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The responses of bone marrow transplant patients to graded exercise testing prior to transplant and after transplant with and without exercise training

Pfalzer, Lucinda Ann, Ph.D.
The Ohio State University, 1989

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THE RESPONSES OF BONE MARROW TRANSPLANT PATIENTS TO GRADED EXERCISE TESTING PRIOR TO TRANSPLANT AND AFTER TRANSPLANT WITH AND WITHOUT EXERCISE TRAINING

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Lucinda Ann Pfalzer, B.S., M.A.

*** ***

The Ohio State University

1989

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Lucinda A. Pfalzer
1989
ALL RIGHTS RESERVED
To My Mother
ACKNOWLEDGEMENTS

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2. Pfalzer LA, Tutschka PJ, and Harper D. Functional capacity of patients before and after bone marrow transplant. APTA Section on Oncology Newsletter, 6(1), Spring, 1988 (abstract).


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LIST OF SYMBOLS AND ABBREVIATIONS

1. VO2: Oxygen Uptake or Consumption
2. HR: Heart Rate
3. SBP: Systolic Blood Pressure
4. DBP: Diastolic Blood Pressure
5. SAC: Symptom Activity Checklist
6. SLGXT: Symptom-limited Maximal Graded Exercise Test
7. RQ: Respiratory Quotient
8. BMT: Allogenic Bone Marrow Transplant
9. GVHD: Graft Versus Host Disease
10. CO2: Carbon Dioxide
11. O2: Oxygen
12. RPE: Ratings Of Perceived Exertion
13. PFT: Pulmonary Function Test
14. HCT: Hematocrit
15. Hb: Hemoglobin
16. WBC: White Blood Cell Count
17. RBC: Red Blood Cell Count
18. ANLL: Acute Non-lymphocytic Leukemia
19. ALL: Acute Lymphocytic Leukemia
20. CML: Chronic Myelogenous Leukemia
21. AA: Aplastic Anemia
22. ESRD:  End Stage Renal Disease
23. ARDS:  Adult Respiratory Distress Syndrome
24. G-I:  Gastro-Intestinal
25. ATLS:  Acute Tumor Lysis Syndrome
26. CsA:  Cyclosporine-A
27. A-VO₂:  Arterio-venous Oxygen Difference
28. NCI:  National Cancer Institute
30. MUGA:  Multiple Gated Analysis
31. VO₂ MAX:  Maximal Oxygen Uptake or Consumption
INTRODUCTION

Life is more than survival -
Samuel B. Chyatte

This research project grew out of a need expressed by Dr. Peter Tutschka, Professor of Medicine and Director of the Bone Marrow Project at The Ohio State University Hospital. Bone marrow transplantation, a relatively new technology for treating cancer patients with leukemia, is an important innovative medical therapy. Patients' subjection to housing in special isolation units, chemotherapy, anti-rejection drugs, and multiple medical procedures, however, all take their toll.

The review of the literature addresses some of the problems seen in chronic disease populations due to their disease, treatment, and reduced activity. Specifically examined, when possible, are the adverse effects of disease and treatment on cancer patients with leukemia undergoing bone marrow transplant. The influence of endurance exercise on the rehabilitation of patients undergoing bone marrow transplant remains unanswered. "The contribution of physical exercise, or physical therapy to the rehabilitation process from disease states and the impact of a conditioned state on resistance to disease are important issues. In particular, the contribution of an exercise program to rehabilitation from cancer is not known. There are, however, anecdotal reports and several studies with animals that suggest a
beneficial effect of exercise during cancer. Few of the studies provide firm evidence as to how exercise, either active or passive, might alter the cancer process, although both mental and metabolic bases have been suggested (Deuster, Morrison, and Ahrens, 1985)*.

Problem Statement

The purpose of this study was: 1) to determine if subjects' status post (s/p) Bone Marrow Transplant (BMT) can improve their functional capacity as a result of participation in a low to moderate aerobic exercise interval training program, and 2) to compare the differences in functional capacity as a result of early versus late exercise intervention.

Research Questions

1. Will either early or late exercise intervention group exhibit a training response to aerobic exercise training?
2. Will aerobic exercise alter subject's disease and treatment related side effects associated with perceptions of symptoms limiting activity?
3. Will subjects in an early intervention exercise group have a statistically different functional capacity from subjects in a late intervention group?

*APA format is used in this dissertation
Hypotheses

All hypotheses are tested for statistical significance at p > .05 level of confidence.

Hal: A training effect will be elicited in the exercise groups as indicated by statistically significant differences from pre- to post-exercise testing decreased: a) resting heart rate, b) resting blood pressure, if elevated, c) heart rate, blood pressure, and perceived exertion at submaximal relative and absolute workloads, and d) total exercise time.

Ha2: Aerobic exercise training will have a statistically significant related effect on subject's treatment and disease related symptoms associated with perceptions of symptoms which limit activity.

Ha3: Functional capacity will be statistically different in an early intervention exercise group versus a late intervention group post-transplant upon discharge from the hospital and upon discharge from the day care unit.

Variables

The independent variable in the study is the low to moderate level bicycle ergometer interval exercise training program and time of institution of the program, early or late. The aerobic exercise training program consists of three sessions a week until discharge from the day care unit.
approximately one hundred days post transplant) with: 1) an early intervention beginning a few days post transplant while housed in inpatient isolation units or 2) a late intervention beginning upon discharge into the outpatient day care unit from the inpatient isolation units (approximately 30 days post-transplant). The dependent variables in this study are the physical and affective manifestations of inactivity, detraining and training measured at the appointed assessment intervals. Aerobic capacity is measured: 1) to provide information on the physical work capacity and train-ability of BMT patients and 2) to determine if a change in physical work capacity is associated with changes in physical and affective manifestations perceived to limit activity. Objective measures of muscle performance were collected to provide information on the detraining and training of BMT patients. Measures of perception of physical and psycho-social symptoms limiting activity were also collected, along with data on the subjects' psychological outcomes.

Significance of the Study

The treatment of cancer patients whose survival is often in question and dependent on relatively new treatment modalities is a controversial issue. The National Cancer Institute (NCI), in 1973, reported one-half million people
develop cancer every year. One-third of the persons with cancer are cured, and the remainder develop recurrent cancer. All persons with cancer require continuing rehabilitation services. In 1984, the cure rate in cancer with treatments had increased to fifty per cent with three hundred thousand patients returning to the community annually (McLoughlin, 1984).

The goal of rehabilitation is to return the patient to "pre-disease" functioning; however, the insidious onset of cancer, continuing over months and years, makes assessment of "pre-disease" status difficult. Rehabilitation is typically defined as optimal re-entry into society, along with attainment of the highest possible level of independent functioning. Cromes (1978) defined cancer rehabilitation as helping a person with cancer to help themselves obtain maximal physical, social, psychological, and vocational function within the limits imposed by the disease and its treatment. Frequently, cancer patients' only rehabilitation outcome measure is survival - "Don't concern yourself with the quality of your life, be happy to be alive." Seldom in cancer therapy is the full advantage of physical therapy or exercise training maximized. The NCI in 1973 determined "survival" was not the same as "recovery" and disease and treatment related effects often left patients with impairments requiring adjustments to new lifestyles.

Rehabilitation outcomes should include not only the
question of "Are you alive?", but also relapses, hospitalizations, complications, physical well-being, emotional or psychological well-being, and social well-being (Lehman, Engel, & Medalie, 1978). Deitz (1969, 1974) described a rehabilitation program based on early intervention which included preventive, restorative, supportive, and palliative goals to meet the patient's physical and personal needs. Hinterbuchner (1978) described a program with emphasis on the physical rehabilitation of a multitude of cancer-associated disabilities. Harvey, Jellinek, and Habeck (1982) reviewed thirty-six rehabilitation programs which utilized physical therapists as core members of the rehabilitation team; however, treatment was more concerned with specific cancer related treatment disabilities, i.e. pain control, increasing range of motion, and decreasing edema, than in overall functional capacity. Essential for the appropriate setting of rehabilitation goals are evaluation of: 1) psychological status, including assessment of self-esteem, self-image, feelings of control, anxiety, depression, and symptoms of fatigue and weakness among others; 2) social status, including assessment of vocational rehabilitation and sexual function; and 3) physical status, including assessment of activities of daily living, strength, endurance, body image, mental acuity and freedom from complications from treatment (Dietz, 1969, 1974;
Hinterbuchner, 1978; Cromes, 1978; Harvey et al, 1982; Lehman et al, 1978; Raven, 1974). All of these variables are assessed in this study, with the exception of social well-being.

Cancer's insidious onset can be overlooked when the mental and physical deterioration correlated with inactivity are present (Hirschberg, Lewis, and Vaughan, 1976). Diffused weakness, fatigue, and pain with diminished functioning and depression are frequent in cancer patients, regardless of the stage or site. Decreased strength and endurance and increased pain diminish the ability to function independently, promoting further reduction in both physical work capacity and ability to conduct activities of daily living. Independence is threatened when treatment and disease related impairments are compounded by the effects of inactivity. Grabois (1979) has reported the use of exercise in reduction of pain syndromes. Cancer cachexia leads to diminished muscle mass, increasing hypophagia and lipid store depletion. Dietz (1974) estimated a loss of up to 3% a day of muscle strength in cancer patients on bedrest and up to a 25% decrease in strength within the first week. Although, the effects of cachexia and bedrest cannot be separated in this study, their combined effects can dramatically impair function.

Intervention during therapy is necessary to break the cycle of disuse (Healey, 1972; Dietz, 1969, 1974; Raven,

There are long lists of the medical problems associated with the disease and therapy in BMT patients: anemia with decreased hemoglobin (Hb) and hematocrit (HCT), nausea and vomiting, fluid and electrolyte imbalances, infection with decreased white blood cell counts (WBC), bleeding disorders, fragile skin, temperature intolerance, Graft Versus Host Disease (GVHD), Cushinoid syndrome with glucose intolerance and slight hypertension secondary to immunosuppressive drugs, respiratory disorders and cardiac dysrhythmias. Many of these problems can be minimized, if not eliminated, by early mobilization and endurance exercise as seen in other chronic disease populations.

Levy (1979) found that depression was the most common psychiatric complaint in patients with end-stage renal disease (ESRD) receiving hemodialysis. Goldberg, Hagberg, Delmez, Haynes, and Harter (1980) reported significantly diminished aerobic capacity in patients with ESRD receiving
hemodialysis with anemia. Guttman, Stead, and Robinson's (1981) report on physical activity and employment outcomes of over 2,000 patients with ESRD reinforces Goldberg's findings on low physical activity levels in patients with ESRD. Carney et al (1983, 1983, 1986) has shown depression found in patients with ESRD is associated with diminished physical work capacity as measured by VO$_2$ max. Carney states the depression in these patients is significantly related to their decreased ability to engage in physical activity. Carney supports Lewinsohn's (1975) theory of causal association between the onset of depression and diminished response-contingent positive reinforcement. With a reduction in these positive "reinforcers", i.e. family, work, sexual, social, and maritally related pleasant or reinforcing activities, depression generally ensued. When ESRD patients have undergone exercise training, improved psycho-social function has been found (Carney et al, 1983, 1986).

Will BMT patients obtain similar results with early intervention and exercise training? When pilot work was initiated, no case studies had been reported in the literature on the response of BMT patients who exercise or undergo aerobic exercise training. Cardiovascular disease patients were one of the first groups of patients with a chronic disease to utilize early intervention exercise training in their therapy. Many of the recognized benefits
of early mobilization in the treatment of cardiovascular disease (Wenger, 1983) may be applicable to any deconditioned chronic disease population. The benefits Wenger has reported include:

1. decreased deconditioning effects of prolonged bedrest,
2. decreased thrombo-embolic complications and pulmonary atelectasis,
3. reduced emotional complications, particularly anorexia and depression,
4. improved functional capacity at time of hospital discharge,
5. earlier exercise testing to be performed if desired,
6. shorter hospital stays with the economic advantages and the potential for more optimal use of hospital beds,
7. earlier and more complete return to work because patients have become neither physically or emotionally deconditioned.

Attention has been focused on cancer patients' increased cure rate and longer survival. The treatment of patients with cancer is changing rapidly, due to new innovative technologies being developed. Survival rates are expected to dramatically increase into the next century. Current state-of-the-art cancer therapy will not meet the
rehabilitation needs of this expanding population.

It is important to determine if late intervention is as effective in minimizing the adverse effects of the BMT protocol and improving functional capacity as an early intervention with reduced risk of infection. Are the risks of an increased number of patient contacts during aplasia counterbalanced by the benefits of early intervention? The risk of infection present in the patients undergoing bone marrow transplant necessitates minimizing the number of patient contacts with other persons. Infection is the leading cause of death post-transplant in these patients (Lantz, Aldolfsson, Lagerlof, Reizenstein, 1980; O'Reilly, 1983; Thomas, Buckner, Banaji, Clift, Fefer, Flournoy, Goodell, Hickman, Lerner, Neiman, Sale, Sanders, Singer, Stevens, Storb & Weiden, 1977).

Many unanswered questions remain about patients' outcomes after treatment including their: 1) quality of life, 2) functional and social independence, and 3) optimal rehabilitation programs. Another important question which remains controversial is what role and effect exercise training plays in the patient's rehabilitation. Exercise training may have a high impact on successful rehabilitation of these patients, i.e. return to work. If exercise training is utilized, it should include all the components required to achieve health-related physical fitness (Haskell, Montoye & Orenstein, 1985).
Definition of Terms

Selected terms which appear in the dissertation are defined as follows:

1. Aerobic exercise: Aerobic exercise is an activity which requires oxygen for energy production (Fox & Mathews, 1981). This study uses an interval training protocol on a cycle ergometer (Winningham, Bartels, MacVicar & Kirby, 1983) as the treatment variable in experimental groups.

2. Interval training: A series of repeated bouts of continuous or interrupted exercise where higher intensity workloads are alternated with lower intensity workloads (Fox & Mathews, 1980; Lamb, 1984; Astrand & Rodal, 1986) (Exercise Protocol - Appendix A).

3. Submaximal workload (Absolute and Relative): A workload less than the individual's maximal oxygen consumption (VO2 Max). During the training period, a low-moderate submaximal workload was maintained between 50-60% and progressed to 60-75% of VO2 Max determined from the symptom-limited graded exercise pretest.

4. Functional capacity: Assessed by the peak VO2 attained on graded exercise testing (ACSM, 1986). Peak VO2 is used synonymously with "aerobic
fitness", "aerobic capacity", and "physical work capacity" (Shepard, 1984; Wilmore, 1982; Fox & Mathews, 1980) and is defined as the maximal amount of O2 consumed during the test.


6. Isokinetic muscle performance test: An objective measure of leg strength, including assessment of maximum dynamic concentric muscle strength throughout the active range of motion of the knee. Evaluation was conducted using a protocol adapted from Lumex Corporation, Cybex Division (1980); Rothstein, Delitto, Sinacore, and Rose (1983) for testing arthritics on high-dose steroids; and Greene and Strickler (1983) for training and testing hemophiliacs who are also at risk for joint bleeding (Appendix D).

7. Disease and treatment related symptoms: Known physical and affective manifestations of leukemia and chemotherapeutic agents utilized in treatment of leukemia.

8. Perceived exertion (RPE): A rating scale used to determine the somato-psychological stressfulness of an exercise (Borg and Noble, 1974; Appendix I).
Limitations and Assumptions of the Study

Internal and external threats to experimental validity were controlled for by: 1) all subjects undergoing the same transplant protocol, 2) random assignment of volunteers to the research groups for the study, 3) subjects consented not to exercise outside of their experimental sessions and, if they did exercise to report to the experimenter the mode, duration, and intensity of the activity, and 4) the utilization of a repeated measures research design.

The following assumptions are intrinsic to the study and this repeated measures design:

1. Self-selection from the population was a possible source of bias. Although random assignment to experimental and control groups occurred, the subjects were volunteers.

2. The transplant protocol, while involving multiple agents, is specific in nature, limiting generalization.

3. The effects of maturation, history, and learning of the subjects over time was felt to be an important possible source of error in this population. Therefore, a repeated measures design which minimizes these sources of error was chosen.

4. The small sample size available and attrition rate due to complications of disease and treatment,
although expected, did limit the statistical analyses which could be utilized in the repeated measures design. The repeated measures design does conserve on the number of subjects required, while increasing the power and sensitivity as each subject serves as their own control and are repeatedly measured over time.

5. Possible carry-over effects from repeated physical performances were controlled for by isokinetic muscle performance being measured prior to bicycle ergometry graded exercise testing.

6. Environmental conditions in the testing laboratory, while monitored, are not controlled and are a potential source of error.

7. Due to the duration of data collection required to obtain even this small sample, seasonal changes in circadian rhythms, which may effect exercise response, could not be controlled.
CHAPTER I
REVIEW OF THE LITERATURE

The literature review includes the major concepts of disease and treatment-induced physiological and psychological symptoms present in cancer patients with a diagnosis of leukemia under-going bone marrow transplant. Brief reviews of the physiological and psychological responses to bedrest, inactivity, and aerobic exercise training are also included.

Cancer and Leukemia

In 1982, fifty percent of all diagnosed cancer occurred past the age of sixty-five. Cancer is, however, the largest disease related killer of young adults from ages fifteen to thirty-four. Cancer deaths are only surpassed by accidents as the leading killer in young females. Only accidents, suicide, and homicide, surpass cancer related deaths among young men. Leukemia is the leading cause of cancer deaths in young males ages fifteen to thirty-four. Leukemia is also the leading cause of cancer deaths in young females from age fifteen for each five-year group up to age thirty. In 1982, the overall five-year survival rate for leukemia was seven percent, dipping to four percent with a diagnosis of acute leukemia and up to sixteen percent in all other forms of leukemia (Silverberg, 1982).
The cancer death rate has steadily declined since 1965 with Silverberg (1982) reporting the decreases are attributed to treatment advances in the care of leukemia, Hodgkin’s disease, testicular cancer, and cancer at several other sites. In 1984, Clink found eight out of ten leukemia patients were surviving bone marrow transplants. There is general agreement that as advances in medical technology, bone marrow transplant, immunotherapy, earlier diagnosis, and new combinations of chemotherapeutic agents increase survival rates, effort must be made during this prolonged survival to optimize functional abilities. Fox (1982) has reported tentative use of psychometrics testing to predict those at risk for cancer and mortality secondary to cancer. This type of testing may hold hope for identifying those patients particularly at high risk.

In humans, the bone marrow functions as the origin of all hematopoietic cells developed from common progenitor cells or stem cells. Hematopoietic malignancies or leukemias are defined as uncontrolled proliferation of immature blood cells involving the bone marrow, spleen, and lymph nodes (Brown, 1976). The proliferation of immature precursor cells (blast cells) reduces the production of normal elements, red and white blood cells along with platelets.

Multiple methods for the classification of various leukemias are utilized (Powles & McElwain, 1982; Brown,
1976). The two major categories of leukemia are lymphocytic and nonlymphocytic. Myelogenous and lymphocytic leukemia are the most common hematopoietic malignancies. Leukemias are also divided into acute and chronic forms. Acute leukemias make up 50% of all diagnosed cases of leukemia, with 80% of the childhood cases diagnosed as lymphocytic and 80% of the adult onset cases diagnosed as myelogenous. The chronic form is characterized by an adult onset, longer survivals, decreased morbidity, and, morphologically, a more mature cell type.

The following blood disorders are defined for use in this study as: 1) Acute lymphocytic leukemia (ALL) - onset in childhood with variable leukocyte concentration, but many lymphoblasts. Approximately 80-90% are low in platelets and anemic; 2) Aplastic anemia (AA) - most common in adolescents and young adults with anemia and thrombocytopenia; 3) Acute non-lymphocytic leukemia (ANL) - onset at any age with variable leukocyte concentration, but severe anemia and low platelet in 90% of patients; and 4) Chronic myelogenous leukemia (CML) - onset in young adulthood with high leukocyte concentration, including many myeloid cells. Approximately 80% are low in platelets and mildly anemic (Powles & McElwain, 1982).

The causes of leukemia are, for the most part, unknown. Ionizing radiation and some chemicals, i.e. compounds derived from benzene, have been shown to be causative. Other
mechanisms proposed are: 1) congenital and genetic conditions, i.e. Down's syndrome and Faconi's anemia, 2) exposure to oncogenic agents, either initiators and/or promoters, and 3) predisposing previous hematologic disorders. Retroviruses are clearly capable of induction of leukemia in animals; however, evidence in humans is lacking.

If acute leukemias are untreated, fatality occurs in a period of months to a year. The complications of the disease which result in death are hemorrhage, infection, and anemia. One of the primary reasons for the low survival rates among leukemia patients treated, not undergoing transplants, are the multiple courses of chemotherapy used to achieve remission and their associated toxicities. Relapse is common and, in adults, remissions are shorter in duration with diminished tolerance of the treatment regimens (Lantz et al, 1980). The most common complications of treatment leading to death are sepsis or infection, hemorrhage, and adult respiratory distress syndrome (ARDS) (Thomas, Buckner, Banaji et al, 1977; O'Reilly, 1983; Lantz et al, 1980; Bodey, 1980; and Brody, Bolivar, & Farnstern, 1982). ARDS is usually secondary to infection and sepsis. One of the major prognostic factors in patients undergoing bone marrow transplant is the initial number and type of abnormal cells (Bostrom, Brunning, McGlave, Ramsay, Nesbit, Woods, Hurd, Krivit, Kim, Goldman, & Kersey, 1985).
DISEASE RELATED SYMPTOMS

The clinical signs and symptoms of leukemia vary from person to person and are non-specific in nature, relating to the diminished numbers of normal hemopoietic cells and invasion of tissue by leukemic cells. Signs and symptoms include: 1) low-grade fever from unknown origin later related to other common sites and signs of infection, i.e. urinary, perirectal, respiratory, sinus, and dental sites, secondary to white blood cell dysfunction which does not totally respond to treatment, 2) a tendency to bleed easily and profusely, i.e. petechiae, ecchymoses, oozing gums with excessive bleeding after tooth extraction, secondary to platelet dysfunction (thrombocytopenia) and excessive use of factors necessary for clotting, and 3) malaise, mild fatigue, pallor and anemia which may have been present for months prior to diagnosis, secondary to red blood cell dysfunction; (Powles & McElwain, 1982; Chessels, 1982; Lisiewicz, 1978). Nutritional and immunological alterations and abnormalities are common in patients with neoplasm (Dionigi & Campani, 1981).

Organs commonly present with clinical involvement at the time of diagnosis of acute leukemia are the liver, spleen, and lymph nodes. Cachexia, anorexia, weight loss, edema and tenderness, and bone pain with migratory joint pain, secondary to marrow infiltration, are common. Cancer patients with cachexia and protein-calorie malnutrition have
diminished immunocompetence with increased risk of infection and decreased survival (Clink, 1984; Shike, Russell, Detsky, Harrison, 1984). If leukemic involvement of the central nervous system has taken place, headaches, blurred vision and cranial nerve impairment may be present (Bodey, 1980).

Cachexia and weight loss appear secondary to multiple factors. Irritation of the mucosal lining of the G-I tract alters the normal process of digestion and absorption of nutrients. G-I hemorrhaging can also be a cause of specific nutritional deficits. The anorexia present in cancer patients with diminished caloric intake compounds the nutritional problems. The exact cause of the anorexia is unknown; however, in many patients the usual drive to eat is absent. Factors which have been hypothesized to contribute to the diminished appetite are central perceptual changes in the ability to taste and smell food.

Diminished lean body mass, primarily from skeletal muscle, upon weight loss may lead to symptoms of fatigue and weakness. Many cancer patients exhibit basal metabolic rates which are different from predicted values. Neoplastic cells which are rapidly growing and dividing have an increased metabolic requirement. Neoplastic cells are also anaerobic, relying primarily upon glucose as an energy substrate for metabolism via glycolysis. The rate of gluconeogenesis is increased to supply precursors, amino acids, as a substrate for glycolysis. Protein catabolism,

Cancer patients’ nutritional status is carefully assessed, although controversy continues over the most reliable method of assessing body composition in cancer patients. Therapy is two-pronged. Antiemetics are given to reduce or prevent nausea and vomiting. Nutritional therapy includes dietary management through: 1) several small feedings throughout the day, 2) ingestion of cool, clear beverages and dry, salty foods, 3) enteral or parenteral hyperalimentation (Dempsey & Mullen, 1985; Shike et al, 1984), and 4) electrolyte supplementation, i.e., magnesium supplementation (Hoffman, 1985)

Anemia

Anemia, a major hematologic complication in treatment of leukemia, results in a low total amount of blood hemoglobin. There are multiple causes for anemia, including blood loss secondary to hemorrhage and diminished production
of red cells secondary to bone marrow suppression either from chemotherapy, radiotherapy, or the malignancy itself. Transfusion with the replacement of red cells via packed cells is common to reduce excessive plasma volume load on the cardiovascular system. Chronic anemia is often compensated for by increasing plasma volume. The multiple transfusions administered to these patients predisposes them to volume overload. Typically, the goal of treatment is to increase hemoglobin levels in the patient above ten milligrams per deciliter (mg/dl). If anemia is due to bleeding, resulting in an acute blood loss, intravascular volume is also replaced.

