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THE ROLE OF MALNUTRITION IN PROLONGED RESPIRATORY FAILURE: THE EFFECT OF ACCELERATED NUTRITIONAL REHABILITATION

Submitted to the
Faculty of Graduate Studies and Research
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ROLE OF MALNUTRITION IN PROLONGED RESPIRATORY FAILURE

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The Role of Malnutrition in Prolonged Respiratory Failure: The Effects of Accelerated Nutritional Rehabilitation

by Candace Hinze

Abstract

To investigate the possibility that malnutrition is an important factor that prolongs respiratory failure (PRF), I studied the effects of pharmacologic injections of recombinant human growth hormone (rhGH), an important anabolic stimulus, on nutritional and respiratory parameters in patients requiring mechanical ventilation for more than three days. Patients were excluded from consideration if dominating factors known to prolong ventilatory failure had not been stabilized. Over ten months, 106 patients in PRF were evaluated, but only six met the selection criteria. Three patients were randomized to receive standard nutritional support, and three into a group that received the equivalent nutrition plus 5 mg/day of rhGH for 14 days or until withdrawal of mechanical ventilation. Baseline characteristics of the selected patients were divergent as demonstrated by body mass indexes ranging from 14 to 42 (kg/m^2), baseline maximal inspiratory pressures (PI_{max}) from -15 to -70 cm H_2O, and Day 1 N balances from -13.5 to 1.2 g N/day. Despite increased plasma insulin-like growth factor-1 concentrations, the mean daily N balances of the rhGH-treated group were no better than the controls (1.3 ± 5.0 vs. 0.4 ± 2.6 g N/day; Mean±SD), nor were there differences in PI_{max}, level of ventilatory assistance required, and days to weaning. The persistence of respiratory failure in the overwhelming majority of patients in PRF appears to be due to factors already known to prevent weaning from mechanical ventilation. Even the carefully selected patients enrolled in the present study were insufficiently homogeneous or stable enough to allow proper testing of the experimental hypothesis.

Rôle de la malnutrition dans l'insuffisance respiratoire prolongée: Les effets d'un rétablissement nutritionnel accéléré

par Candace Hinze

Résumé

Pour vérifier l'hypothèse selon laquelle la malnutrition serait un facteur clé dans l'insuffisance respiratoire prolongée (IRP), on a étudié les effets d'injections de doses pharmacologiques d'hormone de croissance humaine recombinante (rhGH), un important stimulus anabolisant, sur les paramètres nutritionnels et respiratoires chez les patients nécessitant une ventilation mécanique pendant au moins trois jours. Ont été exclus les patients dont l'insuffisance respiratoire n'était pas stabilisée pour d'autres raisons médicales. Parmi les 106 patients évalués sur une période de dix mois, seulement six ont répondu aux critères de sélection et ont reçu un support nutritionnel standard. De plus, trois de ces patients, choisis au hasard ont reçu 5 mg/jour de rhGH. Ce traitement a été donné pendant 14 jours ou jusqu'au retrait de la ventilation mécanique. Les caractéristiques de base des patients sélectionnés étaient très variables, à savoir: des indices de masse corporelle allant de 14 à 42 (kg/m^2), des pressions inspiratoires maximales de base (PI max) de -15 à -70 cm H_2O et des bilans azotés de -13.5 à 1.2 g N/jour. Malgré une concentration plasmatique plus élevée de l'IGF-1 chez les sujets recevant le traitement hormonal, la moyenne de leurs bilans azotés quotidiens n'étaient pas plus élevée que celle du groupe qui n'en recevait pas (1.3 ± 5.0 vs 0.4 ± 2.6 g N/jour; moyenne ± ecart-type). Les paramètres tels que PImax, le niveau d'aide respiratoire requis et le nombre de jours précédant le sevrage du respirateur n'étaient pas non plus différents entre les deux groupes. La persistance de l'insuffisance respiratoire chez la grande majorité des patients souffrant de IRP, semble être causée par d'autres facteurs déjà reconnus qui retardent le sevrage du respirateur mécanique. Même si les patients étaient soigneusement sélectionnés pour cette étude, ils ne formaient pas un groupe suffisamment stable et homogène pour permettre la vérification de notre hypothèse.

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Introduction

Respiratory failure occurs when the workload of breathing imposed on the respiratory system exceeds its supply. One mode of life sustaining therapy during respiratory failure is mechanical ventilation. Some patients requiring mechanical ventilation cannot be promptly weaned (1,2). These patients in prolonged respiratory failure represent a high risk population with a mortality rate at discharge reported to be up to 56% (1).

Protein-energy malnutrition (PEM) contributes to the pathophysiology of respiratory failure. Diaphragmatic muscle mass is dramatically affected by PEM. It has been shown at necropsy that a loss of 30% IBW corresponds to a 40% loss in diaphragmatic muscle mass (3). This loss in respiratory muscle mass translates into a functional loss of respiratory muscle strength. Respiratory muscle strength, as measured by maximal inspiratory pressures, is reduced in poorly nourished patients when compared with well-nourished controls (4,5). Conversely, it has been found that the restoration of protein-energy stores leads to improvements in respiratory muscle strength (6-9). A 10% increase in body cell mass was found to lead to a 25% improvement in respiratory muscle strength (5). These studies suggest that PEM plays a role in the pathophysiology of respiratory failure in spontaneously breathing patients. However, once a machine takes over the work of breathing, does nutrition play a role in prolonging respiratory failure? The present study was designed to examine this question.

The text that follows includes a review of the basic concepts of the relationship between protein-energy malnutrition and the respiratory system. This is followed by a discussion of growth hormone, a potent anabolic agent, that was used as a tool to study this question, and finally by the rationale for and description of the research plan of the present study.

1. RELATIONSHIP BETWEEN PROTEIN-ENERGY MALNUTRITION AND RESPIRATORY FAILURE

1.1 Definitions and Basic Concepts

1.1.1 Protein-Energy Malnutrition

Protein-energy malnutrition (PEM) may be defined as the pathologic depletion of body protein and energy stores. It most often results from consumption of a diet insufficient to meet metabolic demands. In clinical practice, however, increased metabolic rate and accelerated protein breakdown that are characteristic of catabolic illness, contribute to the development of PEM. Despite different, or combined etiologies, the clinical manifestations of PEM are muscle wasting, weakness, malaise, impaired wound healing, immunodeficiency, and ultimately death.

