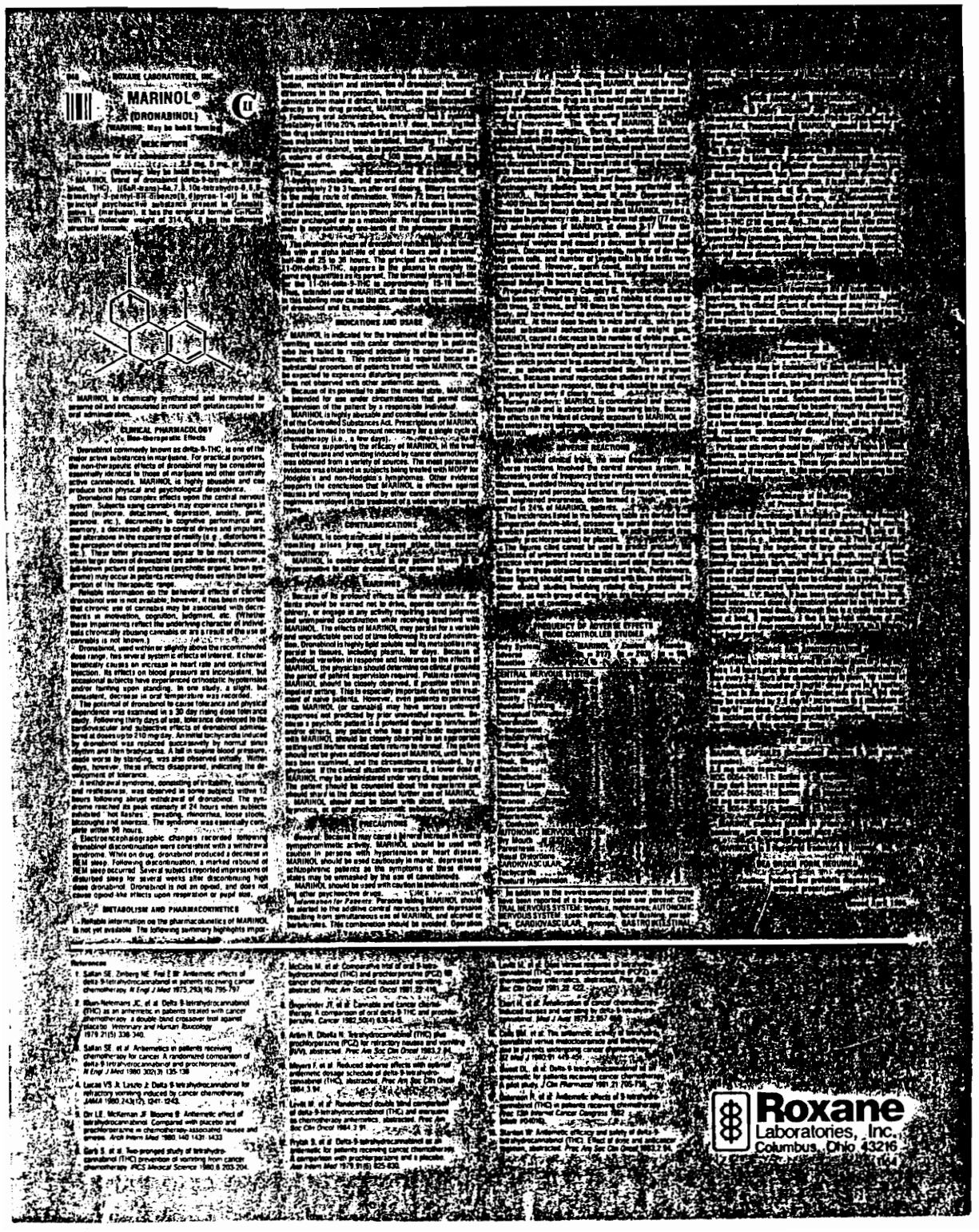
Adverse Reaction	MARINOL % (n = 317)	Control % (n = 263)	Placebo % (n = 68)
Drowsiness	48	33	49
Dizziness	21	6	11
Anxiety	16	3	24
Muddled Thinking	12	2	1
Perceptual Difficulties	11	1	0
Coordination Impairment	9	2	10
Irritability/Weird Feeling	7	3	0
Depression	7	3	15
Weak, Sluggish	6	3	21
Headache	6	4	4
Hallucinations	5	0	0
Memory Lapse	5	1	0
Unsteadiness, Ataxia	4	1	0
Dry Mouth	3	1	1
Paresthesia	3	0	1
Visual Distortions	3	0	0
Paranoia	2	0	0
Depersonalization	2	0	0
Disorientation, Confusion	1	0	2
Tachycardia	1	1	0
Postural Hypotension	1	0	0

† Events reported at a frequency of less than one percent include: tinnitus, nightmares, speech difficulty, facial flushing, perspiring, syncope, diarrhea, fecal incontinence, muscular pains. Easy laughing, elation and heightened awareness, often termed a "high," was observed in 24% of Marinol patients.