Anemia has a pronounced lowering effect on physical work capacity, secondary to decreased oxygen carrying capacity in the blood as indicated by reduced hematocrit (HCT) and hemoglobin (Hb), resulting in diminished systemic oxygen (O2) transport (Woodson, Wills, Lenfant, 1978; Kanstrup & Ekblom, 1984; Charache, Blecker, Bross, 1983). Lindenfeld, in the early 1960's, reported that in dogs systemic oxygen transport was maximal at a normal HCT and fell with either anemia or polycythemia (HCT > 65%). Typically, symptoms of anemia occur during exercise when an increased demand is placed on the O2 transport system which cannot be compensated for by raising heart rate, in turn increasing cardiac output (Lindenfeld, Weil, Travis, Horwitz, 1985; Kanstrup & Ekblom, 1984; Woodson et al,
The response of patients with leukemia to exercise has not been reported; however, exercise responses of patients with various anemias have been studied (Alpert, Dover, Strong, Covitz, 1984; Charache et al, 1983; Davies & VanHaaren, 1973). Woodson et al (1978) and Kanstrup & Ekblom (1984) have shown in normals with acute induced anemia and normals adapted to induced anemia that limitations in maximal oxygen consumption were proportional to the diminished oxygen carrying capacity of the blood. The max VO2 values reported by Woodson et al (1978) are similar to max VO2 values reported in patients with anemia (Charache et al, 1983; Alpert et al, 1984).

Ventilation, heart rate, cardiac output, A-VO2 difference, red blood cell DPG, and blood lactate have been shown to be elevated in patients with anemia during submaximal exercise (Alpert et al, 1984; Charache et al, 1983). The increased heart rate, cardiac output, and increased percent of max VO2 required at any submaximal workload in patients with anemia may be due to increased sympathetic nervous system activity as indicated by increased plasma norepinephrine (Favier, Desplanches, Pequignot, Peurin, & Flandrois, 1985; Filippov, 1985). During exercise in normals with induced hypoxia, the close association between plasma norepinephrine levels, heart rate, and percent VO2 was maintained (Escourrou, Johnson, Rowell 1984; Rowell, Blackmon, Kenny, Escourrou, 1984;
Escourrou, Rowell, Johnson, Blackmon, 1983). Ruddel, Berg, Todd, McKinney, Buell, & Eliot (1985) demonstrated (during exercise in normals) a close relationship between increased heart rate and elevated catecholamines. Kanstrup & Ekblom (1984) showed in moderately trained normals, with and without induced anemia, no differences in ventilation, blood lactate concentrations, and RPE at maximal effort. The O2 disassociation curve is shifted to the right and renal blood flow is lowered in patients with anemia, (Woodson et al, 1978), and there may be adaptations in response to the decreased peripheral oxygen transport, delivery and tissue hypoxia. Patients with iron deficient anemia have exhibited similar hormonal and physiological responses to exercise (Davies & VanHaaren, 1973) and to another physiological stress, cold exposure (Beard, Green, Miller, & Finch, 1984).

Clinically, anemia is evaluated by measures of red blood cell count, hemoglobin, and hematocrit. Careful monitoring of heart rate, blood pressure, respiratory rate, and recovery time are indicated during graded exercise, if the counts measured are reduced enough to possibly compromise cardiopulmonary function. The counts commonly utilized as guidelines for determining the level of activity and intensity of exercise training allowed in leukemia patients are shown in Table 1.
TREATMENT RELATED SYMPTOMS

Treatment of leukemia includes: surgery, radiotherapy, chemotherapy, immunotherapy, and bone marrow transplant following ablative therapy. Chemotherapy is the administration of cytotoxic agents to destroy malignant cells. Almost all chemotherapeutic agents are non-specific to the cell cycle. Rapidly dividing healthy cells tend also to be effected by the anti-neoplastic agent. Chemo-therapeutic agents act by: 1) interfering with DNA structure and function, 2) blocking protein synthesis, 3) inhibiting cell division, and 4) acting as anti-metabolites. Other normal tissues or organs have specific drug affinity, which can lead to drug-induced toxicity reactions (Ghione, 1984).

Acute tumor lysis syndrome (ATLS) occurs commonly in leukemia patients in response to chemotherapy, leading to large increases in metabolites from rapid cell destruction (Cohen, Balow, Magrath, Poplack, & Ziegler, 1980). The metabolite levels exceed the kidneys' excretory capacity. The electrolyte abnormalities found include hyperkalemia, hyperphosphatemia with hypocalcemia, and hyperuricemia with elevated pH (Allegretta, Weisman, Altman, 1985). Symptoms related to each metabolic disorder are shown in Table 2.

Hyperuricemia, if untreated, may result in acute renal failure. Allopurinol is given as treatment which inhibits the enzyme, xanthine oxidase, thus blocking production of uric acid. Hypercalcemia may lead to an apathetic affect...
### TABLE 1
GUIDELINES FOR DETERMINING THE SUBJECT'S LEVEL OF ACTIVITY
(Adapted from Deitz, H; 1979)

<table>
<thead>
<tr>
<th>Counts</th>
<th>No Exercise</th>
<th>Light Exercise</th>
<th>Resistive Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell Count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>&lt;25%</td>
<td>&gt;25%</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Levels</td>
<td>&gt;8 mg/dl</td>
<td>8-10 mg/dl</td>
<td>&gt;10 mg/dl</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>&lt;20,000 mm³</td>
<td>20,000-50,000 mm³</td>
<td>&gt;50,000 mm³</td>
</tr>
<tr>
<td>White Blood Cell Count</td>
<td>&lt;500 with fever</td>
<td>&gt;500</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>
PLEASE NOTE:

Duplicate page number(s); text follows. Filmed as received.
with irritability, nausea, crying, and subtle confusion. Other metabolic complications (Segar & Chesney, 1981; Longo, 1977; Mir & Delamore, 1978) which occur commonly and may lead to medical emergencies are: 1) hyponatremia, 2) hypokalemia, 3) hyper-calcemia, and 4) metabolic acidosis with increased lactate production (see Table 2). Hypo-natremia and hyperviscosity are associated with a presentation of slowed intellect. Tumor lysis syndrome may also occur after ablative therapy which is prior to BMT.

Patients with a diagnosis of cancer are at risk of developing osteoporosis secondary to use of chemotherapeutic agents and acute tumor lysis syndrome. Cyclosporine A (CsA), an anti-rejection agent, and ATLS impair renal function leading to alterations in electrolyte balance and, in turn, calcium metabolism (Keown, Stiller, Laupacis et al, 1982; Gluckman, Devergie, Lokiec et al, 1981; Shulman, Striker, Deeg, Kennedy, Storb, Thomas, 1981; Keown, Stiller, Ulan et al, 1981). Another anti-rejection agent, prednisone, reduces protein matrix deposition in bone, elevates protein catabolism, depresses osteoblastic activity in bone, and induces hyperparathyroidism, resulting in diminished intestinal calcium absorption, all of which lead to osteoporosis of trabecular bone (Hahn, Boisseau, Avioli, 1974; Rickers, Deding, Christiansen, & Rodbro, 1984; Gennari, Imbimbo, Montagnani, Bernini, Nardi, Avioli, 1984; Gennari & Imbimbo, 1985). Patients with leukemia have large
TABLE 2
ABNORMALITIES WITH ACUTE TUMOR LYSIS AND OTHER METABOLIC DISORDERS
(Adapted from Allegretta et al, 1985)

<table>
<thead>
<tr>
<th>Related To Tumor Lysis</th>
<th>Signs And Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERURICEMIA</td>
<td>1) decreased pH with metabolic acidosis, 2) signs of renal failure, 3) fatigue, 4) nausea &amp; vomiting, 5) hematuria, and 6) HTN</td>
</tr>
<tr>
<td>HYPERKALEMIA</td>
<td>1) G-I symptoms, 2) arrhythmias and asystole, 3) EKG changes with QRS widening, and 4) decreased myocardial contractility</td>
</tr>
<tr>
<td>HYPERPHOSPHATEMIA</td>
<td>1) G-I symptoms, 2) signs of renal failure and lactic acidosis, 3) central &amp; peripheral nervous system irritability, 4) changes in mental status, i.e., irritability and confusion, 5) convulsions, 6) photophobia &amp; eye inflammation, 7) joint inflammation, 8) neuromuscular irritability and muscle spasms resulting in tetany, 9) cardiac arrest and, 10) skin changes</td>
</tr>
</tbody>
</table>

Other Metabolic Disorders (And Possible Causes)

| HYPONATREMIA (ANLL, kidney failure, steroids with inappropriate ADH production, excessive vomiting & diarrhea, and hypercalcemia) | 1) arrhythmias, 2) headaches, 3) drowsiness and lethargy, 4) nausea, 5) convulsions and 6) coma |

28
TABLE 2 CONTINUED

HYPOKALEMIA  
(ANLL, vomiting & potentials diarrhea, kidney failure, decreased dietary intake, and Amphotericin B therapy)

HYPERCALCEMIA  
(prolonged bed rest, bone sarcomas or metastasis, increased parathyroid renal insufficiency)

METABOLIC ACIDOSIS  
(lactate acidosis, and excessive vomiting, diarrhea, hyperuricemia, and hyperphosphatemia)

1) arrhythmias, 2) weakness which progresses to paralysis, and 3) hyperpolarization of membranes with altered membrane

1) weakness, 2) nausea & vomiting, 3) constipation, 4) central nervous system depression with drowsiness leading to coma, 5) upper G-I symptoms and ulcers, 6) brady-arrhythmias, 7) EKG changes including broad T waves, increased PR intervals, and decreased QT intervals, and 8) disseminated intravascular and coagulation

1) decreased pH, 2) hyperventilation, 3) central nervous system depression with drowsiness and confusion leading to coma weakness
tumor cell loads predisposing development of ATLS when treated by chemotherapy. Leukemia patients undergoing BMT are on high-dose CsA, initial doses of 25-50 mg/kg/day, which elevates the risk of electrolyte disorders and bone disease (Harwood & Cook, 1985; Montefusco, Goldsmith, Veith, 1984). Inactivity, during the treatment period, adds to the risk already present in these patients for developing osteoporosis (Feldman & Ruehl, 1986; Dalen & Olssen, 1974).

A review of the literature on treatment by bone marrow transplant will be emphasized because it is the therapy used with the subjects in this research project. Regardless of the treatment modality, remission is defined as normal bone marrow functioning with fewer than five percent blast cells, normal peripheral blood cell counts, and no clinical signs of leukemia. In adults with acute leukemia, the remission rate has taken a dramatic upswing approaching sixty to eighty percent secondary to multi-agent chemotherapy (Peterson, Bloomfield, Bosl, Gibbs, Malloy, 1980). Multi-agent protocols, moreover, reduce treatment related toxicities while increasing their effectiveness. As stated previously, although the remission rates have improved, the relapse rate remains high.

**BONE MARROW TRANSPLANT**

Bone marrow transplant was developed as a method of hematopoietic support for bone marrow depression, commonly the dose-limiting factor in treatment of leukemia by
chemotherapy. Most of the bone marrow transplants performed are in patients with a diagnosis of acute leukemia (O'Reily, 1983; Storb, 1979; Thomas et al, 1977; McGlave, 1985; Parkman, 1986). A bone marrow donor is required in three methods of bone marrow transplant after ablative therapy. These three types of transplant are: 1) autologous (patient's own marrow), 2) syngeneic (identical twin marrow), and 3) allogenic (non-twin sibling). The three processes common in all transplants are harvesting, infusion, and regeneration. Allogenic transplant, the type of transplantation done with the subjects in this research, occurs when the donor's bone marrow is not genetically identical to the recipient's. Complications of allogenic bone marrow transplant are shown in Table 3.

Graft versus host disease (GVHD) is a complication seen only post-allogenic BMT. GVHD is really two different clinical syndromes which are both immunological in nature; acute GVHD and chronic GVHD. The allograft contains antigens which the recipient's immune system may recognize as foreign, triggering a response. This immune response is mediated via activation of T-lymphocytes which attack the allograft causing graft rejection and/or GVHD. GVHD commonly affects the skin, liver, and gastro-intestinal tract (Sullivan, Shulman, Storb et al, 1981; Parkman, 1986). Anti-rejection drugs, including cyclosporine and prednisone, are used to combat this immune reaction
<table>
<thead>
<tr>
<th>Complication</th>
<th>Pathology</th>
<th>Presents</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/sepsis</td>
<td>multifactorial virus; bacteria; fungi due to loss of immune function; aplasia</td>
<td>during first four months</td>
<td>fever; dyspnea; decreased FVC &amp; PO;</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>same as above; toxicity; preparative regimen; preparative regimen</td>
<td>acute onset post-drug administration</td>
<td>pericarditis and CHF; EKG voltage decreased; signs and symptoms CHF with reduced cardiac function</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>high-dose cyclophosphamide toxicity</td>
<td>delayed onset weeks to years</td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>multifactorial infection; CHF; Acute Tumor Lysis; cardiomyopathy</td>
<td>during first few months</td>
<td>SOB, cough, and fever</td>
</tr>
<tr>
<td>Acute Tumor Lysis</td>
<td>rapid release of tumor cell metabolites</td>
<td>post-preparative regimen</td>
<td>See Table 2</td>
</tr>
<tr>
<td>Bone Marrow Depression</td>
<td>toxicity of preparative regimen</td>
<td>failure to engraft at 5-7 days</td>
<td>no rise in blood counts; aplasia with secondary bleeding disorders and infections</td>
</tr>
<tr>
<td>Graft Rejection</td>
<td>bone marrow depression; mechanisms not well understood</td>
<td>same as above; transient or no engraftment</td>
<td>same as above or a rise in counts followed by a fall</td>
</tr>
<tr>
<td>Hemorrhage and Coagulopathies</td>
<td>thrombocytopenia; excessive protein losses; losses of co-factors</td>
<td>post-preparative regimen</td>
<td>falling counts; visual signs of bleeding; hypotension; rise in heart rate and breathing frequency; fever</td>
</tr>
<tr>
<td>A) G-I</td>
<td>same as above; high-dose prednisone</td>
<td>same as above</td>
<td>same as above; nausea</td>
</tr>
<tr>
<td>B) Cystitis</td>
<td>high-dose cyclophosphamide</td>
<td>same as above</td>
<td>same as above; pain with hematuria</td>
</tr>
<tr>
<td>Acute Graft Versus Host</td>
<td>donor mismatch; T cells react to host; immune response</td>
<td>5-7 days post-transplant</td>
<td>skin rash; diarrhea; G-I symptoms; elevated liver enzymes</td>
</tr>
<tr>
<td>Chronic Graft Versus Host</td>
<td>immune response</td>
<td>&gt;100 days post-transplant</td>
<td>jaundice; bleeding disorders; skin rash; G-I malabsorption; arthritis; cough; DOE; SOB; infections</td>
</tr>
<tr>
<td>Psychological Stress</td>
<td>isolation and confinement; drug induced and organic</td>
<td></td>
<td>altered mood states; psychoses; personality changes</td>
</tr>
</tbody>
</table>
Unfortunately, the anti-rejection drugs themselves are not without adverse side effects (See Table 4) (Morris, 1981; Montefusco et al, 1984; Keown et al, 1981; 1982). Corticosteroids appear to alter the hypothalamic-pituitary-adrenal axis which may lead to impaired thermoregulation and glycemic control (Gill, Wilson, & Long, 1978). Corticosteroids have been reported also to induce glucose intolerance and a myopathy with atrophy of type II muscle fibers (Stern, Gruener, Kirkpatrick, Nemeth, 1972; Rothstein et al, 1983; Danneskiold-Samaoe & Grimby, 1986; Danneskiold-Samaoe & Grimby, 1986). Hickson & Davis (1981) has shown endurance exercise conditioning may partially prevent the induced muscle atrophy.

Seals, Hagberg, Allen, Hurley, Dalsky, Ehsani, & Holloszy (1984) reported glucose tolerance improved in older adults after endurance training. Ablative therapy is used prior to bone marrow transplant and involves a combination of chemotherapeutic agents and/or total body irradiation, depending on the BMT protocol. The protocol (plan of medical care) includes: 1) type, timing, and dosages of therapy and 2) timing of tests to monitor patient's course and responsiveness to treatment. The Ohio State University Hospital's BMT protocol does not include total body irradiation. Pulmonary function studies and stress MUGA's are
### Table 4
**Complications of Chemotherapeutic and Anti-Rejection Drugs**
(Adapted from Dorr & Fritz, 1980)

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLASSIFICATION</th>
<th>BASELINE STUDIES</th>
<th>TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>Alkylating agent inhibiting DNA synthesis by crosslinking strands preventing division</td>
<td>CBC, differential counts, platelet count, BUN, creatinine, liver enzymes; SGOT, SGPT, Alk. Phosphatase, and bilirubin. Activated and metabolized in the liver; excreted in the urine and breast milk. Plasma half-life of 2-9 hours, with 70-80% present at 8 hours post-administration.</td>
<td>Bone marrow depression about 7-14 days post-treatment with anemia and leukopenia; alopecia (dose related), nausea, vomiting, sterility, acts as a diuretic, diarrhea, and dehydration with hypotremia and decreased urine output, dry skin, restlessness, and weakness.</td>
</tr>
<tr>
<td>METHOTREXATE (intraocular administration)</td>
<td>Antimetabolite</td>
<td>Input/output, BUN, creatinine, CBC, differential counts, platelet counts.</td>
<td>Bone marrow depression, nausea, vomiting, diarrhea, stomatitis, renal toxicity (high dose).</td>
</tr>
<tr>
<td>BUSULPHAN</td>
<td>Alkylating agent</td>
<td>CBC, differential counts, platelet count, BUN, creatinine, liver enzymes; SGOT, SGPT, Alk. Phosphatase, and bilirubin, and pulmonary function tests. Metabolized and excreted in the urine as methane sulfonic acid.</td>
<td>Bone marrow depression about 7 days post-treatment with nadir 14-28 days post. Thrombocytopenia and leukocytopenia of the granulocytes with neutropenia.</td>
</tr>
<tr>
<td>CYCLOSPORINE-A</td>
<td>Anti-rejection agent</td>
<td>Activated and metabolized in the liver, excreted in urine.</td>
<td>Hirsutism, gum hyperplasia, tigamor, renal toxicity, immunosuppression with increased risk of infection and malignancy, epigastric distress with G-I ulceration due to increased HCL secretion and reduced gastric mucus secretion.</td>
</tr>
<tr>
<td>PREDNISONE</td>
<td>Corticosteroid (glucocorticoid with some mineralocorticoid properties)</td>
<td>Activated and metabolized in the liver, excreted in urine. Uric acid, serum electrolytes, especially Ca &amp; PO4, urinalysis, fasting blood glucose. Long term administration: osteoporosis; withdrawal symptoms, joint pain, mood alteration, muscle cramps and weakness, nausea, postural hypotension, polyuria, anorexia, parathesias with tingling in the hands and feet, drowsiness and depression. Alters the hypothalamic-pituitary-adrenal axis.</td>
<td>K, Ca, PO4, loss, fluid retention, insulin antagonist, glucose intolerance, immunosuppression with increased infection risk, reduced healing due to interference with fibroblasts and granulation formation, changes in appetite (anorexia); Cushing appearance: moon face, striae, acne, buffalo hump, truncal obesity; myopathy with fatigue (Type II fibers); personality changes: mood swings, insomnia, nervousness, irritability, euphoria, and psychoses.</td>
</tr>
</tbody>
</table>
performed prior to transplant to assess possible reduction in cardiopulmonary function secondary to toxicity from previous therapy, including pulmonary fibrosis and cardiomyopathy.

CHEMOTHERAPY AND ANTI-REJECTION AGENTS

Severe toxicity from chemotherapy usually occurs when the agent is used alone, requiring high dosage, or when given over a long period of time with cumulative high doses (Minow, Benjamin, Lee, 1977; Mills & Roberts, 1979; Bristow, Mason, Billingham, Daniels, 1981; Buja, Ferrans, & Graw, 1976; Baello, Enabert, Ferguson et al, 1986; Gottdiener, Appelbaum, Ferrans, Deisseroth, & Ziegler, 1981; Bristow, Minobe, Billingham et al, 1981). Symptoms of toxicity, which are often dose-limiting, are bone marrow suppression, mucosal lining irritation and ulceration, and gastrointestinal discomfort and distress. Adriamycin, bleomycin, and busulfan induce cardiac and pulmonary damage, respectively, and, when given in a high dosage (Minow et al, 1977; Batist, Andrews, 1980; Gottdiener et al, 1981; Feingold, Koss, 1969), may limit physical work capacity. Pedersen-Bjergaard, Wissen, Sorensen et al (1980) reported an associated risk of ovarian cancer with busulfan therapy in patients with ANLL. Recently, two case studies were reported relating endometrial cancer with busulfan therapy in patients with CML (Aksoy, Erdem, Bakioglu, Dincol, 1984).
Long-term busulfan therapy effects on the male reproductive system have not been reported.

Ablative chemotherapy includes: bone marrow preparation by busulfan and cyclophosphamide and central nervous system prophylaxis by intrathecal methotrexate. The major toxicities associated with these drugs, along with the anti-rejection drugs, are listed in Table 4. Side effects are usually acute, within a week of treatment, and short in duration, damaging the lining of the G-I tract and hair follicles and supressing the bone marrow (Parkman, 1986). Functional abilities are often temporarily reduced, secondary to these relatively short term side effects. Short term side effects include: nausea, vomiting, diarrhea, weight loss, loss of appetite, alopecia (hair loss), renal toxicity, hemorrhagic cystitis, and increased risk of infection and fatigue (Dorr & Fritz, 1980; Lantz et al, 1980). Another side effect of both cyclophosphamide and cyclosporine-A is reduced renal function secondary to renal toxicity of these agents (Bagley, Bostick, & DeVita, 1973; Montefusco et al, 1984). Another dose-dependent, short-term side effect of cyclophosphamide therapy, reported in an animal study using New Zealand white rabbits, is hyperlipoproteinemia (Loudet, Dousset, Carton, Douste-Blazy, 1984). The hyperlipoproteinemia peaks in sixteen hours post-drug administration, resulting in elevated
triglyceride and cholesterol levels and diminished lipoprotein lipase activity.

Weight loss and anorexia, already a problem secondary to the disease, may be exacerbated by the adverse G-I side effects of the chemotherapy and leads to malnutrition and reduced food intake. G-I symptoms are common due to damage to the G-I mucosa. G-I symptoms include: 1) nausea and vomiting, 2) diarrhea, 3) electrolyte and fluid disturbances, and 4) decreased caloric intake and malnutrition. More importantly, erosion of the G-I lining opens a pathway for infection, the leading cause of death early post-transplant (O'Reilly, 1983; Storb & Thomas, 1979).

Eventually, death ensues if nutritional support is not given. Patients with cancer, after BMT, are often given antiemetics and nutritional support via total parental nutrition (TPN) under the direction of a registered dietician (Dempsey & Mullen, 1985; Shike et al, 1984).
The first complications post-transplant are secondary to the preparative regimen via an acute allergic reaction or toxicity. Complications include anaphlaxis and pericarditis. High-dose cyclophosphamide, one of the chemotherapeutic agents used in the preparative regimen, has been shown to cause pericardiomyopathy with decreased EKG voltage and reduced left ventricle function (Gottdenier et al, 1981; Buja et al, 1976; Mills, Roberts, 1979). Chronic toxicity to the agent often occurs six months to a year or more after treatment has been discontinued and can lead to diminished physical work capacity and long-term disability (Bristow et al, 1982; Bristow et al, 1981; Gottdiener et al, 1981). Baello et al (1986) has confirmed previous findings, indicating a predisposition to cardiotoxicity from high-dose cyclophosphamide may be due to prior anthracycline therapy or concurrent chemotherapy, with toxicity generally evident within three weeks. In seven of seventeen subjects, there was a reduction in resting ejection fraction from pre-transplant to approximately 77 days post-transplant, with four falling into the abnormal range.

Extensive hematopoietic support with blood products, i.e. red blood cells and platelets, is required due to the myelosuppresssion, including panocytopenia and thrombocytopenia which occurs until the patient's bone marrow is regenerated. Fourteen days post-transplant, regeneration of the bone marrow can usually be detected. Lack of engraftment is usually the next complication
encountered, although now rare (Tutschka et al, 1983; Parkman, 1986). Engraftment occurs relatively rapidly by infusion of donor stem cells circulating through the recipient's blood and repopulating the bone marrow; however, recovery of immune function takes as long as a year or more.

GVHD and infection tend to be the next complications post-engraftment (Parkman, 1986). Infection is the leading cause of death post-transplant (Thomas et al, 1977; Lantz et al, 1980). A developing infection can usually be related to compromised host defense mechanisms: 1) decreased number of neutrophils, 2) diminished cell-mediated or humoral immunity, 3) erosion of mechanical barriers - skin and G-I mucosa, and 4) immunosuppression by corticosteroids and chemotherapy. Treatment of the infection is often via antibiotic therapy, especially in granulocytopenia (Schimpff, 1986). All of the above listed mechanisms are present in varying degrees in patients post-transplant. Complications and side effects of allogenic BMT are shown in Table 3.

SOMATO-PSYCHOLOGICAL MANIFESTATIONS

Affective manifestations of depression, feelings of loss of control, anxiety, and large swings in patients with cancer social-emotional status including fear, anger, irritability, nervousness and denial are common problems which occur after transplant in conjunction with changes in patients' medical-physical condition (National Cancer Institute, 1981; Viney & Westbrook, 1981; Brown & Kelly,
Chemotherapeutic agents, antiemetics, and corticosteroids have known effects on mood or cognition which may confound the diagnosis of a mental disorder, i.e., depression, anxiety. High-dose intrathecal methotrexate used in the ablative chemotherapy regimen has been reported to cause neurological alterations and delirium 10-13 days after administration (Dorr, Fritz, 1980). The risk of high-dose corticosteroid-induced psychoses has been widely known; however, changes in mood often go unrecognized (Ling, Pery, & Tswang, 1981). Reported changes in mood include agitation, insomnia, increased appetite, and a labile affect with crying spells and variable depression (Ling et al, 1981). Occasionally a patient will experience difficulty upon tapering of the steroids. Improvement in mental status may be delayed as much as three weeks after cessation of the steroids.