1.1.1.1 Composition of Weight Loss During Semistarvation

The severity of nutrient deprivation can be divided into two categories: starvation, in which all nutrient intake has ceased, or semistarvation, in which nutrient intake is chronically inadequate. The focus of this discussion will be on the latter. Semistarvation results in prolonged negative energy balance due to an intake less than normal metabolic demands. To compensate for the energy deficit, endogenous energy stores are oxidized leading to their gradual depletion. The most easily identifiable result of this process is weight loss. Weight loss itself, however, does not provide any insight regarding the alterations in body composition that accompany semistarvation. The most detailed study concerning the effects of semistarvation on body composition was completed by Ancel Keys and colleagues during the 1940's in the famous Minnesota study. Thirty-two young men volunteered to consume 1600 kcal (6720 kJ), 50 g protein diet that met approximately two-thirds their energy requirements for 24 weeks. By the end of the study the mean total weight loss was 15.9 kg representing a loss of 23% total body

weight. The corresponding changes in body composition were 71% and 24% loss of fat and protein stores, respectively (10). These results showed that the loss of protein stores in semistarvation is proportional to the loss of total body mass.

1.1.1.2. Adaptation to Semistarvation

Adapting to semistarvation is the key to survival. Adaptation is characterized by an attenuation of fat and protein stores depletion resulting from a reduction in resting and total daily energy expenditure coupled with a depressed rate of protein turnover, which together allow the body to remain in protein and energy balance despite a low dietary intake. The process of adaptation to semistarvation can be divided into the early and prolonged phases. Within several days of eating a semistarvation diet there is a decline in the resting metabolic rate (RMR). This initial decline in RMR is thought to be hormonally mediated through alterations in catecholamine metabolism and T3/T4 conversion (11).

To meet the challenge of prolonged semistarvation, RMR progressively declines. Energy expenditure can decline by as much as 30-40%, as was observed in prisoners of the Warsaw ghetto of World War II, and in normal volunteers subjected to 24 weeks of semistarvation in the Minnesota experiment (10,12). This later adaptation involves the sacrifice of lean tissue stores. By reducing the lean tissue stores, the body's metabolically active tissue, and therefore RMR, energy balance can be renegotiated at a lower level of energy intake. In adapted semistarvation, protein stores become depleted, but not to the point of unbearable consequences. This is the result of changes in protein metabolism that serve to diminish the overall loss of lean tissue. The efficiency of protein recycling is improved, which then reduces the rate of protein loss. Secondly, as lean tissue stores become more depleted, retention of dietary protein is increased, partly due to adaptive cellular metabolic changes. As semistarvation continues lean tissue stores decrease requiring fewer dietary amino acids to sustain itself, coupled with improved efficiency of protein recycling and increased retention, a new equilibrium is reached

and net body protein erosion is halted (11).

This life-saving accommodation to semistarvation is disrupted by physiologic stresses, such as sepsis, trauma, or surgery. As previously discussed, the physiologic response to catabolic illness leads to accelerated protein catabolism and an elevation in energy expenditure. Food intake that was once adequate to meet requirements in the previously accommodated state is no longer sufficient, and the patient begins to lose weight again.

The catabolic response to injury is mediated by counter-regulatory hormones (cortisol and catecholamines) and cytokines (tumor necrosis factor, or TNF, and interleukin 1, 2, and 6). TNF is synthesized by macrophages and interleukin-1 by monocytic phagocytes (13,14). Besides the metabolic alterations already described, the catabolic response is also characterized by fever, malaise, a decrease mean arterial pressure, and decreased systemic vascular resistance (14). Another salient feature of the stress response is anorexia (14). Nevertheless, the consequence of catabolic stress superimposed onto an already malnourished state is the rapid depletion of remaining central protein stores (15). With the depletion of central protein stores, the life threatening repercussions of protein-energy malnutrition become more evident.

1.1.1.3 Diagnosis of Protein-Energy Malnutrition

The physiologic, biochemical, and clinical characteristics of protein-energy malnutrition vary according to the severity of the disease, the patient's age, and the predominance of energy or protein deficiency. Assessment of nutritional status has traditionally relied on measures of body composition, such as anthropometric and biochemical data.

The severity of protein-energy malnutrition can be judged by anthropometric measures. Anthropometry refers to the surface measurements of the human body (16). Body weight, the fundamental anthropometric measure, can be simply and accurately measured in ambulatory subjects. Using a simple beam balance, body

weight can be measured with accuracy to one-hundredth of one percent (17). The measurement of body weight in the hospitalized patient is more difficult requiring a specialized chair or bed scale that is generally accurate to 0.1 kg (18). Weight changes can serve as a rough estimate of unbalanced energy input to output given a constant degree of hydration. A loss of more than 10 percent body weight in six months represents "severe" weight loss and the presence of protein-energy malnutrition should be suspected (19). However, a limitation to using changes in body weight as an indication of changes in nutritional status is the fact that differences in weight due to fat, muscle, water and/or bone cannot be differentiated (20). To further complicate matters, in advanced or complicated PEM there is an increase in the extracellular fluid compartment that can essentially "mask" the loss of body energy stores. During critical illness the proportion of patients with generalized edema has been estimated to be up to 25% (21).

Body weight can be evaluated by comparing present weight to usual body weight, as above, or by comparing actual weight to established standards. The most commonly used standards are the Metropolitan Life Standard Tables of 1959. These tables were developed by actuaries for use in the insurance industry. For each height there is a corresponding "ideal weight" associated with the lowest mortality rate. The degree of deviation from the "ideal weight" is used to classify the severity of protein-energy malnutrition (22). A weight-height index of 80-89% mild to moderate and 70-79% severe depletion of protein-energy stores (23).

A major site of fat deposition in the human is subcutaneous (17). It is believed to comprise 30-33% of the total body fat stores (18). Measuring skinfold thickness, using calipers, at several strategic locations, the most common being biceps, triceps, subscapular and suprailiac, provides an approximation of total subcutaneous fat stores (24). An estimation of lean body mass can be determined anthropometrically also. Mid-arm muscle circumference (MAMC) is calculated using the measured triceps skinfold and mid-arm circumference (MAC). The value for MAMC is calculated by inserting these values into an equation;

MAMC(cm)=MAC(cm)-0.314 TSF(mm).

Results of skinfold anthropometry are interpreted either in comparison to previous measurements in the same patient or in comparison to a standard reference. One of the most frequently used standards is from Durnin and Womersley (1979), who took measures in 569 healthy, noninstitutionalized subjects (17). A valid reference standard must reflect the population being evaluated. This is not always possible, for example in the hospitalized or chronically ill patients, for which standards are not available.

To evaluate the status of the visceral protein compartment serum concentration of selected proteins can be measured. These proteins are synthesized by the liver and secreted into the plasma (25). It has been clearly established that total hepatic protein and RNA levels decline during nutrient deprivation leading to a decrease in serum concentrations of proteins synthesized and secreted by the liver, such as albumin, prealbumin, retinol binding protein and transferrin (25-27). The rate of decline in the serum levels of these proteins, due to a decrease in synthesis, is proportional to their turnover rate. Hence, prealbumin with a half-life of 12 hours as compared to albumin (half-life=20 days) is a more sensitive indicator of depletion of visceral protein stores than is albumin (28,29).