Marinol. helping cancer chemotherapy patients complete their course of therapy.

APPENDIX A

INFORMATION ON MARINOL FROM ROXANE LABORATORIES, INC.



ROXANE LABORATORIES, INC.

MARINOL®

(DRONABINOL)

Roxane Laboratories, Inc.
Columbus, Ohio 43216

APPENDIX B

THE TUMOR, NODE AND METASTASES (TNM) SYSTEM FOR STAGING CANCER

(Beahrs and Myers, 1983)

Primary Tumor (T)	
To	No evidence of primary tumor
T1b	Carcinoma in situ
T1,T2,T3,T4	Progressive increase in tumor size involvement, i.e., for breast cancer 0-2cm, 2-5, >5, any size plus skin or chest wall
Regional Lymph Nodes (N)	
No	Regional nodes not demonstrable
N1a,N1b	Homolateral regional nodes (breast): metastases not suspected (a), suspected (b)
N2,N3	Homolateral regional nodes: fixed axillary (N2), homolateral supraclavicular (N3), or edema of arm, metastases suspected
Nx	Regional lymph nodes cannot be assessed clinically
Distant metastasis (M)	
Mo	No known metastasis
M1	Distant metastasis present
Specify site_____	

APPENDIX C

(Wynagaarden and Smith, 1982)

Performance Status - Karnofsky Scale

Criteria of Performance Status (PS)

Able to carry on normal activity; no special care needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated
	20	Very sick; hospitalization necessary; active supportive treatment is necessary
	10	Moribund, fatal processes progressing rapidly
	0	Death

APPENDIX D

ANTINEOPLASTIC AGENTS WITH KNOWN EMETIC ACTIONS

(Yasko, 1983)

Mild Emetic Effect*	Moderate Emetic Effect**	Severe Emetic Effect***
L-Asparaginase	azacytidine	cisplatin
bleomycin	daunorubicin	+cyclophosphamide
chlorambucil	doxorubicin	dactinomycin
hydroxyurea	5-fluorouracil	+methotrexate
L-phenylalanine	hexamethylmelamine	mithramycin
mercaptopurine	procarbazine	mitomycin-C
thioguanine	streptozocin	nitrogen mustard
thiotepa		nitrosureas
vinblastine		
vincristine		
steroids		
tamoxifen		

*Mild Emetic Action: A drug which is associated with a 20% or less incidence of illiciting nausea and/or vomiting.

**Moderate Emetic Action: A drug which is associated with a 25-70% incidence of illiciting nausea and/or vomiting.

***Severe Emetic Action: A drug which is associated with a 75% or greater incidence of nausea and/or vomiting.

+Dose related

This table has been compiled from several sources: (Lokich 1978: Dorr and Fritz 1980; See-Lasley and Ignoffo 1981)

APPENDIX E

FORM FOR RECORDING WEIGHT, NAUSEA AND VOMITING, FOOD INTAKE, APPETITE, AND MOOD STATUS BY SUBJECT

Identification #______

Please circle the appropriate number in each category.

Nausea & Vomiting (Orr et al.,1980)	Food Intake (Sallan et al.,1980)	Appetite	Mood Status (Ungerleider et al.,1982)
0-lack of nausea	0-no food intake	0-none	1-depression
1-nausea present,but not disabling	1-less than usual	1-decreased	2-inactivity
2-nausea impairing normal activities	2-average	2-same	3-anxiety
3-vomiting	3-more than usual	3-increased	4-social withdrawal
			5-distractability
			6-elevated mood
			7-activity
			8-relaxation
			9-interaction
			10-concentration

Date _____	MORNING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
	MIDDAY	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Weight_____	EVENING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Date _____	MORNING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
	MIDDAY	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Weight_____	EVENING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Date _____	MORNING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
	MIDDAY	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Weight_____	EVENING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Date _____	MORNING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
	MIDDAY	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Weight_____	EVENING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Date _____	MORNING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
	MIDDAY	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Weight_____	EVENING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Date _____	MORNING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
	MIDDAY	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Weight_____	EVENING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Date _____	MORNING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
	MIDDAY	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10
Weight_____	EVENING	0 1 2 3	0 1 2 3	0 1 2 3	1 2 3 4 5 6 7 8 9 10

APPENDIX F

FORM FOR EVALUATING

MOOD STATUS OF SUBJECT BY THE "OTHER" PERSON

(Ungerleider et al., 1982)