As previously noted, increased blood viscosity has been associated with presentation of a slowed intellect. Schneider and Zangari have reported an association between an elevated blood pressure, reduced clotting time, and increased blood viscosity with elevated levels of anger, anxiety, fear, and hostility. Several of these affective manifestations such as depression, anxiety, hostility, and low morale have been negatively associated with rates of
survival (Weisman, 1979; Fox, 1982; Cohen, 1982; Jamison, Wellisch, Pasnau, 1978; Viney & Westerbrook, 1981). There appears to be an inherent interaction between the physical and psyche which effects the patients' outcomes.

Weisman points out that affective distress impairs the coping process. Weisman (1979) defined coping as:
"the recognition of a problem from which one seeks relief; doing something about this problem; and the outcome of this action . . . coping is a process, not an isolated set of independent actions. It combines perception, performance, appraisal, and correction, followed by further activity, and directed, motivated behavior."

Fatigue and weakness are major complaints in many cancer patients, regardless of stage or site of the disease (Meyerowitz, Sparks, Spears, 1979; Weisman, 1979), which contribute to diminished independent function. The somatic and psychic manifestations of the BMT, along with the impairment of normal social-emotional functioning, lead to an inability to maintain cognitive functioning and appropriate levels of activity.

The physiological and psychological side effects and manifestations associated with treatment often lead to diminished functional ability. Patients after transplant are confined during the in-patient phase of treatment in specially constructed laminar air-flow isolation units. Strict isolation procedures are employed including:
1) mandatory handwashing, 2) utilization of shoe covers, gowns, gloves, hair covers and masks, and 3) ultraviolet light irradiation, when possible, of every object entering the unit. The special laminar air-flow isolation housing units may lead to low stimulus environments, resulting in diminished socialization, sensory deprivation, and immobilization with reduced activity levels.

Smith (1969) has described confinement as restraints placed on an individual so as to limit mobility or action. Fraser (1966) has described isolation as relative, involving either perceptual, sensory, or social deprivation and separation from a normal environment. Rarely are isolation and confinement separate from each other. To reduce the risk of infection in patients while aplastic and at risk, it is necessary to maintain strict confinement and isolation. Patients who are undergoing transplant exist in an environment which is physically confining, socially deprived, and temporarily restrictive due to the duration of the protective isolation required. Perceptual isolation has been found to induce sensory distortion and disturbances (Zubek, 1982). Steinberg (1980) found that socially isolated subjects quickly begin to talk to themselves or inanimate objects. This verbalization may often be mistaken as disorientation or confusion.

Arnetz, Theorell, Levi, Kallner, & Emeroth (1983) reported, in an elderly population during social isolation, a diminished glycemic control. In a follow-up study in
1984, Arnetz confirmed his earlier results and reported other psychological stresses also diminished glycemic control. Factors which affect or improve the ability to adapt to inactivity, bed rest, and isolated conditions include: 1) a low need for physical activity (Meyers, 1966), 2) marital status (Epstein, 1962), 3) a need for change (Hull & Zubek, 1962), 4) age (Helmreich, 1966), 5) respect for rules and regulations (Gunderson, 1964), 6) aggressiveness, 7) impulse control, 8) emotional maturity, 9) energy level (Weybrew, 1957), 10) quality of interpersonal relationships (Weybrew, 1957), 11) exisistance of interpersonal problems (Weybrew, 1971), and 12) degree of psycho-pathology (Weybrew, 1971). Isolated subjects in disability-related situations are confronted by the following stresses: 1) lack of privacy and sensory input (Haythorn, 1973), 2) boredom, monotony, and loss of sources of social and emotional gratification (Mullin, 1960), and 3) interpersonal conflicts (Kansa and Federson, 1971). Interpersonal conflicts are influenced by the degree of individual adaptability, social interactions and environmental stresses. Social interactions of post-transplant patients tend to be poor due to the low stimulus environment, low quality of communication between patient and medical staff, low social power, perceptions of low status, and hostility displaced onto outside medical staff.

Deterioration of performance and mood have frequently been observed in studies of confinement and isolation
Hammer and Kenan (1980) reviewed the literature from many populations and treatment programs on social isolation, immobilization, bed rest, and inactivity. They found evidence of a positive association between the degree of social isolation and diminished motivation, with impairment of rehabilitation, and decreased level of function. Daily exercise programs have been recommended to reduce neuropsychological deterioration.

The development of secondary disability and functional impairment in cancer patients has also been examined by several authors who concur that exercise should be an element of their continuing care and rehabilitation (Cobb, 1975; Dietz, 1974; Villaneuva, 1975). The magnitude of interaction of the physical and affective factors as they impact upon development of secondary disability and impaired function of patients with cancer is currently unknown. Karnofsky & Burchunel (1949) developed a performance scale to assess affective, physical, and functional parameters. The Karnofsky scale, however, has been shown to be non-uniformly reliable with patients of differing sites and stages of cancer (Hutchinson, Boyd, Feinstein, 1979; Yates, Chalmer, McKegney 1980). Development of tools to appropriately assess quality of life in surviving cancer patients continues (Selby, Chapman, Etazadi-Amoli, Dalley, Boyd, 1984; Selby, 1985). Until objective and reliable measures of the patients' quality of life and functional
capacity can be obtained, the relationship between physical work capacity and the qualitative level of functioning remains undefined.

**SUMMARY**

This review has encompassed the areas of disease and treatment-related physiological and psychological alterations in patients with leukemia undergoing bone marrow transplant. Cancer patients, having diminished physical activity and reduced physical work capacity, may confuse the side effects of disease, therapy, and transplant procedures with physical and affective manifestations of inactivity. Diminishing functional ability, feelings of loss of control, and changes in body image (hair loss and weight loss) occurring with disease and treatment may contribute to the affective manifestations of anxiety, helplessness, and futility as patients lose their ability to function independently. The physical manifestations of deconditioning and inactivity may compound the limitations imposed by the treatment (chemotherapy and anti-rejection drugs) and transplant procedure.

**INACTIVITY AND BEDREST**

Inactivity, bed rest, and immobilization induce several detrimental affective and physical health outcomes. The negative health effects of bed rest are associated with diminished health-related physical fitness which reverse upon resumption of ambulation and increased activity (Saltin, Blomqvist, Mitchell, Johnson, Wildenthal, Chapman,
Inactivity of even a few days results in rapid deconditioning with diminished cardiac output, reduced endurance, and rapid fatigue (Saltin et al, 1968; Fox, Matthews, Bairstow, 1981; Sandler, 1980). Deconditioning is reversible even in very debilitated individuals upon resumption of appropriate activity. Many reviews of the physiological responses to bed rest and inactivity (Table 5) have been published recently including responses of normal healthy people and chronically ill individuals (Kozlowski, 1969; Chobanian, Little, Tercyak, Blevins, 1974; Greenleaf, Kozlowski, 1982; Sandler & Vernikos, 1986).

Inactivity, with removal of postural stimuli related to the change in orientation of gravitational pull, is the proposed inducer of the physiological changes seen during bed rest. After prolonged bed rest, the most notable alteration in bodily function is a diminished ability to perform work. Physical work capacity as measured by peak VO\textsubscript{2} reflects the ability to transport oxygen which is performed by the pulmonary and cardiovascular systems. Other factors demonstrated to affect peak VO\textsubscript{2} max include: age, sex, heredity, ambient and body temperature, level of fitness, Hb content and disassociation characteristics, and O\textsubscript{2} tension of inspired air (Henriksson, Reitman, 1977; Klaussen, Andersen, Pelle, 1981). Upon exercise testing, VO\textsubscript{2} max decreased 20-25% after three weeks of bed rest in untrained college students. A series of studies by
TABLE 5

PHYSIOLOGICAL RESPONSES TO BEDREST


<table>
<thead>
<tr>
<th>Decreased</th>
<th>Increased</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic tolerance (stand, tilt, LBNP)</td>
<td>Syncopal episodes</td>
<td>Resting or exercise arteriovenous oxygen</td>
</tr>
<tr>
<td>Acceleration tolerance</td>
<td>Resting heart rate</td>
<td>differences</td>
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<tr>
<td>$V_{O_{2}}$ max</td>
<td>Diastolic blood pressure</td>
<td>Vital capacity</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>Max heart rate (stress, exercise)</td>
<td>Maximal voluntary</td>
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<tr>
<td>Total blood volume</td>
<td>Diuresis</td>
<td>ventilation</td>
</tr>
<tr>
<td>Heart and ventricular volumes</td>
<td>Nitrogen loss</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>Urinary calcium, phosphorus</td>
<td>Proprioceptive reflexes</td>
</tr>
<tr>
<td>Resting cardiac output</td>
<td>Constipation</td>
<td></td>
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<tr>
<td>Red cell mass, production</td>
<td>Serum fibrinogen</td>
<td></td>
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<tr>
<td>Sweating threshold</td>
<td>Cholesterol</td>
<td></td>
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<tr>
<td>Cerebrovascular tone</td>
<td>Low-density lipoproteins</td>
<td></td>
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<tr>
<td>Pulmonary capillary blood volume</td>
<td>Growth hormone</td>
<td></td>
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<tr>
<td>Total lung diffusing capacity</td>
<td>ECG changes (ST-T)*</td>
<td></td>
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<tr>
<td>Serum electrolytes</td>
<td>Renal diurnal rhythms</td>
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<tr>
<td>Hormones (adrenal, ADH)</td>
<td>Deep vein thrombosis</td>
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<td>Blood coagulation</td>
<td>Urinary tract infections</td>
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<tr>
<td>Balance</td>
<td>Sleep disturbances</td>
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<tr>
<td>Muscle mass, strength</td>
<td>Psychosocial dissociation</td>
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<td>Bone calcium, density</td>
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<td>Serum proteins</td>
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<td>Insulin sensitivity</td>
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<td>Resistance to infection</td>
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<td>Visual acuity</td>
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<tr>
<td>Manual coordination</td>
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*ST = ST segment; T = T wave depressions.
Convertino Brock, Keil, Bernauer, Greenleaf, 1980; Convertino, Hung, Goldwater, Debusk, 1982; Convertino, Sandler, Webb, Annis, 1982) support this commonly found decrease in VO\textsubscript{2} max after bed rest. The proposed mechanisms leading to the reduced VO\textsubscript{2} max due to deconditioning are mediated by the cardiovascular, endocrine, and musculoskeletal systems. The diminished VO\textsubscript{2} max upon changing from supine to the upright position, when exercising after bed rest, appears to be from the addition of orthostatic stress (Chobanian et al, 1974; Convertino et al, 1982).

Signs and symptoms of orthostatic intolerance have been shown to occur after bed rest on resuming an upright posture. Lamb, Stevens, Johnson's (1965) subjects reported dizziness, nausea and vomiting, and syncopy after bed rest upon resuming the upright position. Stryker (1977) found subjects' heat production, sweating, and peripheral vasodilation were increased with a lowered systolic blood pressure and cardiovascular insufficiency. These signs are due, apparently, to reduced efficiency of neuro-vascular reflexes on resuming upright posture after bed rest. Hung, Convertino, Goris (1983) found that after ten days of bed rest peak VO\textsubscript{2} supine was reduced six per cent (non-significant) versus fifteen per cent when upright (significant p>.05). Left ventricle end-diastolic volume was reduced at rest in supine and a larger increase in heart rate was found during upright exercise than supine. Hung et
al concluded an orthostatically-induced diminished cardiac filling, with reduced stroke volume during short-term bed rest, accounted for the decreased exercise tolerance. A minimum of three weeks of exercise training was required by the untrained college students to restore them to their pre-bed rest work capacity in the study by Chobanian et al (1974). The more physically fit the subject was, the more rapid the deconditioning and the greater the amount of training needed to restore the previous work capacity. It is important to note an increased level of activity in ambulatory sedentary individuals may not promote a similar improvement in health-related fitness. In this clinical population, changes due to hypokinesia are compounded by the associated confinement and isolation required for treatment (refer to Table 4).

PSYCHOLOGICAL RESPONSES

Physical weakness, fatigue, and impaired physical work capacity after bed rest may be misinterpreted easily as a symptom of depression (Greenleaf & Kozlowski, 1982). Changes in perception of sensory stimuli, including elevated auditory threshold and reduced near point of visual acuity, have been reported with two weeks of bed rest (Greenleaf, 1984). Other reported perceptual changes include: 1) alterations in body image, and 2) seeing, hearing, or feeling sensations which do not exist (Olson, 1967; Friman, 1977; Sandler, 1980; Sandler & Vernikos, 1986; Bortz, 1984).
Sensory deprivation may be one of the major factors leading to the psycho-social alterations seen upon bed rest.

In the studies done in the Soviet Union, significant neurological and psychological impairment occurred from bed rest. The Soviet studies ranged up to 120 days in duration and documented increased irritability, fatigue, emotional lability, sleep disturbances, psychological dependency, and decreased memory with difficulty in cognitive functioning which required logical thought processes (Agadzhanyan & Chernyakova, 1982; Petukhov & Purakhin, 1968; Krupina & Fedorov, 1977; Ioseliani, Narinskaya, Khisambeyev, 1985). Petukov & Purakhin (1968) found that after two to three days of bed rest subjects showed a gradual shift toward slow frequency cortical response. After twenty to thirty days of bed rest, subjects had impaired central nervous system function with primarily slow waves on EEG, loss of aural discrimination, and decreased respiratory frequency. The EEG brain waves observed may occur secondary to boredom and monotony.

Ryback, Lewis, and Lessard (1971) and Ryback, Trimble, Lewis, and Jennings (1971) showed reduced sleep disturbances in immobilized subjects who exercised during thirty-five days of bed rest. The non-exercised immobilized subjects were found to have greater anxiety levels, hostility, and depression. Steinberg (1980) reported immobilized subjects, deprived of visual and auditory stimulation, demonstrated a magnification of the experience. Immobilized patients have
shown signs of sensory deprivation with reduced perceptions of patterns and forms, time estimation, weight discrimination, temperature sensitivity, and speed of perception (Olson, 1967). The patients in Olson's study had difficulty with problem solving with "a diminished motivation to learn, retain, transfer, and generalize information".

In a review of the psychological effects of immobilization, Hammer and Kenan (1980) concluded:

"The person whose intellectual, emotional, physical or social activities have been limited may be less inclined to initiate activity even when movement is permitted. The process becomes self-intensifying and self-destructive."

Daily exercise sessions have been recommended for patients during immobilization to facilitate circadian rhythm synchronization, improve sleep quality while reducing sleep disturbances, diminish alterations in cognitive functions, and increase sensory stimuli.

PHYSIOLOGICAL RESPONSES

Negative changes occur rapidly upon bed rest and are attributed to decreased mobility and maintenance of the supine position (Greenleaf, 1984). Changes include (Bortz, 1984; Greenleaf, 1984; Sandler, 1980; Sandler & Vernikos, 1986): 1) skeletal muscle atrophy (Saltin et al., 1968; Hyatt, Kamenetsky, Smith, 1969), 2) negative nitrogen balance (Detrick, Whedon, Shorr, 1948) increased calcium excretion (Rambaut & Johnson, 1979), 4) altered lipid
metabolism, 5) decreased glucose tolerance (Greenleaf, Kozlowski, 1982; Dolkas & Sandler, 1974; Dolkas & Greenleaf, 1977), 6) decreased cardiac output (Saltin et al, 1968), and 7) postural orthostasis (Saltin et al, 1968). During bed rest, the sequela of physiological alterations in the musculoskeletal, cardiopulmonary, neural, and endocrine systems is a diminished physical work capacity. Over 160 studies of the responses of normals to bed rest have been done by American, Soviet, and European scientists. Most of these studies were done to evaluate the effects of weightlessness on humans during space exploration using bed rest as a model (Greenleaf, Kozlowski, 1982). A large percentage of the studies examined cardiovascular function.

Cardiovascular Function

The most rapid responses to bed rest begin with fluid and electrolyte shifts and the attendant cardiorespiratory reactions. The proposed mechanism mediating these responses is shown in Figure 1. Immediate adaptation is by hemodynamic change, resulting in a redistribution of blood volume. Hemodynamic changes occur by an increased venous capacitance, resulting from increased venous compliance and reduced leg blood flow. Neural (elevated renal pressure and flow) and hormonal (reduced ADH) changes quickly follow which increase free water clearance by the kidney. In the first twenty-four hours of bed rest, there is an increased urinary excretion with loss of potassium and sodium (Greenleaf, Kozlowski, 1982). A slow rise in urinary
FIGURE 1
MECHANISM OF FLUID AND ELECTROLYTE ADAPTATION UPON POSTURAL CHANGES
calcium excretion occurs which remains persistently elevated during long-term immobilization associated to suppressed adrenal responsiveness (reduced Aldosterone, ADH, Renin, Angiotensin, and Cortisol). The elevated urinary calcium predisposes kidney stone formation and urinary tract infections. The urinary responses are primarily mediated by high pressure baroreceptors in the kidney and carotid artery (Convertino et al, 1980).

The elevated urine volume and decrease in total fluid intake during bed rest induce general dehydration. The loss of 700-800 cm$^3$ in blood volume has been shown to occur after one week or more of immobilization with as much as 1,000 cm$^3$ lost at 25 days of bed rest with a ten to fifteen percent loss of plasma volume (Saltin et al, 1968; Hyatt et al, 1969; Stremel, Convertino, Bernauer, Greenleaf, 1976; Krotov, Titov, Kovalenko, et al, 1977; Coyle, Hemmert, Coggan 1986). Krotov et al (1977) found a 3.4 percent reduction in total body water after 25 days of bed rest, with one-third from plasma volume and the other two-thirds from intracellular fluid including the red blood cell mass. Fluid tends to shift centrally with an elevation in central venous pressure. Interstitial fluid loss from the lower extremities appears to contribute to this during the initial two weeks of bedrest; however after two weeks, the lower extremity interstitial fluid levels increase, resulting in peripheral edema (Greenleaf, 1984). An additional problem incurred by the hypovolemia is the increased blood viscosity
secondary to the slower decline in red blood cell mass (Miller, Johnson, Lamb 1965; Kimzey, Leonard, Johns, 1979; Martin, Gerguson, Wigutoff, Gawne, Schoomaker, 1985) with a concomitant risk of thromboembolism.

The onset of the redistribution of plasma volume is within a few hours of assuming a supine position (Nixon, Murray, Bryant et al, 1979). Upon reclining, a shift in fluid occurs from the lower extremities to the head and thorax, with approximately equal amounts of fluid derived from the thighs and legs (Hargens, Tipton, Gollnick et al, 1983). Elevation in central venous pressure has been demonstrated (increased afterload); however, the overall reduction in plasma volume probably accounts for most of the decreased left ventricular end-diastolic volume, stroke volume and cardiac output which occur during exercise post-bed rest, even in the supine position (Hung et al, 1983; Stryker, 1977; Saltin et al, 1968; Natelson, Goldwater, DeRoshia, Levin, 1985).

Heart rate, total peripheral resistance, and blood pressure are all elevated within three weeks of bed rest during submaximal exercise in the upright position (Gobel, Nordstrom, Nelson, Jorgensen, Wang, 1978; Convertino et al, 1982; Hung et al, 1983; Orlander, Kiessling, Karlsson, Ekblom, 1977) and after eighty-four days of detraining of well-trained athletes (Coyle et al, 1986). In results from the same subjects, Coyle, Martin, Sinacore et al (1984) found a rapid reduction of stroke volume within the first
three weeks detraining, with a ten to fourteen percent drop within twelve days and only a seven per cent drop in max VO₂ in the first three weeks. A forty per cent reduction in oxidative enzymes was demonstrated within eight weeks. Muscle capillarization decreased only seven percent over the entire eighty-four days of detraining. Costill (1985) examined the effects of four weeks of detraining on swimmers and found a fifty percent reduction of oxidative enzyme capacities. In highly trained athletes undergoing detraining, the early reduction in physical work capacity appears to be due to loss of blood volume and subsequent reduction in stroke volume, which is magnified during bed rest.

Patients post-bone marrow transplant have inappropriate ADH secretion secondary to high-dose steroid therapy (Padfield, Morton, 1983). It is not surprising to find difficulty in regulation of plasma volume and, therefore, blood pressure among transplant patients at rest. Plasma volume and blood pressure responses of transplant patients to exercise has not been reported.

Pulmonary Function

Saltin et al (1968) found no change in total lung capacity, forced vital capacity, or 1-second forced expiratory capacity in normals after bed rest. A decrease in total lung diffusion capacity was reported. Residual volume and maximal minute ventilation have been shown not to alter after fourteen days of bed rest (Greenleaf, Bernauer, Young, Morse, Staley, 1977). It is possible, however, that
ventilatory threshold during graded exercise testing may occur at a lower work capacity (Bhambhani & Singh, 1985).

In the supine position, patients on bed rest have shallower and slower respirations, reduced mobilization of secretions, and an increased risk of hypostatic pneumonia and atelectasis. In clinical populations where pulmonary function is impaired, bed rest or immobilization may reduce their already limited maximal gas exchange. Freedman (1979) reported a sixteen per cent increase in VO₂ of pulmonary disease patients post-exercise training. After bone marrow transplant, patients may have reduced pulmonary function, secondary to toxicity from prior treatment as has been previously noted. These patients with impaired pulmonary function may benefit from exercise training.

Musculoskeletal Parameters

Muscle disuse atrophy with reduced lean body mass, negative nitrogen balance, and rapid fatigue have been well documented upon detraining and bed rest (LaFevers, Boder, Crozie, Donaldson, 1977; Guttman, 1977; Greenleaf, Kozlowski, 1982; Booth & Gollnick, 1983; Booth, 1987; Bluemental, Needles, Williams, Wallace, 1981). Estimated protein and calcium losses during immobilization are eight grams per day and 1.54 grams per week respectively. Sitting and standing are active processes requiring the use of antigravity muscles, i.e., quadriceps, spinal erectors, abdominals, hamstrings, and glutei, to maintain the upright posture. During bed rest, the absence of loading leads to
structural musculoskeletal changes. Diminished weight bearing directly unloads compressive forces on the long bones and spine; moreover, indirect loading is reduced due to a loss of muscle pull at sites of boney attachment. During immobilization, continuous loss of muscle mass further diminishes muscle forces.

Muller (1970) demonstrated, after seven days of bed rest, a twenty-two percent reduction in muscle strength, with progressive depletion of strength continuing at a rate of one to one and one-half per cent a day. Hyatt et al (1969) also reported a diminished skeletal muscle mass with a reduction in strength and efficiency of ten to fifteen percent within the first week of bed rest. An inefficient, untrained muscle requires more energy and necessitates a larger oxygen consumption for any given task versus a trained muscle. Therefore, increased demand is placed on an already impaired cellular metabolism in muscle during bedrest. Type I (slow-twitch) muscle fiber atrophy has been demonstrated upon immobilization in a shortened position (Boyes, Johnson, 1979; Tomanek, Lund, 1974; Booth, Gollnick, 1983; Booth, 1987). Type II (fast-twitch) muscle fiber has been demonstrated to increase in size and then atrophy upon immobilization in a lengthened position (Booth, Gollnick, 1983; Booth, 1987).

Greenleaf, Juhos, Young (1985) reported changes in strength, after bedrest, cannot be predicted from changes in VO₂. Strength losses appear to be twice as great in large
muscle, i.e., the trunk and thighs, as in small muscle, i.e., the hand and forearm (Greenleaf et al, 1985). Table 6 reviews other published data available on strength changes from bed rest, specific to muscle assessed. The diminished oxidative capacity may be from shifts in oxidative enzymes (Lortie et al, 1985; Gollnick & Saltin, 1982; Holloszy & Doyle, 1984). Specifically implicated in the production of diminished oxidative capacity has been a shift in lactate dehydrogenase total and isozymes (Greenleaf et al, 1985; Sjodin, 1976; Chi, Hintz, Coyle, Martin, Ivy, Nemeth, Holloszy, & Lowry, 1983) and, during long-term immobilization, a reduction in oxidative enzymes. Reduced oxidative capacity is believed to contribute to weakness and the early onset of fatigue noted in subjects after bed rest.

As noted previously, direct and indirect loading of the skeleton is reduced upon bed rest. Bed rest has been consistently associated with bone demineralization. Differentiation of the amount of the demineralization, due to the diminished loading of bone and altered electrolyte homeostasis has not been reported. Recently, during immobilization, demineralization of trabecular bone has been found to be larger than demineralization of cortical bone. Krolner, Toft, Nielson, Tondewald (1983) found reduced bone density in the lumbar vertebrae of patients with low back pain treated by bed rest, with maximal losses in the initial six months of inactivity. In patients with spinal cord injury, Griffiths, Bushueff & Zimmerman (1976) found
TABLE 6
REVIEW OF MEAN PERCENT CHANGES OF MUSCLE STRENGTH AFTER BEDREST

| Reference | No. of male subjects | No. of days | Exercise duration (min/day) | Exercise mode* | Muscle group | %  \\
|-----------|----------------------|-------------|-----------------------------|----------------|--------------|------
| Friman and Hamra (1976) | 14 | 7 | None | None | Handgrasp | -5  \\
| Trumble and Lessard (1970) | 8 | 7 | None | None | Handgrasp | 0  \\
| Greenual et al. (1983) | 7 | 14 | None | None | Handgrasp | -1  \\
| Taylor et al. (1940) | 6 | 21 | None | None | Handgrasp | -3  \\
| Birnbaum et al. (1964b) | 2 | 21 | 60 | ITEc | Arm | -2  \\
| Birnbaum et al. (1965b) | 4 | 42 | 60 | ITEc | Arm | -5  \\
| Davis et al. (1948) | 4 | 42-49 | None | None | Handgrasp | 0  \\
| Katsura et al. (1970) | 3 | 62 | None | None | Forearm | -36  \\
| Yeremin et al. (1969) | 3 | 62 | 130 | ITEc | Back | -19  \\
| | 1 | 70 | None | None | Forearm | -1  \\
| Panov and Lobzin (1968) | 4 | 11 | None | None | Handgrasp | -3  \\
| Krupina and Tizlo (1971) | 10 | 120 | None | None | Forearm | -36  \\

*Compilation of data from Greenual et al. (1983).
*ITE, isotonic exercise; IME, isometric exercise.
*Isotonic exercise with a cycle.
*Isotonic exercise on a treadmill.
similar maximal losses in the initial six months of inactivity. In patients with spinal cord injury, Griffiths et al. (1976) found similar changes with the trabecular bone of the distal radius which exhibited less density than the cortical bone of the proximal radius.