Although a depression in serum protein concentrations can signal the depletion of visceral protein stores, this marker is unfortunately not specific. The serum protein concentrations are also dependent on the liver function. Impaired function reduces the liver's synthesizing capacity eventually leading to a decrease in serum protein levels even when sufficient nutrients are available (31). Also, as part of the acute phase response, liver albumin synthesis and export decreases even in previously well nourished patients. Hydration status also effects measured serum protein concentrations. With total body water expansion, which is common in critically ill patients, serum protein concentrations will appear lower because of a dilutional effect and conversely, in dehydration will appear fictitiously high.

Over the past ten years there has been growing interest in the impact of

nutrient deprivation and refeeding on the "functional" well being of individuals (8,9,32-35). Specifically, tools to assess skeletal muscle function have been developed and validated. In hospitalized patients, who are unable to exercise on a treadmill or stationary bicycle, two methods have been used, hand dynamometry and the adductor pollicis function test. Hand dynamometry measures the maximal voluntary handgrip force generated. To measure the function of adductor pollicis muscle, the ulnar nerve is stimulated electrically to induce contraction of this muscle. The forces generated at different levels of electrical stimulation, and the relaxation rate are recorded.

The usefulness of these tests is based on the observation that alterations in muscle function precede changes in body composition during periods of nutrient restriction and refeeding (33). In a study of six obese patients placed on a hypocaloric diet (400 kcal/day) followed by a fast, Russell and colleagues compared the response of standard nutritional assessment parameters (serum albumin, serum transferrin, creatinine height index, anthropometric, total body nitrogen and total body potassium) to adductor pollicis function. After two weeks of a hypocaloric diet, skeletal muscle function was significantly reduced accompanied by an increase in muscle relaxation rate and force of contraction at low frequency stimulation (10 Hz). Refeeding prompted rapid normalization of muscle function parameters without residual losses after two weeks. The standard nutritional parameters measured did not respond to nutrient restriction or refeeding (33). These results showed that skeletal muscle function is more sensitive to subtle changes in body function than are measures of body composition during short term dietary restriction and refeeding.

A series of metabolic changes in protein, energy, and mineral metabolism that occur in response to nutrient deprivation within several hours or days are thought to be responsible for the observed changes in skeletal muscle function. After two weeks of hypocaloric dieting (1680 kJ/day) significant increases in intracellular calcium have been observed (32). Additionally, declines in muscle

enzymes have been associated with inadequate energy intakes (32). Alterations in calcium metabolism and muscle enzyme levels most likely play a role in these observed changes in skeletal muscle performance.

Beyond being a sensitive measure of nutrient deprivation and refeeding, muscle function testing is also an effective predictor of postoperative complications. Klidijian et al found in a study of 225 patients undergoing major abdominal surgery, that preoperative hand dynamometry was a better predictor of postoperative complications than was serum albumin, weight loss, or weight for height. Hand dynamometry predicted postoperative complications in 48 of the 55 patients (87%) making it a more sensitive indicator to identify postoperative complications than albumin which detected postoperative complications in only 52% of patients (36).

1.1.2 Energy Metabolism

1.1.2.1. Energy Stores

The fate of ingested carbohydrate, protein or fats is either to be oxidized to produce energy or to be transformed into forms that can be stored as potential energy (37). When exogenous fuel is not available as in an overnight fast, the body derives energy from its endogenous stores (17). The primary storage form of energy is fat. A normal 70 kg male has approximately 16 kg of fat stored in adipose tissue having the caloric value of 150,000 kcal (630,000 kJ) if oxidized. (37). The protein content of a normal male is 11 kg which can be subdivided into 7 kg of intracellular and 4 kg of extracellular protein. The ll kg of protein can yield 45,000 kcal (188,000 kJ) if oxidized. The extracellular component consists mainly of bone ligament, tendons, cartilage and connective tissue that is not available to meet metabolic demands. The intracellular proteins make up the body's active cell mass, and serve many functions but are primarily contractile proteins and enzymes. Protein from this compartment can be mobilized to provide glucose via gluconeogenesis when energy balance is negative but should not be considered a "protein store." Due to the essential functions performed by these proteins, the

loss of protein can lead to adverse functional consequences and is considered the cause of death in long term starvation (11). Besides fat and protein, carbohydrate is stored in the liver and muscle as glycogen. Glycogen stores contain 1,000-3,000 kcal (4,200-12,600 kJ) and can meet immediate energy demands, such as exercise.

1.1.2.2 Energy Balance

Energy balance is metabolizable energy in minus energy expended. Zero energy balance is achieved when energy intake is equal to energy expended. If energy intake is greater than energy expended, then the subject is in positive energy balance and is storing energy. Negative energy balance occurs when energy intake is less than that expended and endogenous energy stores are being oxidized to provide energy (37).

1.1.2.3 Determinants of Energy Expenditure

During substrate oxidation a substantial portion of the liberated energy is captured in the high energy bonds formed when ADP and inorganic phosphorus are transformed into ATP. Conversely, energy expenditure is a term used to describe the hydrolysis of ATP into ADP and inorganic phosphorus or of other high energy bonds. Each fuel has a different heat of combustion and generates a different amount of heat.

Energy expenditure can be divided into three major components. Resting metabolic rate (RMR) or resting energy expenditure (REE) represents 60-70% of total energy expended by most sedentary individuals. The thermic effect of exercise (TEE) is the second largest component of energy expenditure and means the work done by an individual on the environment. The TEE of an individual is dependent on level of physical activity. TEE of an individual not involved in heavy exercise accounts for 15-20% of total daily energy expenditure, but this can be increased by twofold with heavy exercise (37). The third component of energy expenditure is the thermic effect of food (TEF), also known as diet-induced

thermogenesis (DIT). The TEF can account for 10% of the total daily energy expenditure, but this is dependent on several factors including the total energy intake, and composition of meals (38-41). Postabsorptive processes are believed responsible for TEF based on studies that showed a comparable effect when nutrients were administered either orally or intravenously (37). The method of enteral feeding delivery also exerts an influence on TEF. Intermittent bolus feedings provided at zero energy balance were found to increase energy expenditure by 8% to 10%, an effect that persisted from 3 to 6 hours (42). By changing to continuous enteral feedings daily total energy expenditure can be reduced by 4% to 8%. If feedings are infused at a rate that exactly meets or falls just below total energy expenditure, there is no significant increase in REE over fasting levels (41-43).

1.1.2.4 Resting Metabolic Rate (RMR)

RMR is the amount of energy expended by a resting individual in a thermoneutral environment without the effects of physical activity, meal consumption, or other physiologic or psychological stress (37,40,44). Basal metabolic rate (BMR) is defined as the minimal metabolic activity to maintain life including the energy cost of maintaining the biochemical and structural integrity of the body, and the cost of performing work, ion pumps, synthesis and degradation of cellular constituents (37). In addition to the conditions listed above, BMR measurements must be conducted upon awakening in the morning after 12-18 hours of rest and may be slightly lower than the RMR (17,30).