NAME ________________________________ Identification #________

Please circle the appropriate number

<u>Mood Status</u>

1-depression
2-inactivity
3-anxiety
4-social withdrawal
5-distractability
6-elevated mood
7-activity
8-relaxation
9-interaction
10-concentration

Date _____	MORNING	1	2	3	4	5	6	7	8	9	10
	MIDDAY	1	2	3	4	5	6	7	8	9	10
	EVENING	1	2	3	4	5	6	7	8	9	10
Date _____	MORNING	1	2	3	4	5	6	7	8	9	10
	MIDDAY	1	2	3	4	5	6	7	8	9	10
	EVENING	1	2	3	4	5	6	7	8	9	10
Date _____	MORNING	1	2	3	4	5	6	7	8	9	10
	MIDDAY	1	2	3	4	5	6	7	8	9	10
	EVENING	1	2	3	4	5	6	7	8	9	10
Date _____	MORNING	1	2	3	4	5	6	7	8	9	10
	MIDDAY	1	2	3	4	5	6	7	8	9	10
	EVENING	1	2	3	4	5	6	7	8	9	10
Date _____	MORNING	1	2	3	4	5	6	7	8	9	10
	MIDDAY	1	2	3	4	5	6	7	8	9	10
	EVENING	1	2	3	4	5	6	7	8	9	10
Date _____	MORNING	1	2	3	4	5	6	7	8	9	10
	MIDDAY	1	2	3	4	5	6	7	8	9	10
	EVENING	1	2	3	4	5	6	7	8	9	10
Date _____	MORNING	1	2	3	4	5	6	7	8	9	10
	MIDDAY	1	2	3	4	5	6	7	8	9	10
	EVENING	1	2	3	4	5	6	7	8	9	10

APPENDIX G (Ellison, 1980)

CORE DATA

History
Physical
Karnofsky Index
Nutrition intake 4 day

Anthropometrics
Height
Weight
Midarm circumference
Wrist circumference
Triceps skinfold
Biceps skinfold
Subscapular skinfold
Abd. suprailiac skinfold

Blood Tests
Hgb
WBC
Differential
Platelet

Biochemistry
Glucose
Protein
Albumin
Creatinine
BUN
CO2
Cl
Na
K
PO4
Calcium
Transferrin
LDH
Bilirubin
Alk Phos

Urinalysis
24 hr volume
Creatinine
Total Nitrogen
3-Methylhistidine

Skin Tests
TB
Candida
Mumps

APPENDIX H (Carter et al., 1983)

VARIABLES COLLECTED FOR NUTRITIONAL EVALUATION

General
patient I.D. number
patient name
gender
date of birth
date first seen
study number
evaluation
race
patient status
performance
disease status
diagnosis
past and current treatment

Anthropometric Measurements
arm muscle circumference
mid-upper arm circumference
triceps skinfold
biceps skinfold
subscapular skinfold
abdominal circumference
abdominal skinfold
suprailiac skinfold
weight
height
weight/height percent

Biochemical
hemoglobin
hematocrit
white blood count
polymorphs
lymphocytes
SMA=12
iron
total-iron-binding capacity
prothrombin
partial prothrombin time
magnesium
vitamins C, E, A
prealbumin
creatinine/height index
routine urinalysis

Immunological
phyptohemagglutinin
rosette`concanavalin A
poke weed antigen
mixed lymphocyte reaction
erythrocyte
zymosan complement
surface marker immunoglobulin
immunoglobulins-IgG, IgA, IgM

Dietary
dietary history
food intake recall
food frequency array
four-day dietary diary
(12 nutrients analyzed)

APPENDIX I

NORMAL LIMITS FOR LAB VALUES

Test	Normal Limits*
Total Protein	6.0 - 8.5 G/DL
Albumin	2.6 - 5.2 G/DL
Calcium	8.5 - 10.5 MG/DL
Phosphorous	2.5 - 4.5 MG/DL
Cholesterol	140 - 270 MG/DL
Glucose	72 - 128 MG/DL
Uric Acid	2.2 - 9.9 MG/DL
Creatinine	0.7 - 1.4 MG/DL
Total Bilirubin	0.2 - 1.2 MG/DL
Alkaline Phosphotase (Alk. Phos.)	30 - 115 U/L
Lactic dehydrogenase (LDH)	100 - 225 U/L
Glutamic-oxaloacetic Transaminase (SGOT)	7 - 40 U/L
White blood cell (WBC)	7.8 ± 3.0 X 10^3
Hemoglobin Male	16 ± 2.0 GM/DL
Female	14 ± 2.0 GM/DL
Platelet	140,000 - 440,000 CU/MM

*Normal Limits used at Roanoke Memorial Hospitals

APPENDIX J

FORM FOR RECORDING DIET HISTORY (Shils, 1981)