Urinary hydroxyproline is a marker of bone collagen metabolism and is used as an index of bone resorption. Approximately twenty-five percent of the hydroxyproline liberated upon collagen breakdown is not hydrolyzed and is excreted in the urine. Hydroxyproline is a reliable marker when the adult is healthy, i.e., without excessive G-I tract desquamation or impaired renal function, and dietary sources are limited, i.e., no gelatin. During bed rest, bone resorption is marked by urinary hydroxyproline, which peaks at 4-6 weeks and stabilizes at an elevated level upon approximately 10-12 weeks of immobilization. Animal studies (Klein, Player, Heiple, Bahniak, Goldberg, 1982) using dogs support Heaney's conclusions (1962) that the loss in bone density, primarily of trabecular bone, results from elevated rates of bone resorption, while bone formation continues during inactivity at a reduced rate.

Hematological and Blood Chemistry Parameters

Plasma volume, as has been previously stated, decreases with immobilization (Convertino et al., 1980). Hematocrit and plasma osmolality are elevated, with a reduction in red cell mass due to the plasma volume loss (Saltin, Nazar,
Diminished leukocyte phagocytosis has been found after eight to fourteen days of bed rest. In rats and humans, ten to thirty days of immobilization resulted in elevated leukocytolysis which continued following resumption of activity for several days (Fedorov, Fedorova, Pekus, Sakun, 1972). Animal studies with rats and mice immobilized with painful stress have shown suppressed interferon and natural killer cell (NKC) activity (Sukhikh, 1984). A weakness in this study is the lack of control for the age related decline in NKC activity (Mysliwska, J., Mysliwski, A., Witkowski, 1985). Many of the changes in immune function during bed rest are believed to be mediated by the adrenal steroids, i.e., cortisol. Uncoupling of the pituitary-adrenal axis alters adrenal responsiveness (Vernikos-Danellis, Leach, Winget, Rambaut, Mack, 1972; Vernikos-Danellis, Winget, Leach, Rambaut, 1974). Blood glucose elevations and intolerance have been demonstrated in sedentary males (Seals, Hagberg, Allen, Hurley, Dalsky, Ehsani, Holloszy, 1984). This hypoglycemia and intolerance, related to inactivity, are refractory to treatment via endurance exercise (Seals, Hagberg, Hurley, Ehsani, Holloszy, 1984).
SUMMARY

This section of the literature review has addressed reported physiological and psychological alterations occurring upon bed rest. The physical and affective manifestations of deconditioning and inactivity may compound the limitations imposed by the treatment (chemotherapy and anti-rejection drugs) and/or transplant procedure. In most incidences, it is difficult in patients with cancer and many other chronically ill patients to separate the effects of the disease and treatment from the effects of hypokinesia and deconditioning. The fatigue and type II muscle fiber atrophy in these patients on steroid therapy are classic examples of how it is often clinically impossible to differentiate from one another the causative factors of the atrophy and fatigue. The inability to discriminate and control for the effects of disease and treatment versus the effects of deconditioning and bed rest is a limitation; however, it need not prevent study of the exercise responses in the chronically ill patient with cancer. In addition, the inability to discriminate causative factors contributing to physical and affective manifestations present in cancer patients and the chronically ill will not prevent the efficacy of exercise interventions from aiding in resolution of physical and affective manifestations.
RESPONSES TO AEROBIC TRAINING

Aerobic exercise performance is influenced by many factors. One of these factors is exercise economy or efficiency as determined by the oxygen cost of the exercise. Physical work capacity or aerobic capacity measured by testing for maximal VO\(_2\) is also a major determinant of performance. Some of the parameters which alter aerobic capacity and exercise economy include: 1) skill level in complex motor activities, 2) neuro-muscular regulation of fiber recruitment patterns and feedback mechanisms, 3) fiber type and associated biochemical properties, i.e., mitochondria and oxidative enzymes, 4) distribution of blood supply and circulation, 5) fluid and ionic shifts, 6) fuel storage and energy sources available for muscle contraction, 7) anthropometric differences, 8) environmental conditions, 9) cardiac output and its determinants, and 10) psychological differences, i.e., motivation, pain tolerance, and anxiety, to name a few. It has been demonstrated two athletes can vary significantly in aerobic capacity and have similar performance times. Athletes' oxygen consumptions may vary as much as fifteen per cent at the same workloads. Most of this review is designed to examine factors affecting aerobic capacity. It is important to remember changes in exercise economy may significantly reduce the energy requirement for exercise. If an athlete or patient can exercise longer or at a higher per cent of their aerobic
capacity prior to onset of fatigue, performance and functional status will markedly improve without having improved maximal VO$_2$. Continuous endurance exercise improves aerobic capacity and physical fitness; however, the per cent of max VO$_2$ at which blood lactate rises, associated with the onset of fatigue, is not changed. Interval training has enabled athletes and "normals" to exercise at a higher percentage of their max VO$_2$ prior to the onset of blood lactate accumulation.

An improved aerobic capacity may or may not significantly alter the prognosis or severity of the disease in chronically ill individuals. Chronically ill individuals may improve their clinical status and prevent secondary disability by exercise intervention (Kottke, Caspersen, Hill, 1984). The improved aerobic capacity induced by endurance training is secondary to increased oxygen transport and utilization. The improved clinical status in chronically ill patients, secondary to exercise training, may or may not be due to the biological changes which improve aerobic capacity. Other biological changes during exercise training are alterations in: 1) mechanical stresses exerted on musculoskeletal tissue, 2) insulin sensitivity, 3) lipoprotein metabolism, and 4) central nervous system function, to list a few. These biological changes may be the stimuli for the improvement in clinical status or prevention of secondary disability.
They may provide the health related fitness benefits ascribed to endurance exercise.

**PHYSIOLOGICAL RESPONSES**

Increased VO\textsubscript{2} max or aerobic capacity produces several beneficial physiological changes. To elicit a training response to aerobic exercise requires an incremental stress to a physiological system which is specific, overloads, and progresses. Adaptations to aerobic exercise training depend on the frequency, intensity, duration, mode of training, and subject's initial fitness level (ASCM, 1986; AHA, 1977; Wilmore, 1982). When the frequency of training is reduced, Hickson, Foster, Pollock, Galassi & Ruch (1985) demonstrated a high training intensity is essential to maintain max VO\textsubscript{2}, left ventricle mass, and performance improvements gained from intense aerobic training. Low level exercise (< 50-60% of VO\textsubscript{2} max) is associated with: 1) weight loss and anthropometric changes, 2) increased release and utilization of free fatty acids from adipose tissue, 3) reduced stress, 4) improved musculoskeletal integrity, 5) improved selected biochemical reactions, and 6) improved psycho-social functioning. The physiological responses to exercise training seen at rest, submaximal exercise, and maximal exercise are summarized in Table 7.

**Cardiopulmonary Function**

The fact that repetitive exercise exerts a beneficial effect on cardiac performance is generally accepted. The
factors which effect cardiac output during exercise are shown in Figure 2. The cardiac adaptations which occur in response to aerobic training have been described by Rowell (1980) and Blomqvist & Saltin (1983).

After training, at rest or during submaximal exercise, there is no change or a slight reduction in cardiac output due to an increased stroke volume (Ekblom, Astrand, Saltin, Sternberg, Wallstrom, 1968), while heart rate is reduced or stays the same (Wolfe, Cunningham, Rechnitzer, 1979; Blomqvist, Saltin, 1983; Ekblom, Kilborn, Soltysiak, 1973). Some of the increase in stroke volume is accounted for by the increase in ventricular size, volume, and mass found after endurance training (Cohen, Segal, 1985; Wolfe et al, 1979). Elevated myocardial contractility (increased preload and a positive inotropic effect) and reduced afterload (reduced total peripheral resistance) lead to a net increase in ejection fraction (Winters, Leaman, Anderson, 1973). Preload is elevated by an increased venous return and ventricular filling. Training-induced bradycardia has been documented. The mechanism remains to be elucidated; however, the bradycardia is thought to be due to reduced vagal tone (Shephard, 1984) and diminished sympathetic drive (Ekblom et al, 1973). The increased time the heart spends in diastole after training at submaximal workloads accounts for some of the increase in ventricular filling and preload (Rushner, 1976). A drop in resting blood pressure will
### TABLE 7

**PHYSIOLOGICAL ADAPTATIONS TO EXERCISE TRAINING**


<table>
<thead>
<tr>
<th>Organ or function</th>
<th>Increase</th>
<th>Decrease</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locomotor organs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength of bones and ligaments</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic cage</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Muscular mass (myometry)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of muscle cells</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber crosssection</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle strength</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP, phosphocreatine</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>&quot;Aerobic&quot; enzyme activity in muscle</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Oxidative enzyme activity in muscle</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary density, muscle</td>
<td>x</td>
<td></td>
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<tr>
<td>Arteriovenous shunts, muscle</td>
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<td></td>
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<tr>
<td>Blood flow, muscle</td>
<td>x</td>
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</tr>
<tr>
<td>Circulation</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Heart volume</td>
<td>x</td>
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</tr>
<tr>
<td>Heart rate</td>
<td>x</td>
<td></td>
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<tr>
<td>Coronary density, heart</td>
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<td></td>
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<tr>
<td>Coronary collateralization</td>
<td>x</td>
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<table>
<thead>
<tr>
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<th>Decrease</th>
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</thead>
<tbody>
<tr>
<td>Blood volume, total</td>
<td>x</td>
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<td></td>
</tr>
<tr>
<td>Blood volume, resting</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood volume, maximal exercise</td>
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<tr>
<td>Plasma protein concentration</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; Max</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
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<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; Max Difference</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen uptake</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood lactate concentration</td>
<td>x</td>
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</tr>
<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local blood flow, muscle</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Maximal exercise</td>
<td>x</td>
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<td></td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiration</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Lung volume</td>
<td>x</td>
<td></td>
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</tr>
<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal exercise; exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary ventilation</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Total air</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
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<tr>
<td>Maximal exercise</td>
<td>x</td>
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</tr>
<tr>
<td>Diffusing capacity</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Submaximal exercise</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>x</td>
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<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>x</td>
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</tr>
<tr>
<td>Body density</td>
<td>x</td>
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<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>x</td>
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<td></td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
<td>Serum triglycerides</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>High-density lipoprotein</td>
<td>x</td>
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</tbody>
</table>

*Significant to the increase in maximal oxygen uptake.*
FIGURE 2
FACTORS EFFECTING CARDIAC OUTPUT DURING EXERCISE
occur after training, if blood pressure was initially elevated (Choquette, Ferguson, 1973).

The increase in A-VO$_2$ difference found after training is due to an increased extraction of oxygen by the working muscle. This is indicated by a drop in venous oxygen saturation, not a rise in arterial saturation which is unchanged with training (Roskamm & Hahn, 1973). After training at rest and during submaximal exercise, there is a slight rise in vital capacity and a drop in residual capacity and respiratory frequency (Shepard, 1984). Ventilation volume during submaximal exercise after training is reduced (Shepard, 1984).

**Musculoskeletal Function**

Increased oxygen extraction and utilization by the working muscle after training leads to diminished muscle lactate production during submaximal exercise (Gollnick, 1973; Henriksson, 1977; Brooks, Fahey, 1984). After training at submaximal exercise, the lower blood lactate accumulation probably contributes to the improved endurance and diminished leg fatigue (Hurley, Hagberg, Allen, in press). Cellular alterations occurring with endurance exercise training which improve oxygen extraction and utilization include increased:

1) number (>120%) and size (>40%) of mitochondria (Gollnick, Saltin, 1982),

2) myoglobin (Holloszy, 1975; Holloszy & Coyle, 1984),
3) muscle glycogen (Karlsson, Nordesjo, Saltin, 1974),
4) number of type I fibers by the transformation of
type IIA (FOG) (Pette, 1984; Howard, Hoppeler,
Claassen, Mathiew, Straub, 1985),
5) concentration of enzymes in the mitochondria, Krebs
cycle, and oxidative phosphorylation (Saltin,
Rowell, 1980; Gollnick, Saltin, 1982; Lortie et
al., 1985), and
6) utilization and oxidation of free fatty acids as a

After exercise training, increased capillary density
has been demonstrated (Saltin, Rowell, 1980; Hudlicka,
1982). The role which capillary density plays in altering
oxidative metabolism and improving endurance has not been
reported. Stronger connective tissue and increased muscle
fiber size, with the resultant increase in cross-sectional
diameter, improve strength somewhat after aerobic training,
while endurance consistently improves (Jansson & Kaijser,
1977; Matoba & Gollnick, 1984). In addition, exercise has
been utilized to improve bone mineral content (Smith &
Redden, 1977).

Hematological Parameters

The plasma concentration changes during acute exercise
are determined by whether the subject hemoconcentrates or
hemodilutes (Wilkinson, Gutin, Horvath, 1977). As stated
previously, plasma volume is expanded after endurance and
interval training (Convertino et al, 1980; Cohen & Gisolfe, 1982). Hemodilution, secondary to the elevated plasma volume, is responsible for many of the plasma concentration changes present after training (Martin, Ferguson, Wigutoff, Gawne, Schoomaker, 1985). Increases in HCT, Hb, number of red blood cells and decreases in red cell mass, RBC, and hemoglobin concentration are consistently reported at rest after exercise training. Training has been shown to increase platelet number, while platelet adhesiveness is reduced (Jensen, Glud, Arnfred, 1984).

The responses to acute exercise which have been reported are inconsistent. Ohri, Chatterji, Das et al (1983) reported that males, exercising at eighty-five percent of maximal heart rate, had a slight rise in HCT with significant increases in platelet number (Dawson, Ogston, 1969), Hb, platelet aggregation, and blood fibrinogen (Collen, Semeraro, Tricot, Vermylen, 1977). Schmidt and Rasmussen (1984) have demonstrated exercise-induced thrombocytosis results primarily from platelet release by the spleen; however, considerable variation in platelet release from the lungs and liver was found. After a marathon race, Wells, Stern, Hecht (1982) and Krebs, Scully, Zinkgraf (1983) found no change in Hb. Galea & Davidson (1985) did report an increase in concentration. Krebs et al (1983) also reported a significant increase in HCT and albumin, with no change in RBC and plasma globulin.
Reports on alterations in hematological parameters, including immune factors, date back to the early 1900s. Dawson & Ogston (1969) and Ahlborg & Ahlborg (1970) found a transient leukocytosis with a rise in granulocytes and lymphocytes (T cells > B cells). Rocker and Franz (1986) have demonstrated exercise-induced leukocytosis dependent on the intensity and duration of the exercise. Elevated adeninediphosphate, catecholamines, and blood flow to lungs during exercise induce release of WBC from the pulmonary circulation (Robertson, Ramersar, Potts et al, 1981; Priest, Ori, Moorehead, 1982).

Recent investigations have begun to examine other parameters and modulators of immune function besides cell count. Elevated interleukin I has been found after endurance exercise. Inter-leukin I, an endogenous pyrogen released from non-nuclear cells, enhances lymphocyte function. Berk, Tan, Nieman, Eby (1985) and Berk, Nieman, Tan et al (1986) found a decrease in the T lymphocyte helper cell to supressor cell ratio in both marathon runners and sedentary subjects performing exhaustive exercise. Tomasi, Trudeau, Czerwinski, Edredge (1982) demonstrated reductions in immunoglobulin in saliva, mucosa, and respiratory secretions after a 50 km race in trained Nordic skiers. The mechanisms, regulating the alterations of immune function in response to exercise in trained and untrained subjects, have not been reported. Chase and Lowenthal (1984) have reported
significant alteration in lab chemistries with exercise. Golf, happel, Graef, & Seim (1984) have reported altered aldostrone, cortisol, and electrolyte concentrations during exercise after magnesium supplementation. All patients after BMT receive magnesium supplementation.

**PSYCHOLOGICAL RESPONSES**

Hughes (1984) and Taylor, Sallis, & Needle (1985), in reviewing the literature, report over 1,000 articles have been written on the psychological benefits of exercise. A multitude of psychological benefits are associated with increased physical fitness and activity. Again, the exact stimulus is unknown. The determinants of the positive psychological responses which are attributed to improved health-related fitness may be due to altered physiological/biochemical and/or psycho-social stimuli. Stimuli may include:

1) altered sympathetic nervous activity,
2) altered hormonal regulation,
3) altered central nervous system regulation,
4) improved aerobic capacity and muscular tone,
5) changes in body image,
6) enhanced social interaction with reduced stress, and
7) a sense of mastery or achievement.

A number of studies have shown positive correlations between aerobic training, physical fitness, and several psychological parameters (Cureton, 1963; Folkins, Sime, 1981;
positive correlations are found in studies when subjects have had documented psychoses or mood disturbances, i.e., depression and anxiety states, and have undergone aerobic exercise training primarily via running (Geist, Klein, Erschens, Faris, 1978; Taylor et al, 1985). Positive correlations have also been reported with swimming, bicycling, mountain climbing, and rowing (Snyder, Spreitzer, 1974). Brown, Ramirez, Taub (1978), utilizing the MMPI, studied depressed college students, after a ten week running program, comparing them to groups of age-matched which either exercised or were sedentary. Brown et al (1978) reported a significant reduction in negative states on the MMPI in all exercising subjects and an improvement in general activation measured by an activation-deactivation checklist. An improved sense of well-being and morale have also been reported after aerobic exercise training (Sidney & Shephard, 1978; Blumenthal et al, 1981). MaGavin, Gupta, Lloyd (1977) reported low-level exercise, for example walking, improved lifestyle and psychological outlook. Carney, Harter, Templeton (1983) found improved psycho-social functioning with associated diminished signs and symptoms of depression in patients with ESRD on hemodialysis.
Perceived Exertion

Ratings of perceived exertion (RPE) are a standard assessment tool used during exercise stress tests. During testing, monitoring of physiological responses is essential. Knowledge of how the subjects are feeling during the exercise is an important complement to the physiological data to better understand how subjective symptoms relate to objective measures.

The Borg scale or RPE (Figure 3) is a simple 15 grade rating scale with descriptive verbal anchors at every odd number (i.e. 9 = very light and 17 = very hard) which produces greater differentiation at the ends of the measurement range (6-19) (Borg, 1970; Borg, Noble, 1974). Numbers are selected to coincide with the individual's perceptions of the exercise intensity. Originally, Borg designed the RPE to increase linearly with work intensity and heart rate during cycle ergometry. During the development of this instrument, each subject estimated the intensity level which corresponded to his exercise perception at any point in time or exercise level. The rating of perceived exertion selected, multiplied by 10, represented the subject's heart rate. A score of six was viewed as the baseline sensation for a particular task which represented no exertion or rest. Twenty was viewed as the most work a person could perform at a task and represented the greatest degree of exhaustion a person could feel.
<table>
<thead>
<tr>
<th>RPE</th>
<th>New Rating Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0 Nothing at all</td>
</tr>
<tr>
<td>7</td>
<td>0.5 Very, very weak</td>
</tr>
<tr>
<td>8</td>
<td>1 Very weak</td>
</tr>
<tr>
<td>9</td>
<td>2 Weak</td>
</tr>
<tr>
<td>10</td>
<td>3 Moderate</td>
</tr>
<tr>
<td>11</td>
<td>4 Somewhat strong</td>
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<td>5 Strong</td>
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<td>13</td>
<td>6</td>
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<td>14</td>
<td>7 Very strong</td>
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<td>8</td>
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<td>16</td>
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</tr>
<tr>
<td>17</td>
<td>10 Very, very strong</td>
</tr>
<tr>
<td>18</td>
<td>Maximal</td>
</tr>
<tr>
<td>19</td>
<td>Very, very hard</td>
</tr>
</tbody>
</table>

**FIGURE 3**

BORG'S ORIGINAL AND REVISED RPE SCALES
(Adapted from "Psychophysiological basis of perceived exertion", by G. Borg, 1982, published in Medicine and Science in Sports and Exercise, 14, 377-381.)
The RPE is based on the assumption that perceptions of physiological changes, during exercise, serve as a potent sensory cue for perception of work intensity. Physiologic responses are monitored at a conscious and subconscious level during the exercise. Sensation related to heart rate tends to be a subconscious awareness, while sensory signals of respiration and ventilation are a conscious perception. Two categories of physiological factors, local and central, are proposed as primary determinants to explain the variability in RPE during exercise (Ekblom, Goldberg, 1971; Pandolf, Noble, 1973; Pandolf, 1978).

Local cues are derived from feelings of strain in active muscles, tendons, and joints and include muscle aches, tremors, cramps, pain, fatigue, and twitches (Cafarelli, 1982). Most of the literature assumes local factors are the predominant sensory cues during exercise and, as the strain on muscle increases, local signals become more intense (Ekblom, Goldberg, 1971; Pandolf, Burse, Goldman, 1975). Lactate, produced as a metabolic end product of anaerobic metabolism, appears to be a potent sensory stimulus in generation of local cues (Allen, Pandolf, 1977; Edwards, Melcher, Hesser, Wigertz, Edelund, 1972; Gamberle, 1972), and, therefore, a major determinant of perceived exertion. However, Mihevic (1981) and Lollgen, Graham, Sjoogaard (1980) have shown at low exercise intensity the importance of lactate as a sensory cue is
insignificant. This explains some of the variability which occurs during exercise involving differing intensities and varying amounts of muscle mass, for example, arm versus leg exercise.

Central factors are primarily derived from feelings of strain from the cardiopulmonary system (Robertson, 1982; Edwards et al, 1972; Ekblom, Goldberg, 1971). Most of the literature assume central factors act to potentiate or amplify local signals as exercise intensity increases (Cafarelli, 1977; Pandolf, 1982; Noble, 1986). Young, Cynerman, Pandolf (1982) suggests a more significant role for sensations of respiratory distress or effort in determination of perceived exertion. The majority of the research on perceived exertion is correlational. The literature does not allow a direct or cause-effect relationship between central and local factors and perceived exertion to be determined. When more direct methods of study have been used, there is little support for increasing heart rate (Young et al, 1982; Squires, Rod, Pollock, Foster, 1982; Davies, Sargeant, 1979; and many others) and increasing lactate (Lollgen et al, 1980; Robertson, Gillespie, Hiatt, Rose, 1979; and others) as causing an increase in perceived exertion; although, both rise as work intensity and perceived exertion increase. Borg, Ljunggren, Ceci (1985) and Noble, Borg, Jacobs, Ceci, Kaiser (1983) using Borg's category-ratio scale (Borg, 1982) (Figure 3),
again through correlational research, suggest heart rate and blood lactate combined together are good predictors of perceived exertion.

Pandolf et al (1975) and Pandolf (1982) have suggested differentiated ratings (ratings of specific regions of the body) be obtained versus a single overall rating. Subjects' rating of local cues, i.e., leg fatigue, versus ratings of central cues, i.e., respiratory effort, may provide a better grasp of the overall rating of perceived exertion. Pandolf's proposed scheme for differentiated ratings is shown in Figure 4.

Morgan (1973) and Pandolf et al (1975) have found some of the variability in perceived exertion may also be explained by psychological integration of motivation, past experience including previous consequences, cultural and social background, sex, personality, and health status. Further research by Robertson et al (1977) and Pandolf (1983) supports the involvement of the central nervous system in adjusting and integrating perceptions of exertion.

Ratings of perceived exertion have been correlated to heart rate and exercise intensity, with coefficients reported between .80 and .90 in athletes and healthy sedentary individuals (Skinner, Hutsler, Bergstrinova, Buskirk, 1973; Borg, Noble, 1974). Cardiac patients have been found to rate their exercise perceptions as 7 (very, very light) throughout an entire graded exercise test (Williams et al, 1981; Gutman, Squires, Pollack, Anholm, 1981).
FIGURE 4
PANDOLF'S MODEL OF FACTORS REGULATING PERCEIVED EXERTION
(Reprinted from "Influence of local and central factors in dominating rated perceived exertion during physical work" by K. B. Pandolf, 1978, published in Perceptual Motor Skills, 46, 683-698.)
Also, patients seeking disability, early retirement, or workman's compensation have been found to exhibit a large discrepancy in their psychological and physiological responses to exercise (Noble, 1982). The subject's perceptions of stressfulness may be of considerable importance for exercise prescription in clinical populations; for example, patients with diabetes mellitus or cardiac disease whose metabolic and cardiovascular responses to exercise may be asynchronous with their psychological and behavioral responses (Noble, 1982; 1986).

Clinical use of perceived exertion as a method of exercise prescription has been reviewed by Noble (1982). Smutok, Skrinar, Pandolf (1980) showed use of low exercise intensities were inaccurate in predicting heart rate and, therefore, of limited use in clinical populations with low maximal heart rates training at lower work intensities. Sidney (1977) supports this idea in older subjects where heart rates declined with training and perceived exertion was unchanged. Gutman et al (1981) showed in cardiac patients perceived exertion and heart rates during training were similar to those obtained during stress testing. It must be noted, however, the methodologies of the studies by Gutman et al and Smutok et al differ, as presented by Noble (1982). The use of RPE to determine and monitor training intensity in patients after transplant has not been examined. However, RPE in patients after transplant would be
expected to be similar to other patients with metabolic disturbances.