1.1.2.5 Factors that Affect RMR

Age. Increasing age is associated with decreasing energy expenditure, as lean body mass decreases and total body fat increases (45).

Sex. Males are more likely to have higher energy expenditure than females of similar size due to an increase of lean tissue mass. Thus the difference between

the sexes is more pronounced when expressed in units of kg per body weight and becomes distinguishable when based on fat free mass (45).

Body Temperature. Humans, as with other homeotropic species, maintain a constant body temperature independent of the environmental temperature. The influence of body temperature was first characterized by DuBois, finding that metabolic rate is increased by 13% per degree Celsius and 7.2% per degree Fahrenheit. Conversely, a decrease in body temperature reduces metabolic demands and leads to a decrease in energy expenditure (46).

Disease States. Most disease states increase RMR, an effect thought to be related to the release of neurotransmitters and inflammatory mediators, futile substrate cycles, and increases in protein turnover (47). The severity of the injury affects the height of this energy response.

Drugs. The effects of various drugs on the metabolic rate are important in the clinical setting. Drugs that stimulate the sympathetic nervous system can increase energy expenditure, while, anaesthetics and sedatives can have a depressive effect. This will be discussed in detail in Section 1.4.

1.1.3 Techniques for Measuring Energy Expenditure

1.1.3.1 Direct and Indirect Calorimetry

Oxidation is the final common pathway for all the cellular fuels, carbohydrate, fat and protein. During oxidation chemical energy is released as cellular fuels are ultimately broken down into carbon dioxide and water. Some of this chemical energy is captured in the high energy phosphate bonds of ATP and the remaining is lost as heat. Direct and indirect calorimetry, two distinct types of calorimetry, measure two different products of the same reaction and provide identical rates within 2% of energy expenditure under steady state conditions (48).

With the technique of direct calorimetry, a direct measurement of heat loss is obtained. The total heat loss is equal to the rate of energy utilization when the body temperature is constant (49). To measure heat generation a subject is

confined in a thermically isolated chamber. Because the apparatus required is costly and requires that the subject remain in a physically isolated environment, it is not a feasible method to measure energy expenditure in the clinical setting.

By contrast indirect calorimetry utilizes less costly mobile equipment, making bedside evaluations possible. The use of indirect calorimetry in the clinical setting is becoming more widespread (50). The term "indirect" refers to the fact that energy (heat) production is based on measurements of the materials consumed and produced during metabolism. Specifically, it involves the measurement of oxygen consumption (O_2) and carbon dioxide production (CO_2) (51,52).

The abbreviated Weir equation is frequently used to determine energy expenditure from $V0_2$ and $VC0_2$ (53). The Weir equation is:

$$\text{Energy Expenditure} = (3.94 \times VO_2) + (1.11 \times VCO_2)$$

As is shown by the equation, VO_2 consumed is the greater determinant of energy expenditure. The ratio of carbon dioxide produced to oxygen consumed, the respiratory quotient, can be easily calculated and provides information about substrate utilization (54). The oxidation of each fuel (carbohydrate, fat and protein) consumes differing amounts of oxygen and produces a distinct amount of carbon dioxide (55-57).

1.1.4 Techniques for Measuring Protein Stores

1.1.4.1 Nitrogen Balance

Nitrogen (N) balance is the most widely used method to detect changes in lean body mass (LBM). The concept is simple. N intake and output are measured. The difference represents the change in body N stores. When the N input exceeds output, one is in positive N balance and this suggests N retention. Conversely, when N intake is less than output, the subject is in negative nitrogen balance. A limitation of this method as with other balance techniques is that it cannot quantify the absolute amount of body N, only changes in it (37).

In practice, accurate N balance studies are difficult to achieve. First, all

intake must be carefully analyzed for protein content. This is simplified in patients receiving Total Parenteral Nutrition (TPN) or enteral nutrition for the protein content listed by the manufacturer's is fairly accurate. The protein content of formula is within 5% of that listed (58). N input can be easily calculated using the relationship of ingested protein divided by 6.25. Secondly, the exact portion size of all food must be determined by weighing all food before and after meal service.

The largest loss of N is in the urine, being the route of excretion for the end products of N metabolism. Urea is synthesized in the liver and is distributed throughout the total body water. Urea comprises 80% of total urinary nitrogen (TUN) (59). During periods of physiologic stress, however, the ratio of urinary urea N (UUN) to TUN is not constant and has been found to vary from 10-90% (59). Besides urine, the N content from all bodily excrement including stool, any drainage, integumental and miscellaneous (blood, sweat, saliva, and tears) sources must be collected to obtain absolute N output determinations (59). The measurement of all the excreta is not always possible in the clinical setting. As a result, most commonly urine samples are collected, while integumental and faecal losses are estimated (60).

Total urinary creatinine can be measured daily to validate of the completeness of urine collections. Creatinine is the component of urinary nitrogen that is the waste product of creatine. Creatinine is the by-product of phosphocreatine, a high energy phosphate form of creatine used in muscle metabolism. The formation of creatinine is constant within individuals and represents 1.7% to 2.0% of the creatine produced (61).

1.1.5 Respiratory System in Health and Disease

The interrelationship between protein-energy malnutrition and the respiratory system has been long recognized, and is the subject of this research. This section provides background information about the respiratory system.

1.1.5.1 Control of the Respiratory System

A series of complex interactions between the nervous system and the respiratory musculature control respiration. These interactions enable the respiratory system to respond to changing metabolic demands, which are integrally related to overall substrate use.

Automatic respiration is governed by the brain stem, whereas voluntary breathing is controlled by the cerebral cortex (62). The signals generated by the central nervous system (CNS) are modified in the spinal cortex by afferent impulses from the periphery in response to changes in metabolism. These modifying messages originate in the peripheral chemoreceptors that respond to changes in $Pa0_2$, PaO_2, and pH. Chemoreceptor activity is stimulated by a reduction in $Pa0_2$, and pH, and an increase in $PaCO_2$. The response is an increase in minute ventilation (tidal volume times respiratory rate). Central chemoreceptors of the medulla respond to changes in $PaCO_2$ and pH, but do not respond to changes in PaO_2 (62). Therefore, changes in substrate utilization can affect the demands placed on the respiratory system.

Protein intake, independent of its effect on $PaCO_2$ and PaO_2, can influence ventilatory drive (63,64). Askanazi and colleagues found in normal subjects receiving 7 days of infusions of either 5% dextrose or an isotonic amino acid solution, the group receiving amino acids had an enhanced ventilatory drive. A similar response was seen in nutritionally depleted patients who received either high protein (121 g /day) or low protein (21 g/day) TPN. The group receiving the high protein TPN had an enhanced ventilatory response to $PaCO_2$, evidenced by a reduction in $PaCO_2$ from 39.9 mm Hg to 37.6 mm Hg ($p<0.05$) (63).