Name_____ Identification #_____

Address_____

Phone # _____ Date_____

DIET HISTORY

1. a. What is your usual weight? _____pounds
   b. What is your height? _____feet _____inches.
   c. Wrist Circumference_____ Frame Size: S M L
   d. Desirable Body Weight _____
   e. In the last two months, have you gained weight?
      _____ No _____Yes
      If yes, how many pounds? _____
   f. In the last two months, have you lost weight?
      _____ No _____Yes
      If yes, how many pounds? _____
2. Is your present appetite usual?
   _____ better? _____ worse than normal?
3. a. Do you have a problem related to eating?
      _____ No _____ Yes
      If yes, check the appropriate reason(s):
      _____ Sore mouth _____ Swallowing _____ Chewing
      _____ Choking _____ Salivation _____ Change in taste
      _____ Food aversion _____ Nausea _____ Vomiting
      _____ Diarrhea _____ Constipation
      Other _____
4. Do you wear dentures? Upper ___ Lower ___ None ___
5. a. Were you previously on a special diet? No ___ Yes ___
      If yes, specify_____
   b. Do you take vitamins or minerals? No _____ Yes _____
      If yes, what kind?_____
   c. Do you have any personal or religious dietary restrictions?
      Kosher? _____ Vegetarian? _____
6. Do you have any allergies or intolerances for food?
   No _____ Yes _____
   If yes, please list:_____
7. Do you take any other special food regularly?
   No _____ Yes _____
   If yes, please list:_____
8. Do you have any major food dislikes? No _____ Yes _____
   If yes, please list:_____
9. Describe your eating pattern six months ago.
   _____
   _____
   _____

APPENDIX K

FORM FOR RECORDING MEDICAL HISTORY (Shils, 1981)

Date _____ Name_____Identification # _____

MEDICAL HISTORY

1. Diagnosis _____
2. TNM Stage _____
3. Karnofsky's Index _____
4. Metabolic and other problems:

Diabetes _____	Hyperlipidemia _____
Hypertension _____	Heart Disease _____
Persistent fever _____	Severe trauma/burns _____
Alcohol/drug abuse _____	Renal disease
Liver disease _____	GI fistula _____
GI obstruction	Malabsorption
Partial _____	Type _____
Complete _____	Other_____

5. Drug/therapy history

a. Present medications _____
_____

b. Expected treatment plan: Surgery _____ RT_____
Chemotherapy _____
Emitegenic Potential _____

PHYSICAL EXAMINATION

1. Ht: _____ Adm Wt _____
   Preillness wt: _____ lbs. _____ kg.
   Percentage wt change (%): _____
   (preillness - Adm/preillness X 100)
2. Anticipated problems due to illness or treatment plan?
   No _____ Yes _____
3. Edema/ascites: (site) Degrees - 0-4+
   Ascites _____ Sacral _____

APPENDIX L

FORM FOR RECORDING DIETARY INTAKE

Date _____ Name_____ Identification #_____

Please write everything you eat on this day. Include snacks and beverages. Begin with the first thing you consume when you get up in the morning. Include any condiments used and method of preparation of food items (eg. baked, fried).

FOOD HOW MUCH ? (cups, ounces)

APPENDIX M

SAMPLE CALENDAR FOR RECORDING DIETARY INTAKE

DAYS TO RECORD DIETARY INTAKE

NAME _____ Identification #_____

AUGUST

Sun	Mon	Tue	Wed	Thu	Fri	Sat
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

SEPTEMBER

Sun	Mon	Tue	Wed	Thu	Fri	Sat
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

OCTOBER

Sun	Mon	Tue	Wed	Thu	Fri	Sat
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

NOVEMBER

Sun	Mon	Tue	Wed	Thur	Fri	Sat
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

APPENDIX N

DEFINITIONS OF MOODS USED TO EVALUATE MOOD STATUS

DEPRESSION - in low spirits

INACTIVITY - not active, not lively

ANXIETY - worry or uneasiness about what may happen

SOCIAL WITHDRAWAL - to go away from, to remove oneself from people

DISTRACTIBILITY - to draw the mind away in another direction, to be confused or bewildered

ELEVATED MOOD - to have a lifted or raised state of mind or feeling

ACTIVITY - to be active, liveliness

RELAXATION - to become less tense, rested

INTERACTION - to do things with other people

CONCENTRATION - to focus one's thoughts, efforts in a certain direction

VITA

Nancy Sacks was born on September 25, 1958 in Harrisburg, Pennsylvania. She attended the University of Arizona where she received a Bachelor of Science degree in Human Nutrition and Dietetics. In 1985, she entered the Master's program at Virginia Polytechnic Institute and State University and is expected to complete her M.S. degree in Human Nutrition and Foods in the summer of 1988.

Nancy Sacks

Nancy Sacks