CLINICAL STUDIES OF EXERCISE TRAINING

In the past twenty years, research on the effects of aerobic training of clinical populations has rapidly expanded. Reports on the effects of aerobic training on several chronically ill populations have shown improvement in functional capacity. Improving physical work capacity is a significant factor in diminishing fatigue and promoting the ability to engage in the prolonged activity necessary to function independently. Even with low-level exercise training, there have been reported beneficial peripheral changes. Saltin et al (1976) and Henriksson & Reitman (1977) have both documented decreased lactate production during exercise in trained muscle. Greene, Zabetakis, Gleiss et al (1979) demonstrated an increased endurance after ten weeks of treadmill exercise in patients with a diagnosis of end-stage renal failure. Goldberg, Hagbert, Delmez, Haynes, Harter (1980) reported low-level cycle ergometer exercise of six months duration in end-stage renal patients on hemodialysis was able to improve functional capacity. Of clinical significance, the exercise training resulted in reduced blood pressure and improved lipid and carbohydrate metabolism.

Exercise training to improve functional capacity in the elderly (Sidney, Shepard, Harrison, 1977) or secondary
prevention for patients with cardiovascular disease, whether medically (Pollock, Wilmore, Fox, 1984) or surgically (Soloff, 1978) managed, is an integral part of cardiac rehabilitation. Patients with type II diabetes mellitus have also been shown to benefit from exercise training with improved physical work capacity (Richter, 1985). Exercise training has expanded into use in other chronically ill populations, i.e., patients undergoing heart (Kavanagh, Yacomb, Campbell, Mertens, 1986) and renal transplant (Painter, Messer-Richek, Hanson, Zimmerman, Glass, 1986) and patients with type I diabetes mellitus (Richter, Ruderman, Schneider, 1981; Wolfe, DiCarlo, 1983).

SUMMARY

This section of the literature review has addressed reported physiological and psychological alterations occurring upon aerobic exercise training, the exercise intervention utilized in this project. The intensity, duration, and frequency of exercise which should be encouraged in cancer patients during therapy has not been determined. A conditioning threshold for cancer patients on chemotherapy and, in this case patients after BMT, has not been established.

Recently, research on the effects of aerobic training of clinical populations has expanded. Improvement in functional capacity has been reported in various chronically ill populations subsequent to participation in aerobic training.
Patients undergoing transplant should benefit from diminished fatigue and an improved ability to participate in prolonged activity to promote functional independence by improved physical work (Holtzan, 1987; Pfalzer, Tutschuka, Harper, in press). Even with low-level exercise training, there have been reported beneficial peripheral changes in many chronically ill populations.

SUMMARY OF THE LITERATURE REVIEW

The need for the general population to pursue chronic aerobic exercise is widely accepted. Chronic exercise is imperative for patients with cancer who are already at risk for poor health due to their hypokinetic lifestyles. As summarized, the effects of disease and treatment are pervasive and severely diminish the overall health of the patient with cancer. The literature supports a beneficial effect of chronic exercise on the psycho-social functioning of subjects with derangements in functioning. The literature, while controversial, suggests a similar effect in normals. Many reports of diminished psycho-social functioning in patients undergoing bone marrow transplant are noted in this review. In answer to one of the research questions, it appears consistent with the literature to expect, if impaired, improved psycho-social functioning in these subjects with chronic exercise.

The predominant physiological alterations, consistent with the literature review, are in the hematological, renal,
cardio-pulmonary and musculoskeletal systems as a result of the disease and treatment. Factors involved in the physiological alterations demonstrated by the literature include:

1) reduced cell counts and anemia from the disease and treatment, resulting in diminished O$_2$ transport,

2) decreased cardiac function, possibly due to myopathy, body fluid changes, and electrolyte disturbances with decreased output also leading to diminished O$_2$ transport,

3) shifts in metabolism resulting from the disease and/or inactivity with early onset of anaerobic metabolism, resulting in lactic acidosis,

4) fluid overload from excess drug-induced fluid retention, renal impairment, and extensive hematopoietic support required by these subjects,

5) drug-induced and/or inactivity-induced type II muscle atrophy leading to many physiological alterations, and

6) low initial fitness levels secondary to disuse and isolation.

In regards to the other research questions posed in the introduction, the results of the literature review support a beneficial effect of chronic exercise on tumor-bearing animals and humans. The mechanism by which the exercise
alters the cancer process is unknown. However, in the literature review, several studies demonstrated reliably that patients with chronic diseases, which induce generalized muscle atrophy and anemia and which are treated with similar anti-rejection protocols, respond similarly to exercise. The subjects in these reports have included patients with cardiopulmonary diseases, diabetics, and renal disease and transplant. The results of this literature highlight the importance of exercise for prevention of secondary disability. Questions which remain unanswered in patients with cancer are: "Will exercise training reverse the process of secondary disability?", "Will they respond to chronic exercise in the same manner as the normal sedentary person?", and "What are optimal and safe exercise conditions, i.e., duration, frequency, intensity, and environment, to induce a training response?".
CHAPTER II
EXPERIMENTAL DESIGN AND RESEARCH METHODS

Experimental Design

The study uses a three group design with repeated measures. The two experimental groups were drawn from patients volunteering to participate in a low to moderate (50-75% VO₂ Max) aerobic, interval, exercise training protocol using a cycle ergometer three days per week. The research design was as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=6)</td>
<td>O₁</td>
<td>O₂</td>
<td>O₃</td>
</tr>
<tr>
<td>ET (n=8)</td>
<td>O₁</td>
<td>R₁</td>
<td>O₂</td>
</tr>
<tr>
<td>LT (n=7)</td>
<td>O₁</td>
<td>O₂</td>
<td>R₂</td>
</tr>
</tbody>
</table>

Subjects were randomly assigned to each group. Group 1 (n=8) exercised post-transplant while in the in-patient unit and continued to exercise on discharge to the day care unit; Group 2 (n=9) exercised only after discharge into the day care unit, approximately thirty days post-transplant. Group 1 and 2 continued to exercise until discharged from the day care unit. Group 3 (n=6) was the control group. All three groups were pre-tested prior to transplant, re-tested upon discharge to the day care unit, and post-tested on discharge.
from the day care unit post-transplant. Collected pre-test data included a stress MUGA and resting 12-lead EKG by the Department of Cardiology, a pulmonary function study by the Pulmonary Function Laboratory, resting blood chemistry and hemotological values, a standard body weight and skinfold measures for estimation of percent body fat, an isokinetic muscle performance assessment, a SLGXT with monitoring of blood pressure, 12-lead EKG, gas collection, and RPE every two minutes with determination of peak VO$_2$ during the test, and completion of a Symptom Activity Checklist (SAC). Pulmonary function testing and the stress MUGA were part of the initial patient evaluation only, while all other data was again collected on intermediate and post-testing.

Research Methods

SAMPLE

The sample consisted of patients with the diagnosis of acute non-lymphocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia and aplastic anemia undergoing BMT at The Ohio State University Hospital. Subjects were identified by the head nurse of the in-patient BMT unit. Each subject was then interviewed by the investigator and a Past Medical History form completed (Appendix E).

Selection criteria consisted of the following:

1. no uncontrolled diabetes mellitus, hypertension, or known cardiovascular disease,
2. not currently on cardio-toxic drugs,
3. completed referral from physician responsible for bone marrow transplant,
4. participation in tri-weekly exercise sessions for nine weeks as an outpatient per attending physician's approval, and
5. not currently engaged in an exercise program and the agreement that if one is started on off days, additional activity will be documented on the SAC.

If the subject met eligibility requirements, the patient's physician was requested to submit a referral (Appendix F). A pre-test date and time were set, and arrangements were made to transport the subject to the testing site in Larkins Hall. Prospective subjects were given detailed information regarding the study's purpose and procedures. Prior to exercise testing, a written informed consent was signed by each subject (Appendix G), and subjects were informed of potential risks and benefits of the study.

MEASUREMENT PROCEDURES

The measurement procedures utilized are discussed in the following order: 1) test or measurement, 2) description, 3) rationale for choice, 4) reliability of instrument, 5) application, and 6) data recording.

Anthropometric Measurements

The subject's age, height, weight, and skinfold measures for determination of percent body fat (Appendix H)
were recorded prior to testing. Body composition was determined by skinfold measurements using calipers, as hydrostatic weighing was not feasible for this clinical population secondary to the life-threatening risk of infection. The subjects were from a wide age range.

Jackson and Pollack's (1985) method is one of the few body fat nomograms in which measures have been formulated over an equally wide age range. The reliability and validity of assessing body composition, by use of Jackson and Pollack's method in patients with cancer, has been questioned (Cohn, Ellis, Vartsky et al, 1981; Shike et al, 1984; Shizgal, 1985). An equation utilizing non-invasive measures, i.e., skinfolds, circumferences, or diameters, which is generally accepted for patients with cancer has not been developed to date. The need is well recognized, however, for accurate body composition assessment in patients with cancer to monitor nutritional status and response to therapy.

Skinfold measurements were taken on the right side of the body at three sites using a Harpenden skinfold caliper: 1) the tricep, suprailiac, and anterior thigh for females, 2) the pectoralis, abdomen, and anterior thigh for males. Siri's equation calculating percent body fat from body density was utilized according to the method of Jackson & Pollock (1978, 1978, 1985) and is as follows: percent body fat = 100 \( \frac{4.95}{\text{body density} - 4.5} \).
Symptom-Limited Maximal Graded Exercise Test Protocol

Symptom-Limited Maximal Graded Exercise Test (SLGXT): A continuous graded bicycle ergometer exercise test providing an objective measure of physical work capacity and baseline data for the exercise prescription.

The SLGXT is conducted as a pre-test, intermediate test, and post-test to quantify and evaluate the response to aerobic exercise training on physical work capacity. Aerobic training effects are parameters of the dependent set of variables (SLGXT Protocol-Appendix B).

Workload: A specific amount of resistance on the bicycle ergometer which sets the work intensity. Resistance can be increased or decreased, depending upon the amount of resistance applied to the fly wheel on the bicycle. The amount of resistance, measured in watts or kiloponds on a gauge, is measurable and repeatable when the ergometer has been calibrated. In this study, workload increments are 25 watts for the SLGXT and 12.5 watts for the interval training sessions (Winningham et al, 1983).

Physical Work Capacity: Assessed by the VO2 max attained on graded exercise testing (ACSM, 1986). VO2 max is used synonymously with "aerobic fitness", "aerobic capacity", and "physical work capacity" (Shepard, 1984; Wilmore, 1982; Fox & Mathews, 1980; Noble, 1986) and is defined, in this study, as the maximal amount of O2 consumed during the test.
The data yielded by the SLGXT had four purposes: 1) to compare the results of the three stress tests for each subject, 2) to provide baseline data, 3) to compare low to moderate exercising immediately post-transplant versus starting approximately thirty days post upon discharge from the in-patient unit into the day care unit, and 4) to serve as the basis for the exercise prescription for the two groups of experimental subjects entering the exercise program.

When evaluating athletes and trained individuals, the test subject is encouraged to work to exhaustion, which was defined as the point at which oxygen consumption plateaus while the workload continues to increase. Symptoms in clinical populations, i.e., leg fatigue, shortness of breath, or generalized fatigue, often limit the person's ability to continue performing increasing work. When a specific symptom or symptoms cause termination of the test, the individual's peak oxygen consumption has been reached and physical work capacity attained. This approach, a SLGXT, was selected for this study as symptoms were expected to cause test termination.

Three graded exercise tests per subject were performed at The Ohio State University Laboratory of Work Physiology, Cardiac Rehabilitation and Metabolic Testing. Each test required approximately one hour to complete. The protocol consisted of continuous discrete workload intervals over a
specific period of time. In this study, workload was initiated at zero watts and increased every two minutes by twenty-five watts until completion of the test (Winningham et al, 1983; Appendix B).

Potential contaminating variables included laboratory conditions such as the lab environment, i.e., temperature and humidity, which could not be controlled. Laboratory conditions determined for all three SLGXT's included: barometric pressure, temperature in degrees centigrade, and relative humidity. The metabolic cart was allowed a minimal warm-up period of one hour for optimal operation prior to the test session. Within thirty minutes prior to testing, ambient temperature, barometric pressure, and percent relative humidity were measured in the testing laboratory by means of a mercury thermometer, a mercury barometer and a sling psychrometer respectively. A known gas sample (O2, CO2) was used to calibrate the oxygen and carbon dioxide analyzers. A 1000 milliliter volume syringe was used to calibrate the volume meter. The metabolic cart and bicycle ergometer were recalibrated before each test.

A twelve-lead electrocardiograph was recorded on a Computer Assisted System for Exercise (CASE) Marquette EKG Unit. Blood pressure was measured with a Trimline mercury sphygmomanometer. Although recently examined by Rasmussen, Stasts, Driscoll, Beck, Bonekat, & Wilson (1985) and deemed to be more valid and reliable, direct measurement of blood
pressure was unable to be utilized on these subjects. In addition, as these subjects were performing cycle ergometry exercise instead of treadmill exercise, more precise measures of indirect blood pressure were obtained (Smolak, 1982). Cycle ergometry was performed on a Monarch ergometer model #868. The pace of fifty cycles per minute was set by a Franz electric metronome. The investigator was Advanced Cardiac Life Support Certified and a physician was available for all SLGXT's.

Subjects were shown the equipment and the purpose of each piece was explained to familiarize the patient with test procedures. Standard weights were taken on the day care unit prior to the test. Following skin preparation, ten electrodes were applied at standard sites for a resting 12-lead EKG and the subject lay supine for five minutes prior to the recording of the EKG and resting blood pressure.

The subject was then seated on the cycle ergometer with the seat adjusted to the appropriate height using the Winningham et al (1983) protocol. A face mask, connected to a one-way valve for collection of respiratory gases, was placed over the subject's face and head gear adjusted to ensure that all expired air was collected for measurement and analysis of VO2 and CO2 by the Erich Jaeger Ergo-Pneumo Test II Metabolic Cart. Calculation of corrected gas samples to STPD (standard temperature, pressure, dry) were
made by a pre-programmed Hewlett-Packard model #9815A calculator. Body weight of the subject in kilograms was entered into the computer for respiratory gas calculations. There was a two minute rest in the seated position during which EKG, blood pressure, and respiratory gas exchange measures were made. At the end of two minutes, the subject began a warm-up by pedaling the ergometer at fifty cycles per minute at zero load. Heart rate, blood pressure, and RPE were monitored every two minutes throughout the test during the last forty-five seconds of each two minute stage. Respiratory gas values were collected every thirty seconds by the metabolic cart.

Criteria for terminating the SLGXT included the following:

1) leg fatigue, evidenced by inability to continue pedaling at fifty cycles/minute for more than one minute,
2) failure of systolic blood pressure to rise with increasing workload, a drop of ten mmHg or more of systolic pressure, an increase in systolic pressure to 250 mmHg or more, or a rise in diastolic pressure to more than twenty mmHg,
3) shortness of breath,
4) complaint of nausea,
5) complaint of excessive generalized fatigue,
6) subject voluntarily terminated the test, and
8) preseence of any EKG changes and abnormalities which were consistent with the ACSM (1986) GXT guidelines for discontinuing a test.

Exercise heart rate responses may vary according to sex, age, levels of anxiety or anger, disease, food intake, ie., caffeine, physical fitness, time of day, and medications.

At the conclusion of the test, the face mask and head gear were removed, and the subject cooled-down by continuing to pedal at zero load for two minutes. The subject was seated on a chair with feet elevated for an additional two minutes of recovery. EKG and blood pressure continued to be monitored at two minute intervals, until the subject was recovered with a heart rate below a 100 beats/minute.

Baseline data on resting blood chemistry and hemotological values the day of the SLGXT were evaluated prior to the subject performing the SLGXT.

Isokinetic Muscle Performance Assessment

Isokinetic Muscle Performance Assessment: An objective measure of leg performance by dynamic assessment of maximum concentric muscle torque production throughout the active range of motion of the knee. The evaluation was conducted using a protocol adapted from Lumex Corporation, Cybex Division (1980), Rothstein et al (1983), for testing arthritics on high-dose steroids, and Greene & Strickler
The Cybex II Isokinetic Dynamometer may be used to objectively measure torque during concentric muscle contraction, joint motion, and peak torque in relation to joint angle and timing between repeated contractions. Work, power, and fatigability can be calculated from the data. Speeds are controlled from 0 to 300 degrees per second. Muscle contractions are performed concentrically with reciprocal contractions of antagonists. Peak values are lower as the speed of contraction increases. This is expected due to the force-velocity relationship in skeletal muscle. The isokinetic dynamometer was selected for use with these cancer patients for the following reasons:

1) Isokinetic exercise is less traumatic to joints and weakened ligaments than isotonic weight lifting for deconditioned individuals.

2) This population has increased risk of stress fractures and joint bleeding. Joint bleeding secondary to diminished clotting ability, if repeated, can lead to progressive joint destruction and disabling arthropathy. Therefore, safety is important.

3) There are many rehabilitation patients for whom resistive exercise is indicated, depending upon presence of pain or stage of healing (Campbell &
Alternating reciprocal concentric muscle contractions and range of motion are easily assessed, objectively, on the Cybex II Dual Channel Recorder.

External weight can produce traction, torsion, and compression on joints and supportive structures which the debilitated patient may not be able to tolerate. High speed settings on the dynamometer may be used to produce high velocity isokinetic exercise. High velocity exercise diminishes the maximum force generated at the joint by the contracting muscle, however, it continues to provide maximal resistance to muscle contraction throughout the joint range. This method of testing offers safe, early resistive strength assessment when high load effort may be contraindicated. If pain or cramping occurs at any point in the joint motion during exercise testing, the subject can cease the motion and the resistance is removed.

The test protocol includes four aspects of strength assessment to ensure repeatability: 1) subject positioning and stabilization, 2) test speeds or speed, 3) reciprocal or unidirectional movement, and 4) number of repetitions of contraction. The test protocol was adapted from a protocol suggested by Lumex Corporation, Cybex Division (1980), and Greene & Strickler (1983) in a study performed with
hemophilia patients. The protocol was designed to meet the following specific concerns of this study: 1) the obtainment of an objective baseline measure of knee flexion/extension muscle strength, 2) the application of a form of strength assessment which would be safe in this clinical population with their increased risk of joint trauma, and 3) the development of a clinical method of strength assessment which allowed for the non-invasive determination of type II muscle fiber atrophy (Barnes, 1980; Rothstein et al, 1983). The velocity of contraction set by the dynamometer can be used to simulate the muscle contraction used while on the bicycle ergometer and in activities of daily living. Wyatt & Edwards (1981) showed rehabilitation of the knee to enable normal gait requires work ratios between 200-300 degrees per second.

Reliability and validity of the Cybex II have been established (Thistle, Hislop, Moffroid et al, 1967; Moffroid, Whipple, Hofkosh, Lowman, and Thistle, 1969). Major limitations of the Cybex II are:

1) It is an artificial condition which does not normally occur during activity. Normal motion occurs in multiple planes around various axes at variable speed and constant resistance. The external force applied to create motion does vary throughout the joint range due to changes in lever arm length and the angle of pull of the muscle.
2) The effect of gravity on the limb being tested produces distortion in the test results which may effect major changes in the flexion/extension ratio (Winter, Willis, and Orr, 1981; Nelson & Duncan, 1983; Fillyaw, Bevins, and Fernandez, 1986). The error due to gravity is present in the results of all subjects tested, as gravity was not corrected in this study so a comparison with previously published data could be made.

3) Torque under and over shoot occurs due to: a) the construction of the device, and b) the rapid acceleration and deceleration by subjects during the initial and final phases of the range of motion (Rothstein et al, 1983; Sapeka, Nicholas, Sokolow, and Saraniti, 1986).

4) For inter-subject and group comparison, the factors of age, sex, weight, and height should be considered (Larsson, Grimby, and Karlsson, 1979; Wyatt & Edwards, 1981; Alexander & Molnar, 1973; Molnar & Alexander, 1973, 1974).

Potential contaminating factors during isokinetic testing are: 1) the loss of instrument calibration, 2) the variations in trunk and thigh position between subjects, 3) the improper positioning of the lever arm axis of rotation, 4) the learning effect from repeated trials, and
5) improper positioning of the lever arm interfering with normal ankle motion. The Cybex II was calibrated prior to the testing session using known weights. The subject was seated at the table with the trunk and thigh being tested stabilized by velcro straps attached to the table. The axis of rotation of the Cybex II was aligned with the anatomical axis of the subject’s knee. The lever arm was attached just proximal to the subject’s ankle mortis, and ankle motion was assessed for restrictions. Subjects were allowed to warm-up at each speed to minimize a possible learning effect. Testing of both knees was done in the following order at speeds of 90, 180, 300 degrees per second at the Physical Therapy Department, The Ohio State University Hospital (OSUH), the day prior to the symptomlimited graded exercise test. Subjects rested sixty seconds between each trial. The dominant leg was determined to be the strongest leg, unless a history of musculo-skeletal injury was present.

Analyzed data consisted of the peak value from the four repetitions performed by the hamstring and quadriceps muscles. The data report form is shown in Appendix D. Peak torques were obtained at 90, 180 and 300 degrees per second for knee flexion and extension; flexion and extension to body weight ratios were calculated.
Pulmonary Function Test

Pulmonary function testing (PFT) was done by the Pulmonary Function Laboratory at The OSUH, according to their lab protocol (Appendix K). A Collins DS/560 PFT System with computer link to Apple II Plus was used to conduct the PFT.

Laboratory Values

Blood chemistry and hematological counts were performed by the Clinical Chemistry and Hematology Laboratories, respectively, at The OSUH. Chemistries were done by a Beckman Astra 8 with blood glucose calibrated every two hours, and BUN, Creatine, albumin, and total protein were re-calibrated every eight hours. Re-calibrations were also performed when reagents were changed or if a problem was cited by the computerized monitoring system. Controls were run every twelve to fifteen patients. Normative laboratory values are shown in Appendix M. Blood chemistries were performed prior to the exercise to eliminate possible contaminating effects of the exercise on chemistries, i.e. creatinine kinase (Apple, Rogers, Casal, Sherman, Ivy, 1985; Chase & Lowenthal, 1984).

Resting EKGs & Stress Mugas

Resting 12-lead EKGs, recorded by a Hewlett-Packard Electro-cardiograph, were interpreted by the Department of Cardiology at The OSUH prior to transplant. Stress mugas
were performed in the Cardiovascular Nuclear Medicine Laboratory at The OSUH, also prior to transplant (Appendix L).

**Symptom Activity Checklist**


The checklist developed by Winningham (1983) for use by patients with breast cancer quantifies the physical and psychological signs and symptoms which subjects perceive as limiting activity. It is a forty-eight item survey based on a Likert scale with closed end responses rated from one to five as follows:

1) do not have symptom,

2) have symptom, but it doesn't affect activity level,

3) slows me down a little,

4) interferes with work/recreation, and

5) forces me to sit/lie down frequently.

The form was field tested by surveying cancer patients, oncology nurses, and physicians. It was also used in pilot work and a subsequent, on-going study by MacVicar & Winningham who investigated responses in breast cancer patients. Reliability of the checklist for use with patients undergoing bone marrow transplant has not been reported, although patients with various sites and stages were utilized in the development of the survey. Subjects completed the checklist weekly and before undergoing SLGXT.
Psychological Assessment

The psychological testing was completed by the subjects before transplant and approximately one hundred days after transplant by a member of the Clinical Psychology Department. The SCL-R-90 (Deragotis, Akiloff, Melisaratos, 1979) was one of the tools used to assess the subject's psychological state and level of functioning. The SCL-R-90 is a 90 item self-report questionnaire, covering nine areas of symptoms (depression, anxiety, etc.) on a five-point scale.

Exercise Training Protocol

Interval Training: A series of repeated bouts of continuous or interrupted exercise where higher intensity workloads are alternated with lower intensity workloads (Fox & Mathews, 1980; Lamb, 1984; Noble, 1986; Astrand & Rodal, 1986) (Exercise Protocol-Appendix A).

Submaximal Workload: A workload less than the individual's maximal oxygen consumption (VO2 max). During the training period, a low-moderate submaximal workload was maintained between 50-60% and progressed to 60-75% of VO2 max, determined from the SLGXT pre-test.

The training program was adapted from a protocol suggested by the American Heart Association, "Interval Training: Prescriptions for Calibrated Bicycles" (AHA, 1975) and developed by Winningham et al (1983). The cycle ergometer was selected for use with these cancer patients for the following reasons:
1) For deconditioned individuals, especially BMT patients at risk of injury by joint bleeding and/or stress fractures, cycle ergometry is less traumatic to joints and weakened ligaments than jogging or walking. However, it produces similar physiological exercise responses.

2) Symptoms of weakness and fatigue are common in debilitated individuals and patients on chemotherapy. After bed rest, balance on postural changes may be impaired, secondary to orthostasis from diminished pressor re-responses. Cycle ergometry supports the body weight, decreasing the risk of injury. Ergometry also enables easier and more accurate physiological measures. Cycling has many pluses as an exercise mode for debilitated subjects; however, the smaller amount of muscle mass utilized in cycling versus jogging or walking may elicit higher blood pressure responses to exercise.

3) The cycle ergometer's resistance or workload can be accurately repositioned to allow exact measurement of work performed (Wilmore, Constable, Stanforth et al, 1982). Regulation of the subject's exercise within prescribed limits in severely deconditioned individuals is accurate and easy.
4) Physiological parameters, i.e., blood pressure and heart rate, are easily monitored, because the patients are in a stable position.

5) The cycle ergometer can be more cost effective than treadmills, allowing repeated group exercise usage (Mellerowicz and Smollaka, 1981; Smollaka, 1982).

6) Space is severely restricted in the BMT patient units.