Along with an intact CNS, adequate strength and endurance of the respiratory muscles is mandatory for normal ventilation. Although the actions of the respiratory muscles are numerous, they can be divided into those whose primary function is either inspiratory or expiratory. Inspiration is always an active process involving muscular contraction. The diaphragm is the main muscle of inspiration.

It is a thin dome-shaped muscle that moves down when it contracts thus generating a negative pleural pressure that initiates airflow into the lungs. (65). Expiration is usually passive, but is an active process when demands on the respiratory system are high. The strength of the respiratory muscles can be assessed by measuring the maximal pressures that can be generated during inspiration and expiration, called peak inspiratory (PI_{max}) and expiratory (PE_{max}), respectively.

1.1.5.2 Chronic Obstructive Pulmonary Disease

In the broad sense pulmonary disease can be classified as obstructive airflow and restrictive disease, both chronic and acute. As the name implies, chronic obstructive pulmonary disease (COPD) is characterized by persistent slowing of airflow after expiration (66). COPD is an ill defined term applied to patients with emphysema, chronic bronchitis or both. The clinical presentation of COPD commonly includes dyspnea on exertion and a productive cough (66). Cigarette smoking is a major risk factor in the development of COPD (66).

Emphysema is an anatomic lesion of the lung. There is an enlargement of the airway space distal to the terminal bronchiole. The clinical presentation commonly includes complaints of shortness of breath for several years, chronic cough, and poor exercise tolerance. It is characterized by a loss of alveolar wall with destruction of the capillary beds (66).

Chronic bronchitis is characterized by excess mucus production in the bronchial tree in quantities that are sufficient to cause excessive expectoration of sputum. Pathological findings are hypertrophy of mucous glands in the large bronchi with the small airways becoming narrow and showing inflammatory changes including cellular infiltration and edema of walls (66).

The severity of COPD can be determined by chest radiography and pulmonary function tests showing impaired expiratory airflow obstruction. The simplest test is forced expiration. The forced expiratory volume in the first second after maximal inspiration, ($FEV_{1.0}$), is often severely reduced in COPD. For

example, a young, healthy adult male may expire 4.0 L in the first second, while in severe COPD this can decline to 0.8 L (66). Forced vital capacity (FVC) is the total volume expired in one breath and is also reduced in COPD (66).

COPD is very common in the general population. Chronic bronchitis occurs in 20% of all males, while 66% of all males and 25% of females have been found to have chronic emphysema in post-mortem studies (67). In fact in the United States, COPD is the second most common cause of disability under Social Security (66).

1.1.5.3 Respiratory Failure

The most important and common cause of respiratory failure is an acute event superimposed on chronic lung disease. Patients with COPD often follow a gradual downhill course with increasing hypoxemia and CO_2 retention. The acute decompensation of the COPD patient is usually precipitated by an acute viral upper or lower respiratory tract infection (66) which leads to rapid deterioration, due to their minimal pulmonary reserves.

1.1.5.4. Mechanical Ventilation

One form of life sustaining treatment to manage respiratory failure is mechanical ventilation. Mechanical ventilation refers to any method of breathing in which a mechanical apparatus is used to augment or entirely satisfy the bulk flow requirements of breathing (65). Ventilatory support has become very specialized and complicated as the understanding of lung pathophysiology and the design of ventilators has improved (69).

The fundamental basis of mechanical ventilation is to generate positive pressure in the airway so that transpulmonary pressure is positive. This causes the lungs to inflate (70). The peak inflation pressure (PIP) required for adequate ventilation is decided by five variables: compliance of the lungs and thorax (C_{LT}), airway resistance (R_{aw}), tidal volume (V_T), inspiratory flow rate (V_{IN}), and baseline

pressure. The mathematical equation that relates these variables is (70):

$$PIP = V/C_{cst} + (R_{aw} \times V_{ta}) + \text{Baseline pressure}$$

From this equation, one can see that several common features of COPD, such as an increase in airway resistance, or a decrease in compliance, can increase PIP requirements.

Ideally ventilatory support should be tailored to each patient's pathophysiology. Therefore, no single mode exists for all patients. The modes of mechanical ventilation currently used range from controlled mechanical ventilation (no opportunity for the patient to breath spontaneously) to total spontaneous ventilation with continuous positive airway pressure (CPAP). Partial ventilatory support bridges the gap for patients who cannot entirely support their own ventilatory needs. In controlled mechanical ventilation, volume or pressure, the clinician selects the respiratory rate, tidal volume, inspiratory flow rate and/or pressure without allowing for spontaneous breathing. This mode of support is indicated for paralyzed or heavily sedated patients incapable of initiating breathing. Assisted mechanical ventilation requires that the patient triggers each breath which is supplemented by a set amount of positive pressure or volume. Assist-control mechanical ventilation allows both spontaneous breaths and supported or controlled breaths. In this mode, ventilation may be triggered by either the patient or a timing device. The timing device is set at a minimal preselected respiratory rate.

In pressure support ventilation, the patient's spontaneous inspiration effort is assisted by positive airway pressure. The patient controls the ventilatory timing, inspiratory flow rate, and tidal volume. Consequently only patients with an intact and reliable respiratory drive are suitable for this mode.

When the mechanically ventilated patient responds to medical therapy, and respiratory status begins to improve, attention becomes focused on withdrawal of ventilatory support. This process of withdrawing mechanical ventilatory support is commonly referred to as "weaning" from mechanical ventilation, and conceptually

is the transfer of the work of breathing from ventilator to the patient. The likelihood of successful weaning is a function of the interplay between the amount of work required for breathing and the capacity of the ventilatory pump to do that work.

During mechanical ventilation maximal inspiratory pressure (PI_{max}) is measured to assess respiratory muscle strength and hence their capacity to do the work of breathing. To measure PI_{max} a one-way valve is used that permits exhalation while inhalation is blocked. This measurement is commonly taken for at least 20 seconds to ensure that the patient is stressed to a level that results in maximal contraction (71). Since respiratory muscle strength contributes to the pathophysiology of respiratory failure, PI_{max} measurements are used to predict weaning success. It is generally accepted that PI_{max} measurements of greater than -30 cm H_2O predict weaning success while worse than 20 -cm H_2O predicts weaning failure. As a reference point, a normal male can generate pressures of 100-140 -cm H_2O.

PI_{max} is a global assessment of inspiratory muscle strength and is not specific to just the diaphragm. To isolate the diaphragm's strength, transdiaphragmatic pressure (T_{di}) can be measured using balloons to find out gastric pressure and then subtracting esophageal pressure (65). This procedure is invasive and difficult to perform and for this reason is rarely used at the bedside.