One of the disadvantages of the bicycle ergometer is the higher systolic blood pressure attained on the cycle ergometer during strenuous exercise when compared to a treadmill (Adams, Bonner, Ribisi, Miller, 1978). Another disadvantage is the high blood lactic acid concentration during exercise with a cycle ergometer (Kostka & Caferilli, 1982), although this is diminished after training (Hurley, Hagberg, Allen, in press). The lower ventilatory threshold exhibited on the bicycle ergometer versus the treadmill may be a reflection of the higher lactate concentration (McConnell, Swett, Missri, 1984). In addition, cardiorespiratory responses to bicycle or treadmill training have been demonstrated to be specific to the mode of exercise (Pechar, McArdle, Katch, Magel, Deluca, 1974).

The exercise prescription contains the five aspects of activity related to improving health and fitness (cardiorespiratory endurance, muscle strength, body composition and flexibility) as outlined by the ACSM (1986) and the AHA
(1977), regardless of disease state, age, or physical fitness. The prescription is based on the results of a graded exercise test: exercise mode, intensity, frequency, duration, and subject's initial physical status.

Mode: Exercise was performed on a calibrated Tenturi cycle ergometer, utilizing a large muscle mass in a rhythmical pattern, pedaling at a rate of fifty revolutions/minute to allow for aerobic exercise training.

Intensity: Workload (resistance) was set in watts, with the subjects' cardio-vascular response to work monitored by repeated heart rate and blood pressure assessment. The subjects' initial resistance level was determined from the graded exercise pre-test. Training intensity was set at that workload which maintained a heart rate initially corresponding to 50-75% of VO$_2$ max. If the patient was unable to maintain this exercise level, the heart rate was reduced to a level corresponding with 40-50% VO$_2$ max until progression was possible.

Frequency: To be effective and to allow a day of rest for bone and joint stress adaptation, exercise periods were three times per week on alternating days in both experimental groups. Exercising two times a week may maintain a level of physical work capacity; however, improvement does not occur (Fox & Mathews, 1981).

Duration: Duration refers to the time spent at high-low resistance intervals and the number of repetitions, not
including warm-up and cool-down periods. High intensity exercise (>90 max VO₂) of 10-15 minutes may elicit a training response; however, deconditioned individuals are not able to tolerate or sustain exercise at high intensity without risk. Exercise sessions of 20-30 minutes are advisable in debilitated subjects. Duration of intervals at high and low resistance were from Winningham (1983).

Initial Physical Status: Determined from the limiting symptoms, any EKG abnormalities, heart rate, blood pressure, and VO₂ max attained on the pre-test.

Research has demonstrated moderate exercise training which enhances physical work capacity is more effective when work is performed intermittently (periods of higher intensity work succeeded by lower intensity work) rather than continuously (Astrand & Rodahl, 1986). This type of physical conditioning is "interval training" and not only has the advantage of increasing cardiac and circulatory reserve, but of simultaneously developing both aerobic and anaerobic energy systems (DeVries, 1980; Fox & Mathews, 1980). Interval training, by improving both energy systems and cardiovascular reserve, allows full participation in the activities of daily living, and thus is the exercise therapy of choice in many debilitated individuals.

The interval training program consists of repeated bouts of alternating high and low intensity workload exercise. The lower intensity workloads function as a
period of recovery from the higher intensity exercise, enhancing blood flow through the working muscle and anaerobic recovery to prevent lactic acid induced discomfort in leg muscles (Fox & Mathews, 1980). Also, interval training generates a greater amount of work in a shorter period of time at a lower heart rate. Type II fiber recruitment may be increased secondary to training for short periods of time at higher intensity than is possible during continuous exercise. This training protocol (Winningham et al., 1983) allows the subject to sustain aerobic exercise for twenty minutes from the first session, promoting gradual cardio-vascular and metabolic adaptation and preventing severe fatigue. Strength is developed by increasing the resistance and duration of time spent working at a higher intensity, while decreasing the time spent at a lower intensity workload. Increasing the overall exercise time also develops endurance.

The steps of the exercise protocol were as follows (Winningham et al., 1983):

1) Beginning each session, the subject was weighed and a sitting pulse and blood pressure were taken (Exercise Session Data Forms, Appendix N).

2) Stretch-out exercises were performed (Appendix O).

3) There were four minutes of warm-up cycling at a reduced load (specific to training load).
4) During the training period, the pulse and blood pressure at peak load were monitored at: 1) five minutes into training, 2) midpoint, and 3) one minute before cool-down. Subjects with a prior history of cardio-toxic drug administration had EKG monitored continuously on telemetry during exercise.

5) A four minute cool-down at reduced load (as in warm-up) was followed by walking, to assist recovery, and stretch-out exercises.

6) Following cool-down, pulse and blood pressure were taken.
CHAPTER III
RESULTS

Statistical Analysis

Pre-test demographic data including weight (Figure 5), height, percent body fat, age, and sex were variance tested to determine if initial group differences existed. No significant difference was found within a 5% level of confidence between the control and exercise group subjects. All primary and secondary analyses were examined for significant differences with the level of confidence set at \( p > 0.05 \). Using paired t-tests from pre- to post-test, primary analyses performed included examining resting (Figure 6), submaximal (Figure 7) and maximal HR (Figure 8), systolic BP (Figures 9, 10, 11), diastolic BP (Figures 12, 13, 14), RER (Figures 15, 16, 17), minute ventilation, breathing frequency, \( \text{VO}_2 \) (Figures 18, 19, 20, 21), and total exercise test time completed (Figure 22) for differences between sample means. The results are shown in Table 9. Paired t-tests on peak torques and percent body weight ratios were computed, and results are shown in Table 10, and Figures 23 through 34. Ordinal data was examined for significant differences by sign testing from pre- to post-testing and were as follows: 1) sub-maximal and maximal RPE and 2)
self-reported symptoms from the SAC. Significant results are shown in Table 11.

Secondary analyses included: 1) paired t-tests of clinical chemistry values (results shown in Table 8 and Figure 35), 2) Pearson correlations (interval data) and Spearman correlations (ordinal data) of Peak VO$_2$, with sex, age, HCT, Hb, BP, HR, and self-reported measures from the SAC, and 3) correlations on peak torques and weight, percent body fat, sex, and age (results are shown in Tables 12 and 13). Frequency distributions were calculated for RPE, self-reported reasons for test termination, and self-reported symptoms from the SAC. These data appear in Table 11.

Data

The anthropometric and clinical characteristics of subjects in the ET and LT groups are summarized in Table 8. Symptom-limited graded exercise testing was completed with the following physiological parameters monitored and reported in Table 9: 1) heart rate, 2) blood pressure, 3) respiratory frequency, 4) minute ventilation, 5) peak VO$_2$, and 6) RPE. Symptom-limited maximal graded exercise tests were successfully completed by all subjects prior to and after transplant with the reason for test termination being leg fatigue on all tests, with the exception of one subject who was terminated secondary to EKG changes (see Table 11). Two subjects in the ET group and three subjects in the LT group failed to complete the training protocol due to
complications requiring re-admission to the hospital for treatment. Complications included acute GVHD and infection.

Resting, submaximal, and peak values for HR, systolic BP, and VO$_2$ with significant differences at the p > .05 level from pre- to post-test upon admission to the outpatient unit, and from post-test upon admission to the outpatient unit to post-test upon discharge from the outpatient unit for both exercise groups are shown in Figures 6 through 21. For all subjects, resting BP was below values described as hypertensive (>140/90 mm Hg), with the exception of one subject who was borderline hypertensive (156/90). Exercise systolic values were below 250 mm Hg, and systolic pressure rose as workload increased during the SLGXTs.

Table 10 and Figures 23 through 34 contain the subjects’ peak torque values of the hamstring and quadracep muscles, upon isokinetic testing at 90, 180, and 300°/second, and torque to body weight ratios. Both exercise groups demonstrated a larger loss of strength at the slow testing velocity of 90°/sec upon post-testing. The LT group demonstrated strength loss in the quadraceps and hamstrings, while the ET group exhibited a selective loss only in the quadraceps. When normalized for changes in body weight muscle torque production at high speeds did not diminish in the early exercise training group, especially in the hamstrings.
During exercise testing with increasing workload, the subjects in the study demonstrated a less linear rise in HR, systolic BP, and VO$_2$ than normals. During submaximal exercise, the expected linear rise in HR, BP and VO$_2$, in response to a rise in workload, was questionable in both exercise groups when the relationship was examined by Pearson correlations, with the least linearity demonstrated during post-testing upon discharge from the inpatient unit to the outpatient unit (see Table 12).
| TABLE 8. MEANS AND STANDARD DEVIATIONS OF PHYSICAL AND CLINICAL CHARACTERISTICS OF SUBJECTS |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| ALL SUBJECTS                                  | MALES                                        | FEMALES                                      | PRE-TRANSPLANT CONTROL GROUP                  | EARLY EXERCISE TRAINING GROUP                | LATE EXERCISE TRAINING GROUP                 | POST-TRANSPLANT 1*                           |
| [n=211]                                      | [n=151]                                      | [n=61]                                       | [n=19]                                        | [n=19]                                       | [n=19]                                       | [n=19]                                       |
| AGE                                           | 30.8 ± 7.3                                  | 30.1 ± 8.3                                   | 31.5 ± 8.5                                    | 28.3 ± 8.5                                   | 33.4 ± 9.2                                   | 170.1 ± 12.1                                 |
| Height                                        | 176.8 ± 10.3                                 | 180.3 ± 10.3                                 | 171.2 ± 9.8                                   | 170.1 ± 12.1                                 | 181.7 ± 10.4                                 | 176.4 ± 10.4                                 |
| Weight                                        | 70.2 ± 12.6                                 | 74.8 ± 10.1                                  | 68.2 ± 14.5                                   | 68.0 ± 16.6                                  | 64.9 ± 13.3                                  | 69.4 ± 12.1                                  |
| % Body Fat                                    | 18.6 ± 6.0                                  | 18.8 ± 6.3                                   | 18.0 ± 6.9                                    | 15.8 ± 6.9                                   | 15.3 ± 6.5                                   | 13.7 ± 5.6                                   |
| WBC                                           | 7.7 ± 10.26                                 | 8.8 ± 10.71                                  | 12.17 ± 7.9                                   | 10.33 ± 16.0                                 | 6.01 ± 8.00                                  | 6.50 ± 3.66                                 |
| Hct                                           | 30.0 ± 6.8                                  | 30.1 ± 6.8                                   | 30.4 ± 6.8                                    | 30.50 ± 6.6                                  | 3.02 ± 0.29                                  | 3.15 ± 0.34                                 |
| Hemoglobin                                    | 11.3 ± 1.3                                  | 11.6 ± 1.2                                   | 11.4 ± 1.2                                    | 10.5 ± 1.0                                   | 11.4 ± 0.7                                  | 10.3 ± 0.6                                  |
| Hematocrit                                     | 33.2 ± 4.4                                  | 33.2 ± 4.2                                   | 33.8 ± 6.0                                    | 33.2 ± 4.6                                    | 33.3 ± 2.3                                  | 33.4 ± 2.3                                  |
| Platelets                                     | 192.18 ± 10^4                               | 191.57 ± 10^4                                | 194.67 ± 10^4                                 | 194.87 ± 10^4                                 | 194.29 ± 10^4                                | 191.78 ± 10^4                                |
| Na                                            | 138.7 ± 3.7                                 | 139.6 ± 3.0                                  | 140.0 ± 0.6                                   | 140.2 ± 1.2                                  | 140.6 ± 1.0                                  | 137.5 ± 5.1                                 |
| BUN                                           | 4.1 ± 9.7                                   | 15.2 ± 10.7                                  | 12.0 ± 3.6                                    | 17.0 ± 12.2                                   | 20.4 ± 10.2                                  | 17.0 ± 4.0                                  |
| SERUM                                         | 1.1 ± 0.4                                   | 1.1 ± 0.4                                    | 1.1 ± 0.4                                     | 1.1 ± 0.4                                     | 1.1 ± 0.4                                    | 1.1 ± 0.4                                    |
| Glucose                                       | 101.9 ± 17.1                                | 101.5 ± 18.1                                 | 105.1 ± 13.1                                  | 101.5 ± 19.0                                  | 109.6 ± 20.4                                 | 137.7 ± 33.1                                 |
| Cholesterol                                   | 107.4 ± 4.3                                 | 107.1 ± 4.2                                  | 111.0 ± 5.3                                   | 107.7 ± 3.3                                   | 109.9 ± 2.8                                  | 105.0 ± 2.0                                  |
| C02                                           | 25.4 ± 3.3                                  | 25.7 ± 3.0                                   | 28.2 ± 2.6                                    | 26.3 ± 2.6                                    | 24.6 ± 0.8                                   | 26.8 ± 2.0                                  |
| Magnesium                                     | 1.416 ± 0.15                                | 1.416 ± 0.05                                 | 1.352 ± 0.14                                  | 1.48 ± 0.25                                   | 1.43 ± 0.15                                  | 1.48 ± 0.24                                 |
| Calcium                                       | 4.453 ± 0.21                                | 4.453 ± 0.22                                 | 4.552 ± 0.13                                  | 4.65 ± 0.22                                   | 4.65 ± 0.24                                  | 4.67 ± 0.19                                 |
| PO4                                           | 3.92 ± 0.43                                 | 3.97 ± 0.45                                  | 3.90 ± 0.25                                  | 3.78 ± 0.45                                   | 3.92 ± 0.27                                  | 3.92 ± 0.36                                 |
| ALKALINE                                      | 0.91 ± 7.9                                  | 0.91 ± 21.2                                  | 100.9 ± 67.4                                  | 88.3 ± 20.0                                   | 101.7 ± 10.6                                  | 93.9 ± 59.9                                  |
| TOTAL PROTEIN                                  | 6.46 ± 0.68                                 | 6.54 ± 0.70                                  | 6.00 ± 0.02                                   | 6.20 ± 0.32                                   | 6.52 ± 0.82                                  | 6.43 ± 0.57                                 |
| ALBUMIN                                       | 4.12 ± 0.53                                 | 4.12 ± 0.16                                  | 4.10 ± 0.26                                   | 3.90 ± 0.15                                   | 4.18 ± 0.39                                  | 4.32 ± 0.34                                 |
| SGOT                                          | 50.1 ± 29.5                                 | 50.1 ± 29.5                                  | 45.3 ± 9.6                                    | 29.3 ± 6.4                                    | 30.8 ± 16.0                                  | 30.8 ± 21.0                                 |
| SGPT                                          | 27.3 ± 30.5                                 | 27.3 ± 30.5                                  | 23.9 ± 6.4                                    | 16.0 ± 4.2                                    | 20.5 ± 10.0                                  | 15.0 ± 21.0                                 |
| PROTIME                                       | 10.1 ± 0.4                                  | 10.1 ± 0.4                                   | 10.1 ± 0.4                                    | 10.1 ± 0.4                                    | 10.1 ± 0.4                                   | 10.1 ± 0.4                                   |
| FIBRINOGEN                                    | 103.2 ± 104.8                               | 103.4 ± 104.8                                | 283.0 ± 66.5                                  | 264.3 ± 118.0                                  | 365.1 ± 16.6                                 | 365.1 ± 16.6                                 |

*Post testing done upon discharge from the inpatient unit.
*One subject's data excluded secondary to hyperglycemia being treated by insulin.
*Data missing for these subjects.
*Significant at p<0.10 pre-transplant to post-transplant.
*Significant at p<0.05 pre-transplant to post-transplant.
*Significant at p<0.10 post-transplant to post-transplant.
*Significant at p<0.05 post-transplant to post-transplant.
*Significant at p<0.10 post-transplant to post-transplant.
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<th>FEMALES</th>
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<th>POST-TRANSPLANT 2*</th>
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<td>PEAK VO2</td>
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<td>(L/min)</td>
<td>99 ± 9</td>
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<tr>
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<td>MAX TIME</td>
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*Post-testing done upon discharge from the ICU unit.
**Post-testing done upon discharge from the transplant unit.
***Significant at p<0.05 pre-transplant to post-transplant.
****Significant at p<0.01 pre-transplant to post-transplant.
*****Significant at p<0.001 pre-transplant to post-transplant.
******Significant at p<0.0001 pre-transplant to post-transplant.
*******Significant at p<0.0001 pre-transplant to post-transplant.
### Table 10. Means and Standard Deviations of Isokinetic Muscle Performance at the Knee

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<tr>
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<th>All Subjects</th>
<th>Males</th>
<th>Females</th>
<th>Pre-BMT Transplant Females Group</th>
<th>Early Exercise Training Group</th>
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<td>37.9 ± 5.0</td>
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*Post-testing done upon discharge from the inpatient unit.
*Post-testing done upon discharge from the outpatient unit.
*Equipment was being repaired; one subject's data was not collected.
'Significant at p<.10 pre-transplant to post-transplant*.
'Significant at p<.05 pre-transplant to post-transplant*.
'Significant at p<.10 post-transplant* to post-transplant*.
'Significant at p<.05 post-transplant* to post-transplant*.
'Significant at p<.10 pre-transplant to post-transplant*.

---

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TABLE 11. FREQUENCIES OF RPE AND SELECTED PARAMETERS FROM THE SYMPTOM ACTIVITY CHECKLIST

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<td>NODE/MEDIAN</td>
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*All subjects responded to the SAC.
*Subjects responded to the SAC.
*Significant at p<0.05 pre-transplant vs post-transplant on sign testing.
*One subject's test was terminated due to EEG abnormalities.
*Significant at p<0.05 pre-transplant vs post-transplant on sign testing.
*Significant at p<0.05 pre-transplant vs post-transplant on sign testing.
TABLE 12. RESULTS OF SECONDARY ANALYSES BY PEARSON CORRELATIONS

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<td>0.713</td>
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<td>*</td>
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<td>0.747</td>
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<td>*</td>
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<td>180°/sec: QUADS</td>
<td>-0.208</td>
<td>0.891</td>
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<tr>
<td>HAMS</td>
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<td>0.514</td>
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<td>*</td>
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<td>*</td>
<td>*</td>
<td>-0.921*</td>
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<td>HAMS</td>
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<td>50°/sec: QUADS</td>
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*Small n did not allow calculation of the r value.
*Significant at p<.05 pre-transplant to post-transplant.
*Significant at p<.05 post-transplant to pre-transplant.
*Significant at p<.05 post-transplant to post-transplant.
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<td>MUSCLE CRAMPS</td>
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<td>*Small n did not allow calculation of the p value.</td>
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<tr>
<td>**Significant at p&lt;0.05 pre-transplant in post-transplant.</td>
</tr>
<tr>
<td>***Significant at p&lt;0.05 pre-transplant in post-transplant.</td>
</tr>
<tr>
<td>****Significant at p&lt;0.05 pre-transplant in post-transplant.</td>
</tr>
</tbody>
</table>
Pre-transplant

C: 77.4 ± 9.1
ET: 65.0 ± 16.5
LT: 69.8 ± 11.6

Post-transplant

C: 69.4 ± 13.9
ET: 64.4 ± 13.3
LT: 69.4 ± 12.1

Post-transplant*

C: 62.6 ± 13.9
ET: 55.9 ± 14.2
LT: 59.0 ± 10.6

** Significant at p > .05 level from pre-transplant to post-transplant.
*** Significant at p > .05 level from pre-transplant to post-transplant.
**** Significant at p > .05 level from post-transplant to post-transplant.

Figure 5
Body Weights of Subjects
Figure 6
Resting Heart Rates for Subjects
**Figure 7**

Submaximal Heart Rates for Subject During Exercise

---

*C* Significant at p > .05 level from pre-transplant to post-transplant.

** Significant at p > .05 level from pre-transplant to post-transplant.

---

Pre-transplant

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** Significant at p>.05 level from pre-transplant to post-transplant1.
** Significant at p>.05 level from pre-transplant to post-transplant1.

Figure 8
Maximal Heart Rates During Graded Exercise Testing
Figure 9
Resting Systolic Blood Pressure in Subjects
Figure 10
Submaximal Systolic Blood Pressures During Exercise Testing in Subjects

** Significant at p > .05 level from pre-transplant to post-transplant*.
*** Significant at p > .05 level from pre-transplant to post-transplant*.
* Significant at p > .05 level from post-transplant* to post-transplant*.

mmHg
Figure 11

Maximal Systolic Blood Pressures During Graded Exercise Testing in Subjects
Figure 12

Resting Diastolic Blood Pressure in Subjects
Figure 13
Submaximal Diastolic Blood Pressures During Exercise Testing in Subjects

Pre-transplant

<table>
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<td>LT</td>
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<td>90 ± 10</td>
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** Significant at p > 0.05 level from pre-transplant to post-transplant.
** Significant at p > 0.05 level from pre-transplant to post-transplant.
** Significant at p > 0.05 level from post-transplant to post-transplant.
Figure 14
Maximal Diastolic Blood Pressures During Graded Exercise Testing in Subjects
Figure 15
Resting Respiratory Exchange Rates in Subjects
Figure 16

Submaximal Respiratory Exchange Rates During Exercise Testing in Subjects

* Significant at p > .05 level from pre-transplant to post-transplant.
** Significant at p > .05 level from pre-transplant to post-transplant.
*** Significant at p > .05 level from post-transplant to post-transplant.
Figure 17
Maximal Respiratory Exchange Ratios on Graded Exercise Testing

** Significant at p<.05 level from pre-transplant to post-transplant**.
*** Significant at p<.05 level from pre-transplant to post-transplant***.
**** Significant at p<.05 level from post-transplant to post-transplant****.
Figure 18

Resting VO2 in Subjects
<table>
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</tbody>
</table>

Significant at p>.05 level from pre-transplant to post-transplant.

Figure 19

Submaximal VO₂ during Exercise Testing in Subjects
**Figure 20**

Peak VO\(_2\) During Graded Exercise Testing in Subjects

**Pre-transplant**

- C: 1.73 ± .23
- ET: 1.20 ± .57
- LT: 1.04 ± .55

**Post-transplant**

- C: 1.74 ± .28
- ET: 1.08 ± .42
- LT: 1.47 ± .14

**Post-transplant**

- C: .80 ± .28
- ET: .86 ± .10
- LT: .82 ± .32

---

**Significant at p>.05 level from pre-transplant to post-transplant**.

**Significant at p>.05 level from pre-transplant to post-transplant**.

**Significant at p>.05 level from post-transplant to post-transplant**.
### Figure 21

**Peak VO₂ During Graded Exercise Testing on Subjects Adjusted for Changes in Body Weight**

<table>
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<td>10.0 ± 3.6</td>
</tr>
<tr>
<td>ET</td>
<td>19.1 ± 5.9</td>
<td>17.6 ± 6.6</td>
<td>14.8 ± 1.0</td>
</tr>
<tr>
<td>LT</td>
<td>11.1 ± 8.5</td>
<td>11.1 ± 4.4</td>
<td></td>
</tr>
</tbody>
</table>

**Significant at p<.05 level from pre-transplant to post-transplant¹.**

**Significant at p<.05 level from pre-transplant to post-transplant².**

**Significant at p<.05 level from post-transplant¹ to post-transplant².**

*mlO₂/Kg/min*
Figure 22

Total Time Attained On Graded Exercise Testing

** Significant at p > 0.05 level from pre-transplant to post-transplant.
*** Significant at p > 0.05 level from pre-transplant to post-transplant.

** Significant at p > 0.05 level from pre-transplant to post-transplant.
*** Significant at p > 0.05 level from pre-transplant to post-transplant.

Minutes
**Figure 23**

QUADRICEPS PEAK TORQUES ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 90 DEGREES PER SECOND
Figure 24

QUADRICEPS PEAK TORQUES ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 180 DEGREES PER SECOND

** Significant at p<.05 level from pre-transplant to post-transplant.
** Significant at p<.05 level from pre-transplant to post-transplant.
** Significant at p<.05 level from post-transplant to post-transplant.
Figure 25

QUADRICEPS PEAK TORQUES ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 300 DEGREES PER SECOND
Figure 26

HAMSTRING PEAK TORQUES ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 90 DEGREES PER SECOND
Figure 27

HAMSTRING PEAK TORQUES ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 180 DEGREES PER SECOND
**Figure 28**

HAMSTRING PEAK TORQUES ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 300 DEGREES PER SECOND

---

**Pre-transplant**

- **C**: 53.0 ± 15.1 ft/lbs
- **ET**: 37.6 ± 22.3 ft/lbs
- **LT**: 40.2 ± 15.6 ft/lbs

**Post-transplant**

- **C**: 43.0 ± 8.5 ft/lbs
- **ET**: 40.5 ± 15.6 ft/lbs
- **LT**: 26.8 ± 12.4 ft/lbs

**Post-transplant**

- **C**: 43.8 ± 17.4 ft/lbs
- **ET**: 37.8 ± 14.0 ft/lbs
- **LT**: 38.3 ± 17.8 ft/lbs

---

* Significant at p > .05 level from pre-transplant to post-transplant.
** Significant at p > .05 level from pre-transplant to post-transplant.
*** Significant at p > .05 level from post-transplant to post-transplant.
Figure 29
QUARACEPS PERCENT BODY WEIGHT RATIOS ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 90 DEGREES PER SECOND
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<tbody>
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<td>LT</td>
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<td></td>
<td>± 10.4</td>
<td>± 2.8</td>
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<td>± 12.5</td>
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<td>± 8.7</td>
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** Significant at p>.05 level from pre-transplant to post-transplant.
** Significant at p>.05 level from pre-transplant to post-transplant.
* Significant at p>.05 level from post-transplant to post-transplant.

Figure 30

QUARACEPS PERCENT BODY WEIGHT RATIOS ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 180 DEGREES PER SECOND
Figure 31
QUARACEPS PERCENT BODY WEIGHT RATIOS ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 300 DEGREES PER SECOND

** Significant at p>.05 level from pre-transplant to post-transplant.
*** Significant at p>.05 level from pre-transplant to post-transplant.
** Significant at p>.05 level from post-transplant to post-transplant.
Figure 32

HAMSTRINGS PERCENT BODY WEIGHT RATIOS ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 90 DEGREES PER SECOND

** Significant at p>.05 level from pre-transplant to post-transplant.
* Significant at p>.05 level from post-transplant* to post-transplant*.