There is no one standard procedure for weaning from mechanical ventilation. Intermittent mechanical ventilation is commonly used in which the patient is allowed to breathe spontaneously while the ventilator is set at specific intervals to provide mechanical inflation if needed. As the patient improves the set number of breaths provided by the ventilator is gradually decreased. Pressure support ventilation (PSV) is also used for weaning. When PSV is used the level of airway pressure delivered by the ventilator is reduced in a stepwise manner as the patient takes over the work of breathing (72). During the weaning process abrupt elevations in PCO_2 and respiratory rate signal that the patients cannot tolerate the increase in workload and is designated as "failure" to wean. Other signs of failure to wean

include decreasing tidal volume, desaturation of arterial blood, and hemodynamic changes.

Mechanical ventilation is becoming increasingly important in the management of respiratory failure. Originally it was used almost exclusively as an emergency procedure in resuscitation or as a last resort in the treatment of the critically ill. Now its use is becoming more widespread. A 50% increase in the number of patients receiving mechanical ventilation was observed over ten years, from 1979-1989. A multi-centre study performed in 1989 (n=3884) reported that 49% of all patients admitted to American intensive care units (ICU) required mechanical ventilation (73).

With the expanded use of mechanical ventilation, some patients require *prolonged* mechanical ventilation. These are patients who have failed previous attempts to withdraw mechanical ventilatory support and resume spontaneous, unassisted breathing. Although a strict definition of prolonged mechanical ventilation does not exist most authors agree that it is greater than two to three days (1,2). Schmidt et al found 73% of all medical patients receiving mechanical ventilation required support for more than three days and that by day 7, 42% were still not weaned (2).

This life sustaining therapy is not benign. In a study of 100 ICU patients who required more than two days of mechanical ventilation, Davis et al found an overall mortality rate of 56% at discharge (1). Mortality rates were found to be greatly influenced by patient's age and primary diagnosis. The lowest morality rate, 29%, was found in patients with COPD as a primary diagnosis (1).

1.2 Prevalence of Malnutrition in COPD

1.2.1 High Incidence of Protein-Energy Malnutrition

There is a high incidence of protein-energy malnutrition in the COPD patient population (5,8,24,74-76). Loss of body weight is the most easily detected measure of protein-energy store depletion. It has been known since the nineteenth century

that emaciation accompanies emphysema (12). Recent studies have found that 24% to 71% of COPD patients are less than 90% ideal body weight (IBW) and/or have reported recent weight loss. In a study of 779 outpatients with COPD, 24% were malnourished which was defined as a weight less than 90% IBW (62). Braun found that almost half (48%) of outpatients enrolled in a pulmonary rehabilitation program (n=60) lost more than 5% total body weight within one year (76). In hospitalized COPD patients, Hunter et al. observed a recent weight loss over an unspecified time in 27 (71%) of 38 patients. Nine of these patients showed a weight loss of 1 to 10% of their usual weight, 7 lost between 11 and 20% of their usual weight, and 11 more lost more than 21% of their usual weight (74). More than half of these outpatient COPD patients were less than 90% IBW (74).

The onset of progressive weight loss in patients with COPD is associated with increased mortality. Vandenburgh found the mortality rate 30% at 3 years and 49% at 5 years after the onset of weight loss, as compared to 25% at 5 years for those without weight loss (77). Anthropometric measurements of triceps skinfolds (TSF), mid arm circumference (MAC), and mid-arm muscle circumference (MAMC) have been used to distinguish between the depletion of protein vs. energy stores in the COPD patient population. Using these measurements, Hunter found hospitalized COPD patients had significantly depleted protein-energy stores when compared to the standard mean values (74). The depletion of protein-energy stores was also observed in COPD outpatients. Braun et. al. found that 29% of non-hospitalized COPD patients were less than 90% the mean standard and another 33% had severe losses of TSF defined as 60% or less of the mean standard (76). As for MAMC, 53% were less than 90% the mean standard without any patients under 60% the mean standard.

The visceral protein stores in patients with COPD appear to be spared as evidenced by serum protein concentrations. Serum albumin levels have been found to be within normal limits even in weight losing COPD patients (24,74,76). Transferrin, which has a shorter half life than albumin, has also been found to be

within an acceptable range (24,74).

From this biochemical and anthropometric data, it appears that visceral protein stores are preferentially retained at the expense of peripheral muscle mass and fat stores in COPD. This is consistent with successful adaptation to semistarvation. During this adapted phase, amino acids are released from peripheral muscle mass and are used to protect the mass and function of the "central" visceral organs, such as the liver, gut and immune system (11). The result is normal levels "circulating" visceral proteins, such as albumin and transferrin. There is a simultaneous mobilization of fat stores initiated by low insulin levels. The depletion of peripheral muscle and fat stores in COPD, as measured by substandard TSF and MAMC, is consistent with adaptation to semistarvation.

1.2.2 Vitamin and Mineral Status in COPD

Unlike the documentation of PEM in COPD, there is very little data concerning vitamin and mineral status of these patients. The intake of calcium, phosphorus, iron, vitamin A, thiamin, riboflavin, niacin, and vitamin C has been reported adequate or even generous when compared to the Recommended Daily Allowance (RDA) (74,78). However, the results of these studies are suspect on two accounts. First, dietary intake is based on dietary recall that may not accurately depict actual dietary intake. Additionally, the use of the RDAs as a standard for any group of diseased individuals is not appropriate since the allowances were established for a healthy population. Confirmation of alleged adequate nutrient intake has not been backed up by sufficient biochemical analysis of vitamin and mineral status in this patient population.

In stable COPD outpatients serum calcium, magnesium (9,34), phosphorus (34) and zinc (74) have been reported to be within normal limits. Likewise, red cell volume and serum iron studies have shown that iron status is also within normal limits in COPD (9,34,74). However, these findings must be interpreted with caution since most patients with COPD have varying degrees of hypoxia causing

polycythemia. Therefore, the elevations in the serum levels of iron status markers may not be reflective of iron status, but instead reflect adjustments to hypoxemia (74). The vitamin status of COPD patients has not been investigated except for Driver et al who measured serum folic acid, vitamin A, carotene, vitamin B_6, vitamin C and vitamin E (79). Unfortunately, actual serum levels were not reported nor compared to normal levels. The lack of data addressing the vitamin status of COPD patients is astonishing considering the potential impact of deficiencies.

Unlike the stable outpatient COPD population, a high incidence of hypomagnesemia has been reported during critical illness. Hypomagnesemia in these patients has been reported to be from 9.5% to as high as 65% (80-82). The etiology of magnesium deficiency in this patient population is multifactorial. First, it is possible there is insufficient dietary intake of magnesium before acute illness. Although dietary sources of magnesium are diverse, the typical American diet falls below the RDA of 5 mg/kg/day (83). Secondly, magnesium losses may be amplified. Intestinal losses of magnesium are increased with diarrhea, intestinal resection, or regional radiation. The kidney is responsible for the fine regulation of magnesium metabolism. Renal excretion of magnesium is increased with alcohol consumption as evidenced by prevalence of magnesium deficiency in this population. Magnesium reabsorption is also linked to calcium and sodium excretion. Increased excretion of either of these cations leads to increased excretion of magnesium. Therefore, diuretic drugs, commonly prescribed in the critical care setting, which act by increasing urinary sodium excretion will also lead to increased magnesium losses (81-83).

The consequence of magnesium deficiency in the critically ill patient with minimal pulmonary reserves could be serious. Magnesium has multiple roles in pulmonary structure and function. Magnesium inhibits vasoconstriction through its interactions with calcium. Calcium binds to sites that lead to smooth muscle contraction. Thus a magnesium deficiency enhances the action of calcium (81). Hypomagnesemia is also associated with a loss in respiratory muscle strength. In

a controlled study of 17 critically ill patients with hypomagnesemia, Molloy showed improvements in respiratory muscle strength as measured by PI_{max} and maximal expiratory pressure (PE_{max}) with the administration of magnesium while there was no change in the control patients (84). Conversely, magnesium excess can cause vasodilatation as was shown in a study of six patients with severe, acute bronchial asthma. These patients had normal serum magnesium levels, and responded to intravenously administered magnesium with increased bronchodilatation.

1.3 Relationship between Nutritional Depletion and Severity of COPD

The degree of nutritional depletion in COPD is related to the severity of the disease (79,85). This was first shown by Driver who compared the nutritional status of inpatients with COPD in acute respiratory failure (n=9) to stable outpatients with COPD. Body weight was significantly lower in the acutely ill group ($p<0.01$) with a mean weight difference of 19%. Body protein and fat stores, as measured by triceps skinfold and mid-arm muscle circumference, were markedly depleted in almost half of the patients with respiratory failure. Significant differences were also seen in serum transferrin and retinol binding protein levels reflecting depleted visceral protein stores in advanced disease.

In a cross-sectional study of 90 patients with varying degrees of COPD, Ficcardori et al confirmed that nutritional status deteriorates as COPD worsens. Patients were divided into three groups: outpatients, hospitalized, and hospitalized in acute respiratory failure requiring ventilatory support. Of the anthropometric measures, % IBM, TEF and MAMC, all were significantly lower in the two inpatient groups as compared to the outpatient group (85). This observation showed that fat stores and peripheral protein mass become increasingly depleted as disease progresses (79). Depletion of visceral protein stores, as measured by albumin, was more advanced in the inpatient groups as compared to outpatients. Hypoalbuminemia as found in the inpatient group is consistent with disruption of the adaptation to semistarvation as precipitated by metabolic stress leading eventually

to a depletion of "central" visceral protein stores (11).

1.4 Etiology of Protein-Energy Malnutrition in COPD

The deterioration of nutritional status is of great concern in COPD since it is associated with increased in mortality and morbidity (77). Despite this association the etiology of protein-energy malnutrition remains obscure. One plausible explanation for the development of protein-energy malnutrition in COPD could be supoptimal nutrient intake. Several investigators have, however, reported the energy intake of COPD outpatients to be approximately 150% predicted requirements, ranging from 119-160% (74,75,77,78). These results seem to suggest that nutritional deterioration ensues despite adequate protein and energy intake (74,75,77,78). But closer examination of the methodology used in these studies reveals that the nutrient intake and energy expenditure data may not be reliable. First, three day diet records (75,77,78) were used to determine nutrient intake. Three day diet records depend solely on a subject's ability to recall their own intake and can be inaccurate, making this an unreliable indicator of actual intake. Secondly, actual energy expenditure was not measured, but was estimated using predictive equations which are not accurate in most patient populations (86-88). Additionally, the energy expenditure needed for activity was estimated from zero to 30%, making comparisons difficult (77,78). As a result of these shortcomings, there is a lack of convincing data regarding the nutrient intake of COPD patients.

Another possible explanation for the PEM observed in COPD could be energy expenditure pathologically increased to a level higher than intake. In fact, elevated resting energy expenditure (REE), as measured by indirect calorimetry, has been reported by several investigators (9,76,89). The resting energy expenditure per kg body weight of malnourished emphysema patients was found to be 23% higher than malnourished control subjects without lung disease, with the REE of the weight-stable versus weight losing COPD patients being indistinguishable (34).

Increased resting energy expenditure (34,90) could be the effect of differences in metabolically active tissue compartment. To investigate this possibility, the REE was adjusted for fat free mass by Schols et al. They found the REE of COPD patients remained significantly higher than the normal controls and hypothesized that there is a disease related increase in REE independent of differences in metabolically active tissue (91).

Two disease related factors, an enhanced thermic response to food (TEF) and/or an increase in the "work of breathing," have been proposed to explain the increased REE in COPD. During refeeding, an enhanced TEF response was observed in malnourished COPD patients but not in malnourished patients free of lung disease. The difference between the TEF of the COPD patients vs. the controls was 5% of predicted REE or about 70 kcal (2940 kJ) per day. A high carbohydrate diet was also found to cause a greater thermic effect than a high fat diet. The authors suggested that the high carbohydrate diet may have increased $PaCO_2$, and subsequently, an increased ventilatory load being responsible for the enhanced TEF seen in COPD. Increased thermic response to food, although only 5% of predicted REE, may contribute to the overall hypermetabolic state in COPD (34).

Increased oxygen consumption of the respiratory muscles, due to changes in respiratory muscle activity characteristic of the underlying pulmonary disease, may also increase resting energy expenditure. Donahoe and colleagues proved this by measuring the oxygen cost of augmented ventilation. A model of augmented ventilation was created by increasing respiratory dead space to simulate COPD in normal subjects. These results were compared to COPD patients weighing more than 90% their ideal body weight (IBM) and those less than 90% IBM. All COPD patients had increased respiratory muscle oxygen consumption, but the malnourished group (less than 90% IBM) had a notable increase in oxygen cost compared to the normally nourished COPD patients and normal subjects. Increased respiratory muscle energy consumption coupled with enhanced TEF,

may account for the elevated resting and total daily energy expenditure observed in COPD.

In trying to identify the etiology of the increased REE in COPD, however, one must entertain the possibility that the etiology is not after all "disease related" per see. As mentioned Schols found an increased REE per kg fat free mass (91). As has been shown in the COPD patient population there is a significant loss of peripheral muscle mass while "central" protein stores remain relatively well preserved (Section 1.2). The turnover rate of "central" stores are much greater than that of the peripheral muscle mass (92). Related to the increase protein turnover, the REE/kg of visceral tissues is greater than that of peripheral tissues. The increase in visceral to peripheral muscle stores itself may be responsible for the increased REE per kg lean body mass due to the faster metabolic rate of the visceral tissues alone. If this is the case, a disease-related cause of increased REE would be negated. This area warrants further investigation.