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<td>C</td>
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<td>± 11.0</td>
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<td>± 7.8</td>
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<td>± 4.3</td>
<td>± 30.2</td>
<td>± 37.8</td>
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</table>
Pre-transplant

C: 36.3 ± 0.0
ET: 32.0 ± 6.4
LT: 29.5 ± 5.2

Post-transplant
C: 29.0 ± 3.5
ET: 31.8 ± 4.8
LT: 22.6 ± 6.0

Figure 33

Hamstrings percent body weight ratios on isokinetic muscle performance testing at 180 degrees per second.
Figure 34

HAMSTRINGS PERCENT BODY WEIGHT RATIOS ON ISOKINETIC MUSCLE PERFORMANCE TESTING AT 300 DEGREES PER SECOND
Figure 35

Resting Blood Glucose Values of Subjects

mg/dl

** Significant at p>0.05 level from pre-transplant to post-transplant.

* Significant at p>0.05 level from post-transplant to post-transplant.

A Significant at p>0.05 level from post-transplant to post-transplant.
CHAPTER IV
DISCUSSION

As reported previously, the literature review suggests a beneficial effect of chronic exercise on tumor-bearing animals and humans (Deuster et al, 1985; Norton et al, 1979). The mechanism, whereby the exercise may alter the disease process, is unknown. Two of the unanswered questions surrounding the effect of chronic exercise with cancer patients remain: "Will exercise training impede or reverse the process of secondary disability?" and "Will they respond to chronic exercise in the same manner as the normal sedentary person?". There are reliable data in the literature indicating the importance of exercise for prevention of secondary disabilities and possibly for primary prevention of several multisystem, chronic conditions. For example, results of exercise training in patients with cardiopulmonary disease (Pollock et al, 1984), cardiac transplant (Kavanaugh et al, 1986), diabetes (Richter et al, 1981, 1985), renal disease (Zabetakis, Gleim, Pasternak et al, 1982), and renal transplant (Painter et al, 1986), which also induce generalized muscle atrophy, have been reported.

Preliminary reports on the rehabilitation status or physical work capacity of patients before and after BMT have
recently been reported (Holtzman, 1987). Initial peak VO$_2$ values reported from M.D. Anderson's transplant unit have been a mean of 19 ml O$_2$/kg/min prior to transplant. The subjects in this study, prior to transplant, demonstrated mean values for peak VO$_2$ of 22, 19, and 15 ml O$_2$/kg/min in the control, ET, and LT subjects, respectively (Figures 20 and 21). The results of this study support previous findings (Pfalzer et al, 1987) of low peak VO$_2$'s before and after BMT, in comparison to reported values for untrained normals (AHA, 1977). The diminished physical work capacity (peak VO$_2$'s) found in this study is also consistent with prior reports of reduced pre- and post-transplant peak oxygen consumption (VO$_2$) and symptoms of deconditioning, i.e., complaints of fatigue, generalized weakness, and difficulty in performing normal daily activities (Pfalzer et al, 1987; Holtzman, 1987). This is consistent with anecdotal reports in the literature of diminished physical work capacity and indicates low initial fitness levels below sedentary normals prior to transplant.

The maximal heart rate and peak VO$_2$ for these subjects are markedly lower on pre-testing (Figure 8 and 21; Table 9) than maximal values reported for sedentary, healthy individuals. Physical work capacity after transplant is expected to increase due to an improved peak VO$_2$ as their anemia improves. Consistent with the literature, an improvement in anemia would elicit a reduction of left ventricular workload by allowing a decreased heart rate at
the same cardiac output through improved O2 transport at
submaximal and maximal workloads (Woodson et al, 1978;
to the lack of improvement in the anemia present in these
subjects, maximal performance remains diminished (Table 8).

The low peak VO2 consumptions and low maximal HRs
demonstrated are supported by previous reports of diminished
physical work capacity, resulting from inactivity of
subjects having low initial fitness levels (Saltin et al,
1968; Chobanian et al, 1974). Deconditioning, due to
inactivity, results from restricted living space in the
special laminar air-flow isolation housing units in which
the subjects must live while hospitalized (Holtzman, 1987).

As noted in the literature review, BMT may induce
multisystem impairment and failure with diminished physical
work capacity. The predominant alterations are in the
hematopoietic, cardiopulmonary, endocrine, and
musculoskeletal systems due to shifts in metabolism induced
by the disease and treatment (Clark & Goodlad, 1971;
Gluckman et al, 1981; Buja et al, 1976; Batist and Andrews,
1981; Karlberg, 1981; Allegretta et al, 1985; Allegretta et
al, 1985). Will these subjects have a training response to
chronic exercise?

The ability of the interval exercise training program
to retard loss of muscle torque production, when normalized
for body weight in the quadriceps as compared to controls
(Figure 29, 30, and 31), and to prevent loss and improve
torque production, when normalized for body weight of the hamstrings in the ET group, is significant (Figures 32, 33, and 34). This indicates an improvement in muscle force production related to the exercise training which is particularly noted in the high speed modes (180 and 300 degrees/second) (Figures 30, 31, 33, and 34). In addition, the LT group exhibited significant improvement from the control group upon beginning of exercise training in the Day Care unit until discharge, producing the same pattern of response as the ET group with loss of force production retarded in the quadriceps and significant improvement in the hamstrings force production at high speed also indicating a training effect. This is unusual as aerobic training typically does not increase muscle strength in normals; however, initial deconditioning in these subjects may have allowed for significant overloading of the muscles being exercised on the bicycle ergometer with the use of the interval training program.

The high doses of corticosteroids used to prevent rejection of the transplant have been shown in different clinical populations to induce type II muscle fiber atrophy with loss of the ability to perform high speed activities. (Stern, 1972; Rothstein et al, 1983; Danneskiold-Samsoe and Grimby, 1986; Danneskiold-Samsoe and Grimby, 1986). Exercise training has been shown to partially prevent the drug-induced muscle atrophy (Hickson and Davis, 1981; Danneskiold-Samsoe & Grimby, 1986). The findings on muscle
strength reported in the figures reported above and Table 10 are consistent with this literature demonstrating prevention of type II muscle myopathy in the exercise training groups, while the controls developed type II myopathy indicated by the reduction in muscle force when normalized for body weight changes at high speed.

Hyperglycemia, acidosis, uricemia are present in these subjects after transplant due to the transplant regimen (Figure 35 and Table 8). The exercise training groups are normoglycemic upon discharge, while the controls remain hyperglycemic. The anti-rejection and chemotherapy agents have been shown to induce alterations in liver and kidney function (Gluckman et al, 1981) and are exhibited in these subjects (see Table 8). Metabolic and electrolyte imbalances, for example, hyperglycemia, hyperlipidemia, hypokalemia, hypomagnesemia, uricemia, and lactic acidosis due to disease and treatment, are common occurrences (Gluckman et al, 1981; Loudet AM et al, 1984; Karlberg et al, 1981; Allegretta et al, 1985). Bedrest and inactivity exacerbate and contribute to altered electrolyte balance found in these subjects (Greenleaf et al, 1984). These factors have a negative inotropic effect and increase left ventricular workload in these subjects. The effect of cyclosporine-A and high-dose steroids, anti-rejection drugs on exercise capacity is unknown, although they are thought to limit performance (Painter et al, 1986). The reduction in hyperglycemia in the exercising groups may have
contributed to their increased ability to exercise as compared to the controls.

Another factor limiting physical work capacity is acidosis from the onset of accumulation of blood lactic acid (LA). The high ratings of perceived exertion at low peak VO2 values (Table 9) found in this study, high submaximal RER's (Figure 16) with many subjects ceasing to exercise due to leg fatigue, is consistent with the literature, suggesting metabolic acidosis may be limiting exercise capacity (Kostka and Caferilli, 1982; Borg et al, 1985). In 1982, Kostka and Caferilli demonstrated metabolic acidosis, indicated by a lowered pH during ergometry testing, limited exercise capacity during exercise testing. The premature onset of anaerobic metabolism during exercise in patients with renal disease (Nakoa, Fujiwara, Isoda, Miyahara, 1982), cancer (Karlberg et al, 1981), anemia (Kanstrup and Ekblom, 1984), and who are receiving high-dose prednisone (Danneskiold-Samsoe and Grimby, 1986), results in early LA accumulation. Inactivity has also demonstrated this effect (Greenleaf et al, 1985). Greenleaf et al, in 1985, demonstrated a shift of lactate dehydrogenase (LDH) isozymes and LDH total activity in subjects after bedrest, which led to altered metabolism in muscle and thus to premature and increased LA production. This early and elevated LA production results in acidosis, limiting exercise capacity consistent with Kostka's report. In addition, Clark & Goodlad demonstrated that patients with cancer shift
metabolism toward glycolytic pathways with higher levels of lactic acid at rest.

After exercise training, ET and LT groups had a significant retarding of decreases in peak VO\(_2\) in the ET group as compared to the controls and the LT group upon admission to the Day Care unit (Figure 20 and 21). The LT group had a significant improvement upon beginning an exercise training program upon admission to the Day Care unit until discharge (Figures 20 and 21). Both exercise groups were approaching normal sedentary values as compared to the control group upon discharge which continued to exhibit further reduction in oxygen consumption beyond that demonstrated by the two exercise training groups (Table 9). Peak VO\(_2\) in the ET group was not significantly increased; the peak VO\(_2\) attained by the controls and LT group during hospitalization was significantly reduced in comparison. The exercise appears to slow the loss of physical work capacity after transplant during the exercise training in the ET group, while significantly improving peak VO\(_2\) in the LT group upon admission to the Day Care unit until discharge with the initiation of exercise training.

Peak VO\(_2\) is a determinant of physical work capacity. The small improvement in peak VO\(_2\)'s after training was expected and is consistent with findings from other clinical populations with multisystem impairment, i.e., patients after cardiac transplant, renal transplant, and on hemodialysis (Kavanaugh et al, 1986; Painter et al, 1986;
Zabetakis et al, 1982). The subjects demonstrate reductions in hemoglobin, RBC, and HCT (Table 8). Patients after BMT tend to be anemic with low hematocrits (Hct), reduced RBC, and decreased arterial oxygen concentrations (Allegretta et al, 1985; Thomas et al, 1977; Lantz et al, 1980). Anemia is expected to improve as bone marrow function returns. Improved bone marrow function is indicated by elevated hemoglobin (Hb), red blood cell counts (RBC), and normal hematocrit (HCT). Consistent with the reduction in physical work capacity found, subjects remained anemic after transplant and exercise training, possibly due to the short duration of the study (Table 8). Low total amounts of Hb, RBC, and Hct, although improved after training, had not returned to normal values at one hundred days after transplant in these subjects (Table 8).

The persistent anemia is one factor contributing to the lack of a large improvement in peak VO\textsubscript{2} after training. Previous reports of exercise testing responses in subjects with acutely induced anemia (Kanstrup and Ekblom, 1984), chronic anemia (Davies and VanHaarn, 1973), and sickle cell anemia (Charche et al, 1983) have demonstrated the importance of low total amounts of hemoglobin in the early onset of anaerobic threshold. These reports have also demonstrated that low total amounts of hemoglobin limit maximal VO\textsubscript{2} and work capacity by diminishing oxygen transport, which results in hypoxia and onset of blood lactic acid.
Submaximal exercise VO$_2$s were significantly diminished in the controls post-transplant during hospitalization and upon admission to the Day Care Unit until discharge (Figure 19). The ET group maintained submaximal VO$_2$ levels during hospitalization, while the LT group significantly diminished their submaximal VO$_2$ levels and then improved them significantly after admission to the Day Care unit until discharge with initiation of exercise training (Figure 19). This supports the premise of the exercise training retarding the physiological effects of the BMT and treatment regimen and in the LT group eliciting a training response upon the initiation of exercise training.

Resting systolic and diastolic blood pressures are elevated after transplant in all subjects secondary to the anti-rejection therapy via CsA and steroids to prevent graft rejection (Figures 9 and 12). Figure 10 demonstrates a significant training effect by reducing submaximal exercise systolic blood pressure in the ET group upon discharge; this training effect was not apparent in the LT group or controls. The duration of the training program may have not been of a long enough duration in the LT group to elicit the training response. Figure 7 demonstrates this same pattern of response in submaximal exercise heart rates with the LT group not attaining a significant drop in heart rate and the controls heart rate continuing to be elevated.

Cardiovascular functioning in cardiac and end-stage renal disease patients, prior to transplant, appears to be
important in determining physical work capacity and may
limit rehabilitation. (Painter et al, 1986) Due to an
increased risk of developing congestive heart failure, this
may also be true in subjects undergoing BMT. Contributing
factors often present in subjects are: 1) hypervolemia from
fluid overload and inappropriate anti-diuretic hormone
secretion, 2) hypertension, 3) alterations in oxygen
carrying capacity secondary to replacement of blood products
(Apstein, Dennis, Briggs, Vogel, Frazer, Valeri, 1985), and
4) cardiopulmonary toxicity from the preparatory regimen
increases in resting systolic and diastolic BP was
demonstrated by these subjects as reported above. One
subject developed cardiopulmonary toxicity in response to
the transplant protocol.

Decreased cardiac output is indicated by low maximal
heart rates attained on post-testing (Figure 8; Table 9) and
are consistent with Baello's (1986) recent findings of
diminished ejection fractions. Diminished cardiac output is
another factor which may limit subjects' peak VO$_2$
by
decreasing O$_2$ transport. One subject demonstrated an
arrhythmia consistent with abnormal cardiac function.
During BMT, patients undergo chemotherapeutic regimens,
including high-dose cyclophosphamide, busulphan, and
methotrexate, which may alter cardiopulmonary structure and
function (Gottdiener et al, 1981; Baello et al, 1986;
Chemotherapeutic drug-induced cardiomyopathy has been reported, risk factors identified, and structural changes described (Buja et al, 1976; Gottdiener et al, 1981; Baello et al, 1986). Baello et al, (1986) recently reported resting ejection fraction fell in seven of seventeen BMT patients 77 days after transplant, with four in the abnormal range. In addition, ten of the subjects had exercise radionuclide ventriculography with normal responses. A normal response was defined as a greater than 5% increase with exercise.

The subjects exhibited elevated resting and submaximal RERs and high minute ventilations during maximal exercise with low peak VO$_2$'s (Figure 16; Table 9). Drug-induced interstitial pulmonary fibrosis has also been reported, structural changes described, and risk factors identified. Fibrosis, resulting in restrictive lung disease with diminished diffusion capacity, leads to hypoxia in high-demand situations, i.e., exercise (Batist and Andrews, 1981). Cardiac output, at maximal effort, is limited by any of these factors. Monitoring of gas exchange during progressive exercise has been demonstrated to be the most sensitive test for detecting progressive interstitial fibrosis in patients with restrictive parenchymal lung disease, secondary to drug-induced toxicity (Keogh and Crystal, 1980). Disease progression is indicated by increasing hypoxia, early onset of anaerobic threshold, and
respiratory frequency and ventilation beyond the normal range during progressive exercise.

The intensity, duration, and frequency of the exercise prescription to be utilized, during therapy and after transplant, is unknown. It is important when developing an exercise prescription for this population to appreciate that a prescription based on HR alone possibly may be dangerous. These subjects demonstrated less linearity between increasing work, HR, BP, and VO$_2$ than normals (Table 12). During exercise in normals and patients with cardiovascular disease, a linear relationship exists between increasing workload, VO$_2$, and HR (Pollock, Wilmor, Fox, 1984). Clinically, the linear relationship between HR and VO$_2$ is utilized to determine exercise training HR ranges (Pollock et al., 1984). The exercise training HR ranges are derived from the HRs which correspond to exercising between 60-70% of maximal VO$_2$ attained on a GXT. Exercise training at this intensity, initially, is required to produce a training effect. The lack of such a linear relationship has been proven to be therapeutically significant in renal transplants and diabetics (Painter et al., 1986; Richter et al., 1981). The mechanism to explain the loss of linearity between increasing work, HR, BP, and VO$_2$ in these patients has not been elucidated totally, although it is thought to be due to an excessive catecholamine response to the exercise. The premature onset of anaerobic metabolism during exercise in patients with renal disease (Nakoa et al,
1982), cancer (Karlberg et al, 1981), anemia (Kanstrup and Ekblom, 1984), those receiving high-dose prednisone (Danneskiold-Samsoe and Grimby, 1986), or after inactivity (Greenleaf et al, 1985) may be a contributing factor. The development of guidelines for safe and beneficial exercise prior to and after transplant is necessary.

LIMITATIONS

The following assumptions were intrinsic to the study and the repeated measures design utilized, and, therefore, constitute limitations to the study:

1. Self-selection from the population was a possible source of bias. Although random assignment to experimental and control groups occurred, the subjects were volunteers.

2. The transplant protocol, while involving multiple agents, was specific in nature and did not utilize total body irradiation, limiting generalization.

3. The effects of maturation, history, and learning of the subjects over time was felt to be an important possible source of error in this population. Therefore, a repeated measures design which minimized these sources of error was chosen.

4. The small sample size available and attrition rate due to complications of disease and
treatment, although expected, did limit the statistical analyses (Type two error common with small n's) which could be utilized in the repeated measures design. The repeated measures design did conserve on the number of subjects required, while increasing the power and sensitivity as each subject served as his own control and was measured repeatedly over time.

Some of the internal and external threats to experimental validity and reliability were controlled for by pilot work, the research design, and some by the statistical analysis:

1. All subjects underwent the same transplant protocol.
2. Random assignment of volunteers to the research groups for the study was done.
3. Use of standardized testing and interval exercise training protocols which were reliable within a five percent confidence limit (Winningham et al, 1983) when checked on pilot testing.
4. The utilization of a repeated measures design allowing for each subject to serve as their own control over time.
5. Maturation effects and history controlled for by the repeated measures design with a
control group.

6. Possible carry-over effects from repeated physical performances were controlled for by isokinetic muscle performance being measured prior to bicycle ergometry graded exercise testing.

7. Environmental conditions in the testing laboratory, while monitored, were not controlled and were a potential source of error.

8. Due to the duration of data collection required to obtain even this small sample, seasonal changes in circadian rhythms which might effect exercise response could not be controlled.

9. Subjects consented not to exercise outside of their experimental sessions, and, if they did exercise, they were to report to the experimenter the mode, duration, and intensity of the activity; however, this was by self-report.

10. Volume overload and transient hypertension may have occurred in some subjects, although this was screened for by indirectly monitoring blood pressure and not testing any subject who was defined as hypertensive (Resting BP>140/90).
CONCLUSIONS

In conclusion, the individual effects on exercise capacity of deconditioning, disease-related and treatment-related factors, i.e., anemia, muscle atrophy, lactate acidosis, etc., cannot be determined directly from this study. These factors have been indirectly examined in this study and the literature. The symptoms of secondary disability and hypokinesia may compound physical limitations from the chemotherapy and anti-rejection drugs used in the transplant protocol. The interactive effects of these factors on exercise has not been determined, although these factors are probably of major import in limiting exercise capacity. It is important to emphasize triangulation of the physiological parameters; muscle torque, heart rate, oxygen consumption, blood pressure, and RPE indicate:

A) Early exercise training was more beneficial than late exercise training during the time course of this study;

B) Early and late exercise training appear to limit or prevent the diminished work capacity found after BMT in the control group, although, all three groups exhibit diminished work capacity after BMT the loss of physical work capacity was demonstrated to be larger in the control group than in the exercising groups during the time course of this study;
Subject's treatment and disease related symptoms associated with perceptions of symptoms which limit activity were reduced in the exercise training groups as compared to the control group.

Equally important were the results demonstrating:

1) the initial diminished exercise capacity of subjects on GXT prior to bone marrow transplant indicates these persons will benefit from an appropriate exercise training program to improve physical work capacity prior to BMT,

2) an exercise prescription based on heart rate alone may not be appropriate or safe in patients after transplant, and

3) the low peak VO2 values before and after transplant are important in determining physical work capacity and may be the limiting factor in early rehabilitation of these patients, although further investigation is required.
RECOMMENDATIONS AND FUTURE RESEARCH

The physical and affective responses, timing, benefits, and short-term and long-term efficacy of low to moderate level exercise regimens after BMT, routinely performed to prevent symptoms of debilitation from restricted living space and diminished activity, requires further investigation:

1. A project with a larger sample size to allow stratification of subjects and blocking based upon specific characteristics, for example, patient diagnosis, current treatment protocol, previous therapy received, high risk versus low risk subjects, and anti-rejection therapy;

2. A project utilizing alternate modes of exercise testing and training, intensities, and frequencies to aid in development of safe exercise guidelines;

3. A project with long-term follow-up is required to examine efficacy of the exercise intervention, for example, return to work rates, quality of life issues, independence in activities of daily living, and complication rates.

This study is a reasonable first step for further investigation. Exercise testing and training of bone marrow
transplant patients may be safely performed as indicated by the ability to complete GXT's and exercise training during the acute transplant phase under careful monitoring and supervision without complications. One subject demonstrated EKG changes consistent with side effects of chemotherapy on 12-lead EKG monitoring during the GXT allowing for identification of this subject. This study strongly suggests the efficacy of initiating physical rehabilitation in the early stages of transplantation.

Before moderate to high intensity exercise may be widely utilized, the adaptive responses and regulatory mechanisms occurring during single bouts of exercise, and after exercise training exercise in these patients needs further investigation:

1. Peripheral muscle and fat responses at rest, during exercise, and after training to examine metabolic alterations, for example, key enzymes regulating glycolysis, gluconeogenesis, and free fatty acid regulation (GK, GP, PFK, PK, LDH, HSTGL, LPL);

2. Hormonal responses and regulation, for example, insulin, c-peptide, catecholamines, and parathyroid hormone.

3. Blood levels of glucose, lactate, and other metabolic substrates.
BIBLIOGRAPHY


APPENDIX A.

EXERCISE PROTOCOL
APPENDIX B.

SYMPTOM-LIMITED GRADED EXERCISE TEST PROTOCOL
**BICYCLE ERGOMETRY TEST**

**THE OHIO STATE UNIVERSITY CANCER PATIENT FITNESS PROJECT**

Name ____________________________ Age ______ Date ______/____/____

Body Weight ______ lbs. Height ______ Supine HR ______ Resting HR ______

Estimated HR, max = 220 - (age) = ______ Supine BP ______/____ Resting BP ______/

<table>
<thead>
<tr>
<th>Prednisone in protocol?</th>
<th>Yes</th>
<th>No</th>
<th>Currently on prednisone?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Speed (rpm)</th>
<th>Intensity</th>
<th>Duration (minutes)</th>
<th>Elapsed Time</th>
<th>Heart Rate<em>Blood Pressure</em></th>
<th>P.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0 0</td>
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<td>4</td>
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<td>125 2 1/2</td>
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<td>9</td>
<td>50</td>
<td>225 4 1/2</td>
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<td>2</td>
<td>20-22</td>
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Immediately upon cessation

Recovery period: 50

<table>
<thead>
<tr>
<th>Duration (minutes)</th>
<th>Elapsed Time</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
</tr>
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<tbody>
<tr>
<td>0-2</td>
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</tbody>
</table>

HR, BP recorded during final 30 seconds of each exercise
6 recovery stage

Total Exercise Time

Maximum HR Achieved

Maximum BP Recorded

Reason for stopping:
(1) leg fatigue (2) short of breath
(3) chest discomfort (4) high SBP
(5) high DBP (6) abnl EKG
(7) other _______________________

Test Administrators ___________________
CANCER PATIENT FITNESS PROJECT -- GRADED EXERCISE TEST DATA FORM -- The Ohio State University

Note: Values for MV, \( O_2 \text{ml/kg-min} \), \( O_2 \text{L} \), \( \text{CO}_2 \text{L} \), RQ, VEQ, and BF are an average of the two values obtained from the second minute of each workload. HR values should be obtained directly from the EKG printout while SBP and DBP can be obtained from the GXT data form. PE can likewise be obtained from the GXT data form.

<table>
<thead>
<tr>
<th>Watts</th>
<th>Supine</th>
<th>Rest</th>
<th>0</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
<th>150</th>
<th>175</th>
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<th>225</th>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Watts</th>
<th>HR</th>
<th>SBP</th>
<th>DBP</th>
<th>PE</th>
<th>MV(L)</th>
<th>( O_2 \text{ml/kg} )</th>
<th>( O_2 \text{L} )</th>
<th>( \text{CO}_2 \text{L} )</th>
<th>RQ</th>
<th>VEQ</th>
<th>BF</th>
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</tbody>
</table>

Height _____ in = _____ cm  Occupation ____________  Age _____  Training HR:
\( @60\% \)  \( @75\% \)  \( @85\% \)

EKG Findings: ________________________________

Body Fat Skinfolds ___  % Rat Wt. ___  LBW ___

Max Time: _____ min.

Reasons for stopping: ________________________________

Reasons for stopping code: (1) leg fatigue
(2) short of breath (3) chest discomfort
(4) other.  

[Image of document page]
APPENDIX C.

SYMPTOM ACTIVITY CHECKLIST
PLEASE NOTE:

Copyrighted materials in this document have not been filmed at the request of the author. They are available for consultation, however, in the author's university library.

These consist of pages:

Appendix C 213-214
1. Set up Cybex II Isokinetic Dynamometer for right knee extension/flexion.

2. Calibrate dynamometer per standard procedure (Lumex Corporation, Cybex Division, 1980).

3. Record date of test; whether pre, intermediate, or post test; torque (ft-lbs) and range of motion (degrees) scale settings, and speed of first trial (degrees/second).

4. Adjust seat back support, seat belt, thigh strap, align axis of rotation with axis of right knee, and adjust shin pad to just above the ankle mortis when foot is flexed.

5. Familiarize patient with testing procedure/isokinetic exercise allowing a trial of 3-5 submaximal contractions at first trial speed of 90°/sec with one and a half minutes rest prior to trial.

6. Adjust recorder pens on dual channel recorder to baseline for torque and range of motion channels.

7. Instruct subject to hold on to closed handles on bench but not to "hold breath", to kick three times consecutively through the full range of motion up and down without resting "as hard and fast as you can".

8. Repeat steps five through seven for trials two and three at 180°/sec and 300°/sec respectively.

9. Switch patient to bench for left knee and repeat steps four
through seven for the first trial at 90'/sec and steps five through seven for trials two and three at 180'/sec and 300'/sec respectively.
ISOKINETIC STRENGTH ASSESSMENT FORM

NAME_____________________________ DATE_______ TEST_______
WEIGHT_______ ID#_______

PEAK TORQUE
RLE: 90'/SEC 180'/SEC 300'/SEC LLE: 90'/SEC 180'/SEC 300'/SEC

QUADS

HAMS

FLEX/EXT RATIO
RLE: 90'/SEC 180'/SEC 330'/SEC LLE: 90'/SEC 180'/SEC 300'/SEC

QUADS

HAMS

% BODY WEIGHT RATIO
RLE: 90'/SEC 180'/SEC 300'/SEC LLE: 90'/SEC 180'/SEC 300'/SEC

QUADS

HAMS
APPENDIX E.

PAST MEDICAL HISTORY FORM
CA\N\ER PATIENT FITNESS PROJECT
HEALTH AND FITNESS QUESTIONNAIRE

All information given is personal and confidential. It will enable us to better understand you and your health and fitness habits.

NAME _____________________________________ AGE __________________ DATE________________

ADDRESS ________________________________________________________________

TELEPHONE NO. (HOME) ( ) (OFFICE) ( ) OCCUPATION ________________

1. PERSONAL HISTORY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Arthritis</td>
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<tr>
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<td>Allergy</td>
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<td>Convulsions</td>
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<td>Headaches</td>
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<td>Depression</td>
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<td></td>
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<tr>
<td>Chest Pain</td>
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<td></td>
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<tr>
<td>Arm Pain</td>
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<tr>
<td>Shortness of Breath</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Thyroid</td>
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</tbody>
</table>

Comments on above: __________________________________________________________

Severe Illness (what and at what age): ______________________________________

Hospitalization (why and at what age): ______________________________________

Major Surgery (what kind and at what age): ________________________________

Remarks: __________________________________________________________________

(please go on to next page)
2. FAMILY HISTORY

Have any of your grandparents, parents, brothers or sisters had any of the following:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Grandfather(s)</th>
<th>Grandmother(s)</th>
<th>Father</th>
<th>Mother</th>
<th>Brother(s)</th>
<th>Sister(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Attack</td>
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</tr>
<tr>
<td>Diabetes</td>
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<td>Stroke</td>
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<tr>
<td>Heart Disease</td>
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<td>Circulatory Disorder</td>
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<tr>
<td>Asthma</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Other</td>
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</tbody>
</table>

How old is your father, if living? ______ Father's age at death? ______

Cause of death? ____________________________

How old is your mother, if living? ______ Mother's age at death? ______

Cause of death? ____________________________

3. MEDICAL HISTORY

Name of your physician: ________________________

Date of your most recent physical: ________________

Do you know your resting blood pressure? yes no unsure

Do you know your resting heart rate? yes no unsure beats per minute

Do you know your cholesterol level? yes no unsure

Do you know your triglyceride level? yes no unsure

Have you ever had an exercise EKG? yes no unsure

Have you ever taken:

- Digitalis yes no unsure
- Nitroglycerin yes no unsure
- High Blood Pressure yes no unsure
- Sure Medication yes no unsure
- Seconal yes no unsure
- Thyroid Medication yes no unsure
- Diabetes ("sugar") Medication yes no unsure

Remarks (please list medications and dosage):

______________________________________________________________________________

______________________________________________________________________________

(please go on to next page)
4. EXERCISE HISTORY

A. Do you currently exercise? yes no

1. What type of exercise do you do?

- gardening
- walking
- jogging
- calisthenics
- swimming
- cycling
- aerobic
- dance
- other (sports etc.)

Remarks: ............................................

2. Frequency of activity: ______ days/week. Irregularly

Remarks: ............................................

3. Duration of exercise period: ______ min/day

Remarks: ............................................

4. Intensity of activity: ______ heart rate?

- Do you breathe heavily? yes no sometimes

- Do you exercise to the point of sweating profusely? yes no sometimes

5. How long have you been exercising regularly? ______ months ______ years

B. If not exercising regularly now, have you exercised regularly in the past 18 months?

- yes no If yes, explain: ............................................

5. HEALTH HISTORY

Height ______

Estimated Body Weight:

<table>
<thead>
<tr>
<th>Current</th>
<th>At Age 20</th>
<th>At Age 30</th>
<th>At Age 40</th>
<th>One Year Ago</th>
<th>Most Weighed</th>
<th>Least Weighed</th>
</tr>
</thead>
</table>

- Do you use Health Foods? yes no If yes, explain: ............................................

- Do you take Vitamin pills? yes no If yes, explain: ............................................

- Are you dieting? yes no If yes, for how long?

- Approximate your daily intake: coffee tea liquor decaffeinated cola beer wine

- Do you currently smoke? yes no How many years? Chewing Tobacco

- Estimate your daily usage: Cigarettes Cigars Pipes

- Have you smoked regularly in the past? yes no If yes, explain: ............................................

(please go on to next page)
I hereby authorize the release of information obtained during my graded exercise test on ___________ and ___________, as well as other information gained through this study, to my physician:

Dr. ______________________

Date ________________

(signature) ______________________

(witness) ______________________
PLEASE NOTE:

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These consist of pages:

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APPENDIX F.

PHYSICIAN REFERRAL FORM
THE OHIO STATE UNIVERSITY -- CANCER PATIENT FITNESS PROJECT

TO BE COMPLETED BY PHYSICIAN

Name of Patient_____________________________________________________

Chemotherapy Protocol______________________________________________

Other Medications___________________________________________________

Disease and Stage___________________________________________________

Are there any exercises or physical activities which are contraindicated for this patient?

_________________________________________________________________

_________________________________________________________________

Are there any other problems, medications, or abnormalities in this person's medical history which should be considered in developing an exercise program?

_________________________________________________________________

_________________________________________________________________

I certify that the individual whose name appears above may participate in a maximal graded exercise test to evaluate functional capacity and that the same individual may also participate in a supervised physical activity program, taking into consideration the above mentioned restrictions.

Date / / ________________________________________________________________________________________

(Physician's Signature)______________________________________________________________________

Address: _____________________________________________________________________________________

___________________________________________________________________________________________

Phone: ______________________________________________________________________________________

___________________________________________________________________________________________

SEND TO:

CINDY PFALZER, PT, M.A
The Ohio State University
College of Nursing
1585 Neil Avenue
Columbus, Ohio 43210

:bws/040184 #11
APPENDIX G.

HUMAN SUBJECTS CONSENT FORMS
The experimental (research) portion of the treatment or procedure is: the measurement of oxygen consumption during the test and to record the highest heart rate that can be attained at symptom related maximal exercise.

This is done as part of an investigation entitled: Bone marrow transplantation and exercise.

1. Purpose of the procedure or treatment: to evaluate the patient fitness level for this research maximum heart rate and oxygen consumption will be used to prescribe the appropriate intensity of exercise during the training.

2. Possible appropriate alternative methods of treatment: the-bicycle ergometer is the best instrument in this population since space is limited and it reduces joint impact of conventional training.

3. Discomforts and risks reasonably to be expected: local muscular fatigue and soreness with possible general exertion fatigue.

4. Possible benefits for subject/society: to return bone marrow transplant patients back into social and occupational main stream by increasing functional capacity at an early time.

5. Anticipated duration of subject's participation: one day of pre- and post-testing with intermediate testing 30th day post transplant with exercise period until 100th day post transplant.

I hereby acknowledge that has provided information about the procedure described above, about my rights as a subject, and have answered all questions to my satisfaction. I understand that I may contact him/her should I have additional questions. He/she has explained the risks described above and I understand them. He/she has also offered to explain all possible risks or complications.

I understand that, where appropriate, the U.S. Food and Drug Administration may inspect records pertaining to this study. I understand further that records obtained during or in obtaining in this study may be made available to the sponsor of this study and the records will not contain my name or other personal identifiers. Beyond this, I understand that my participation will remain confidential.

I understand that I am free to withdraw my consent and participation in this project at any time after notifying the project director without prejudicing future care. No guarantee has been given to me concerning this treatment or procedure.

In the unlikely event of injury resulting from participation in this study, I understand that immediate medical treatment is available at University Hospital of The Ohio State University. I also understand that the costs of such treatment will be at my expense and that financial compensation is not available. Questions about this study should be directed to the Human Subject Review Office at 432-5046.

I have read and fully understand the consent form. I sign it freely and voluntarily. A copy has been given to me.

Date: __________________ Time: ____________________ Signed: ____________________

Witnessed: ____________________________________________

I certify that I have personally completed all blocks in this form and explained them to the subject or his/her representative before requesting the subject or his/her representative to sign it.

Signed: ____________________________
THE OHIO STATE UNIVERSITY

CONSENT TO INVESTIGATIONAL TREATMENT OR PROCEDURE

Protocol No. 2

1. I hereby authorize or direct or associates or assistants of his or her choosing, to perform the following treatment or procedure (describe in general terms): to administer a strength test using an Cybex II isokinetic dynamometer which measure strength of a specific muscle group.

[Signature or name of subject]

The experimental (research) portion of the treatment or procedure is: pre and post testing of leg and arm strength.

This is done as part of an investigation entitles: Bone marrow transplantation and exercise

1. Purpose of the procedure or treatment: to evaluate the effect of a 100 day program of bicycle ergometer on leg and arm strength.

2. Possible appropriate alternative methods of treatment: none

3. Discomforts and risks reasonably to be expected: local muscle fatigue and soreness.

4. Possible benefits for subjects/society: riding a stationary bicycle can strengthen the lower body muscles resulting in an early increase in functional capacity leading to a more independent lifestyle.

5. Anticipated duration of subject's participation: one day pre and post testing with intermediate testing the 30th day post transplant.

I hereby acknowledge that has provided information about the procedure described above, about my rights as a subject, and he/she answered all questions to my satisfaction. I understand that I may contact him/her should I have additional questions. He/she has explained the risks described above and I understand them; he/she has also offered to explain all possible risks or complications.

I understand that, where appropriate, the U.S. Food and Drug Administration may inspect records pertaining to this study. I understand further that records obtained during my participation in this study may be made available to the sponsor of this study and that the records will not contain my name or other personal identifiers. Beyond this, I understand that my participation will remain confidential.

I understand that I am free to withdraw my consent and participation in this project at any time after notifying the project director without prejudice future care. No guarantee has been given to me concerning this treatment or procedure.

In the unlikely event of injury resulting from participation in this study, I understand that immediate medical treatment is available at University Hospital of The Ohio State University. I also understand that the costs of such treatment will be at my expense and that financial compensation is not available. Questions about this should be directed to the Human Subject Review Office at 622-5104.

I have read and fully understand the consent form. I sign it freely and voluntarily. A copy has been given to me.

Date __________________________ Time __________________________ Signed __________________________

Witness(es) ____________________________ (Subject)

[Signature or name of person authorized to consent for subject - if required]

I certify that I have personally completed all blanks in this form and explained them to the subject or his/her representative before obtaining the subject or his/her representative to sign it.

Signed __________________________
conceived to investigative treatment or procedure

1. ______ hereby authorize or direct ______ or associates or assistants of his or

her choosing, to perform the following treatment or procedure (describe in general terms), to measure body composi-
tion (lean body mass) using hand-held calipers for which norms have been

established.

The experimental (research) portion of the treatment or procedure is: to measure body composition

and body fat.

This is done as part of an investigation entitled: bone marrow transplantation and exercise.

1. Purpose of the procedure or treatment: to evaluate the patient's lean body mass and body fat
during pre and post exercise program.

2. Possible appropriate alternative methods of treatment: none

3. Discomforts and risks reasonably to be expected: none

4. Possible benefits for subjects/society: exercise helps to maintain lean body mass while
reducing body fat levels.

5. Anticipated duration of subject's participation: pre and post 100 day exercise program.

I hereby acknowledge that _________________________ has provided information about the procedure described above,
about my rights as a subject, and has answered all questions to my satisfaction. I understand that I may contact him/her
should I have additional questions. He/She has explained the risks described above and I understand them. He/she has also
offered to explain all possible risks or complications.

I understand that, where appropriate, the U.S. Federal and Drug Administration may request records pertaining to this study. I
understand further that records obtained during my participation in this study may be made available to the sponsor of this study
and that the records will not contain my name or other personal identifiers. Beyond this, I understand that my participation
will remain confidential.

I understand that I am free to withdraw my consent and participation in this project at any time after notifying the project
director without prejudice future care. No guarantees have been given to me concerning this treatment or procedure.

In the unlikely event of injury resulting from participation in this study, I understand that immediate medical treatment is
available at University Hospital of The Ohio State University. I also understand that the costs of such treatment will be at my
expense and that financial compensation is not available. Questions about this should be directed to the Human Subject Review
Office at 22-10.

I have read and fully understand the consent form. I sign it freely and voluntarily. A copy has been given to me.

Date: ____________ Time: ______ AM or PM

Signed: ____________________________ (Subject)

Witness(es) (if required): ____________________________

If required ______________________________________

I certify that I have personally completed all blanks in this form and explained them to the subject or his/her representative
before requesting the subject or his/her representative to sign it.

Signed: ____________________________
APPENDIX H.

PERCENT BODY FAT COMPUTATION FORM
BODY COMPOSITION DATA FORM

SKINFOLDS

Tricep
Suprailliac
Thigh
Total ______ mm
% BF (est) ______

Body Weight_______ lbs = ______ kg
Lean Body Wt. _____ lbs = _____ kg

Additional skinfolds:

Bicep _______ Subscapular _______

IDEAL Body Weight_______ lbs = ______ kg

Pectoralis
Abdomen
Thigh
Total ______ mm
% BF (est) ______
APPENDIX I.
RATING OF PERCEIVED EXERTION SCALE
PERCEIVED EXERTION

6
7    Very, very light
8
9    Very light
10
11   Fairly light
12
13   Somewhat hard
14
15   Hard
16
17   Very hard
18
19   Very, very hard
20
APPENDIX J.
LABORATORY VALUES DATA FORM
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**NOTES:**
- Rest EKG:
- Stress MUGA:
- Pulmonary
- Func Test:
- Other:
APPENDIX K.

PULMONARY FUNCTION LABORATORY PROTOCOL
OHIO STATE UNIVERSITY HOSPITAL PULMONARY DIVISION

GUIDELINES FOR PULMONARY FUNCTION TESTING

A. SPIROMETRY (BASED LARGELY ON SNOWBIRD CRITERIA ARRD, VOL. 119;831.

1. FVC - A minimum of 3 "acceptable" FVC maneuvers must be performed on each patient. "Acceptable" tests are those which have the following characteristics:
   a) a smooth, continuous exhalation without coughing, glottal closure, or obstructed mouthpiece
   b) An apparent maximal effort
   c) No evidence of leaks around the mouthpiece
   d) A satisfactory start of expiration without hesitation (i.e., peak flow should be reached within 100 ml or 10% of FVC)
   e) A satisfactory termination of the test (i.e., expiration > 5 sec or, if average flow is less than 50 ml/sec, over 0.5 sec; in obstructed patients at least 10 sec is desired if it can be tolerated)

   - The best two FVC tests must be within ± 5% or 100 ml of each other, whichever is larger
   - The FVC chosen for final report is the highest achieved

2. FEV1. The FEV1 chosen is the largest measured within the 3 "acceptable" FVC maneuvers

   There are no established criteria for reproducibility of FEV1 measurements

3. FEF25-75 is chosen from the FVC maneuver which has the highest sum of FEV1 + FVC

4. PEF is chosen as the highest flow achieved during any FVC maneuver.

5. Response to bronchodilators: A minimum of 10 (preferably 20) minutes should elapse following administration of a bronchodilator before spirometry is repeated. Follow the instructions for the particular bronchodilator administered (e.g., metaprel: 2 or 3 slow inhalations from RV with 2 to 3 second breath hold at TLC. It should not be administered to pregnant women or children under 12 unless directly ordered by the physician).

   - The same criteria for selecting acceptable tests pre-bronchodilator should apply for post
6. Inspiratory flow-volume measurements

At least 3 maximum inspiratory efforts following maximum FVC maneuvers should be performed. Results for the three best inspiratory FVC's should agree within 10% as well as the two best FIF25-75% measurements.

Report the ratio of FIF25-75/FEF25-75 in the "comments section" of the final report. Also report the normal value which is > 1.5.

Technicians should automatically perform inspiratory loops anytime an upper airway obstruction is suspected (i.e., when PEF is low due to a flattened expiratory flow-volume curve or the patient exhibits inspiratory stridor).

B. STATIC LUNG VOLUMES

1. FRC: At least 2 "acceptable" He dilution FRC determinations must be performed on each patient. Acceptable tests are those which:
   a) agree within 200 ml or 10%, whichever is larger
   b) the patient breathes with a reasonably regular breathing pattern without sudden large shifts in end expiratory volume
   c) there is no evidence of leaks (spirometer continues to move down (pen up))
   d) At least 1 minute past the time required for He equilibration in the previous test must elapse between consecutive tests
   d) equilibration is considered the point at which He changes less than 0.05% in 30 sec.

- The FRC reported should be the average of the two acceptable tests
- Note 1: The He analyzers require 1 hour warm up
  Note 2: The Collins should compensate for small errors (< .3L) in turning the patient into the system exactly at FRC but only in the absence of leaks and when the patient exhibits a reasonably constant end expiratory lung volume.

2. SVC, ERV, and TLC

At least 2 "acceptable" SVC maneuvers must be made. Additional SVC maneuvers, if needed, can be done independent of FRC determination. The following criteria should be met.
   a) the two largest SVC's should agree within 10% or 200 ml, whichever is greater.
   b) the two largest ERVs's must agree within 100 ml or 10%, whichever is greater.
   c) The SVC maneuver should be performed only after a reasonably constant FRC is exhibited (at least 4 to 5 breaths). The maneuver begins with a slow expiration from FRC to RV. Expiration should not be terminated until flow is reduced below 50 ml/sec for 0.5 sec or until at least 5 sec has elapsed (same as FVC maneuver). Expiration is followed by a maximum inspiration to TLC.
- Report the largest acceptable SVC obtained as final SVC
- Report the largest acceptable ERV obtained as final ERV
- Add the largest VC measurement from both the SVC and FVC determination to RV to obtain TLC

Note 1: Don't trust the Collins to always calculate ERV appropriately. Always check your computer printout with a rough estimate from the actual spirogram. When in doubt, accept your hand calculated measurements of ERV, adjusted to BTPS.

Note 2: ERV is a critical measurement because it is used to calculate RV and TLC. TLC is the primary determinant of hyperinflation or restrictive lung disease so accuracy on this measurement is important.


At least two acceptable DLCO measurements must be done on each patient which meet the following criteria:

1. Inspired volume must exceed 90% of the patient's VC (FVC or SVC when available)
2. Breath holding time should be between 9 and 11 sec.
3. Maximum inspiration and expiration should occur as rapidly as possible
4. The two best DLCO measurements must agree within 5%  
5. The $V_A$ measurements of the two best DLCO tests must agree within 10% or 200 ml, whichever is larger  
6. The patient's vital capacity must exceed 1 liter  
7. At least 4 minutes should elapse between consecutive tests

- The final DLCO reported should be the average of the two best DLCO$^{(SB)}$ measurements
- The final $V_A$ reported should be the average of the two TLC$^{(SB)}$ measurements on the Collins taken from the best DLCO tests.
- If no static lung volumes are obtained prior to the DLCO tests then TLC$^{(SB)}$ is not available. Report $V_A^{(SB)}$ and make the following note in comments: "$V_A$ based on single breath test"

* This may be subject to change when new normal values are implemented
APPENDIX L.

STRESS MUGA PROTOCOL
EXERCISE PROTOCOLS

STRESS MUGA PROTOCOL

The following is to be followed for all stress MUGA exams:

1. All patients will be appropriately tagged and have an IV in place.
2. Three resting views (RAO, LAO and lateral) will first be obtained.
3. A resting ECG (limb leads plus V2 and V5) will be assessed.
4. The computer in-put form is to be completed up through the background history prior to the study. Both the chart and patient input should be used.
5. The oscilloscope on the gate should be operational and the audible beep on. This is so that any arrhythmias or misgating, can be audibly as well as visually detected.
6. A baseline BP should be obtained and baseline HR recorded.
7. The patient should begin exercise at 150 kpm/min and every two minutes the workload is to be increased unless acquisition occurs at that stage.
8. At any stage where acquisition is to be performed, the patient should be allowed to equilibrate for one minute. Acquisition is to be for two additional minutes in the LAO only.
9. Two stress acquisitions are performed; a mid-stress and a maximal stress. The mid-stress should be done at HR of 115-120. The maximal stress image is then acquired when fatigue is obvious or significant ST depression is present. Do not increase the workload while acquisition is ongoing (so HR remains stable). If the patient attempts to stop during acquisition, verbally encourage him and, if ineffective, physically help him turn the ergometer pedals and slightly reduce the workload. The patient must exercise the entire two minute acquisition period.
10. The end-point should consistently be fatigue or marked S-T depression. An adequate stress is considered present when the double product (HR x systolic BP) exceeds 20,000.
11. PVC's will interfere with appropriate ejection fraction calculation. If any appear, abolish them with IV lidocaine. More than 1 PVC for every tenth beat will interfere with the study.
12. Post-exercise study should be acquired at 2-3 minutes following the end of the stress period. At this time, catechols remain high while workload is off. The post-exercise study frequently has the greatest ejection fraction.
13. At the completion of the study be sure to note reason for discontinuing study and interpretation of ECG results on computer form. A running tally of HR, BP, ECG changes, time and arrhythmias is kept by the ECG technician.
**DURING THE STRESS MUGA STUDY**

During the stress MUGA exam, certain acquisition parameters should be noted by the cardiology fellow to insure a good study.

1. Be sure there is good positioning with adequate LV/RV separation.
2. The general purpose collimator can be used as long as count rates exceed 1/000. Check the terminal and if the count rate is < 17K, then the high sensitivity collimator is to be used.
3. The computer input from the gate will calculate a heart rate. This should match the heart rates obtained from the oscilloscope and ECG tracing. If these do not match, then misgating is occurring and the study will not be accurate. Often misgating is due to interference of the ECG on the oscilloscope, arrhythmias or lack of an adequate ECG signal. Different leads or sensitivity settings often will correct the problem. Ventricular arrhythmias should be treated with lidocaine and replacement of leads should correct for artifact in most cases.
4. The remainder of the radionuclide acquisition is handled by the technologist. The fellows are encouraged to participate in the work-up of all the data when time permits. During the rotation, one should go through each of the steps in data work-up at least once to become familiar with the data manipulation process.
APPENDIX M.

CLINICAL CHEMISTRY AND HEMATOLOGICAL LABORATORY NORMATIVE VALUES
NORMAL: RANGE OF LAB VALUES

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APPENDIX O.

FLEXIBILITY EXERCISES
FLEXIBILITY AND STRETCHING EXERCISES

Omit any of the following exercises which may be inappropriate for you because of injuries or chronic problems.

Each of the following stretching/flexibility exercises should be performed at least three times for a period of five seconds for beginners and progressing to five times for a period of twenty seconds. It is important to relax between each of the exercises to promote recovery and circulation. For those exercises in the standing position, the individual may use a chair or another firm object for support. All these exercises are to be done on a "no pain, low tension" basis; that is, each movement should progress until the individual feels the tension, but never to the point of pain. It is important to maintain a relaxed position through the flexibility routine.

LEG MUSCLES

SHALLOW KNEE BENDS (R,L)

STRADDLE STRETCH (R,L)

ACHILLES WALL STRETCH (R,L)

HAMSTRING STRETCH (R,L) (USE A WALL WITH A DOORWAY OR A TREE--MOVE BODY IN AS TENSION ADJUSTS)

SUPINE INDIAN POSITION (FOR ADDUCTOR MUSCLES--PROGRESS TO SITTING POSITION)
PROGRESSION

KNEE TO CHEST PULL (R,L)

KNEE TO NOSE PULL (R,L)

QUAD STRETCH (OPTIONAL, FOR MORE ADVANCED INDIVIDUAL (R,L))

ALTERNATE HAMSTRING STRETCH (R,L--START WITH TOE POINTED, BRING LEG UP, PROGRESS WITH TOE POINTED TOWARD THE NOSE)

TRUNK MUSCLES

TRUNK ROTATIONS (R,L)

SIDE BENDS (R,L)
NECK AND SHOULDERS
(FOR POSTURAL FLEXIBILITY, SITTING OR STANDING)

LATERAL NECK FLEXION
(R,L)

NECK ROTATION
(R,L)

NECK FLEXION AND EXTENSION
(BE SURE MOUTH IS CLOSED)

SHOULDER CIRCLES (BOTH)
(START WITH SHOULDER ROLL FORWARD, THEN BACKWARD)

SHOULDER STRETCH, REAR (BOTH)
(FROM REAR, TOUCH HANDS, THEN OPPOSITE ELBOW WITH EACH HAND; RETRACT SHOULDERS)

DO NOT DO NECK AND TRUNK CIRCLES IN OLDER POPULATIONS OR IN INDIVIDUALS WITH NECK OR BACK PROBLEMS