The increased REE observed in COPD is met by increased carbohydrate and protein oxidation, with fat oxidation remaining similar to controls. This was measured using indirect calorimetry. When energy intake was adjusted to meet the increased REE, these researchers showed that emphysemic patients achieved a nitrogen balance equivalent to the malnourished control subjects (34). Since COPD patients gained nitrogen at the same rate as the malnourished controls, protein catabolism does not seem to be accelerated in COPD. This finding was supported by Aguilaniu and colleagues who also found that protein catabolism was not augmented in COPD. They demonstrated that severely malnourished COPD patients responded to hypercaloric feedings by decreasing muscle protein breakdown as measured as net release of 3-methylhistidine across the leg in the same manner as did other malnourished patients without COPD (90). This decrease in protein degradation, in response to hypercaloric feedings, shows again that COPD patients do not have accelerated catabolic protein wasting when energy intake is sufficient.

The failure of some COPD patients to adapt to semistarvation may ironically be a side effect of the medications used to treat the underlying disease. A well known consequence of long term glucocorticoid administration is protein wasting. The mechanism responsible for this process appears to be accelerated proteolysis (93,94). In a study of eight normal volunteers given pharmacologic doses of prednisone (0.8 mg/kg/day) for seven days, Haymond and Horber showed, using leucine kinetic data, that the observed negative N balance was due to a significant increase in proteolysis without a corresponding change in protein synthesis rates (93). Using a phenylalanine forearem kinetic method, Sherwin and colleagues also observed an increase in protein breakdown associated with glucocorticoid (8 mg dexamethasone/day) administration in healthy volunteers. Their results also suggested that muscle tissue was not the site of glucocorticoid-induced proteolysis (94). Given these metabolic effects, glucocorticoid treatment has been reported to adversely affect the respiratory muscles. Recent animal models have demonstrated that the administration of high doses of glucocorticoids results in generalized muscle atrophy. This has also been reported to occur in humans. In three case reports of patients receiving high doses of glucocorticoids, Decramer et al observed respiratory muscle weakness, as measured by PI_{max} and PE_{max}, accompanied general muscle weakness. Tapered glucocorticoid doses resulted in recovery of respiratory muscle strength (95).

COPD patients are also often prescribed medications that stimulate the sympathetic nervous system that can increase both VO_2 and VCO_2 (96). One of these compounds, ephedrine, can enhance norepinephrine secretion and stimulate adrenergic receptors to increase sympathetic activity, and therefore, elevate energy expenditure by 10% (96). A similar increase in energy expenditure was demonstrated with the administration of nebulized salbutmol, a selective beta-agonist, used to treat bronchospasm. Other compounds that can increase energy expenditure are xanthines, including theophylline and caffeine, which have been shown to increase REE by 8%. The effect of concomitant administration of

theophylline and ephedrine is a 20% increase in energy expenditure (97). Therefore, the medications used to treat COPD itself may serve to accelerate the deterioration of nutritional status in COPD by further elevating energy requirements.

1.5 Nutritional Requirements in COPD

1.5.1 Interrelationship between Protein and Energy Intake in PEM

The interrelationship between proteins, and their constituent amino acids, nitrogen intake, and energy yielding substrates have been reported in the literature. The mechanisms controlling the cellular regulation of protein metabolism, such as folding and aggregation, intracellular traffic of newly synthesized proteins and transport across membranes, have been identified. Most of these reactions are energy dependent requiring ATP or GTP to proceed. Therefore, the basis of the interrelationship between energy and protein intake is on a molecular and cellular level.

It is known that nitrogen balance is sensitive to both energy and protein intake (37). The effects of nitrogen and energy intake on nitrogen balance in normal subjects were described by Calloway and Specter in 1959 (28). They analyzed the results of several studies and showed that nitrogen balance depends on energy intake at constant values of nitrogen intake. Likewise, nitrogen balance was shown as a function of nitrogen intake when energy intake is held constant. With zero nitrogen intake from no energy intake to 700 kcal (2940 kJ) per day, an increase in nitrogen balance from -12 to -7 g/day was observed. Further increases in energy intake, up to 3000 kcal (12600 kJ) per day, had no additional effect (28). When energy balance is positive, nitrogen balance will continue to increase with increasing intake. However, in the well-nourished patient, at zero energy balance further increases in nitrogen intake will lead to only a transient positive nitrogen balance. This transient positive nitrogen balance is thought to be the result of retention of protein in the "labile" protein pool, which is lost when nitrogen intake is decreased (29). This deposition of protein occurs because nitrogen excretion

lags behind the changes in intake. Nitrogen excretion will catch up to intake and nitrogen balance will return to zero in 3-4 days (37).

Given the same level of nitrogen and energy intake, the nitrogen balance of malnourished subjects is the same as that of the well-nourished individual (98). However, there is an important difference. Malnourished patients can achieve positive nitrogen balance at zero energy balance. In a study of 10 nutritionally depleted patients being fed at an energy intake equal to total energy expenditure a prolonged positive nitrogen balance was observed in both the high (2.27 g protein/kg) and low nitrogen (1.12 g protein/kg) diets of 0.61 mg and 0.21 mg N/kg per day respectively. This data suggested that the lean body mass of malnourished patients can be restored without excessive energy intake (98).

The rate of nitrogen excretion is increased in response to injury or sepsis. Both the severity of the injury and the dietary intake affects the extent to which nitrogen is lost. Therefore, to study the impact of different disease states on nitrogen excretion the same dietary conditions must be maintained. Elwyn and colleagues did so by measuring the nitrogen losses in patients with various diseases who received intravenous solutions of 5% dextrose (99). The results of this study showed that nitrogen losses increased as severity of disease worsened, with thermal injury causing the greatest losses.

1.5.2 Protein Requirements

Given that stable COPD patients are hypermetabolic, not hypercatabolic, their protein requirements should be similar to those of other nutritionally depleted patients assuming that their increased energy needs are met. A protein intake ranging from 1.0 to 1.5 g protein/kg BW/day has been recommended for this patient population (100). Nutritionally depleted patients in zero energy balance have achieved positive nitrogen balance at protein intakes of approximately 1.1 g protein/ kg body weight per day (98). It has been observed that a similar intake, 1.0 g protein/kg body weight per day is sufficient to promote positive nitrogen in

nutritionally depleted patients with moderate to severe COPD (101).

1.5.3 Energy Requirements

Increased cost of breathing contributes to increased resting energy expenditure in spontaneously breathing COPD patients. If the work of breathing is taken over by mechanical ventilation, will these patients remain hypermetabolic? Accurately estimating energy requirements is particularly important in the mechanically ventilated patient with minimal pulmonary reserves since both underfeeding and overfeeding can have deleterious consequences.

Most studies examining energy requirements during mechanical ventilation have been during the postoperative period (102,103). The recommendations derived from these studies have often been presumed to be applicable to the non-surgical, mechanically ventilated patient population (104). The guidelines proposed by Long are among those commonly used and will be presented here to illustrate the level of energy intake that is typically recommended for critically ill, mechanically ventilated patients. First, the Harris-Benedict equation is used to predict the BMR (see Section 4.7). The predicted BMR is adjusted according to the "activity" which is a factor of 1.2 if confined to bed. Next, a subjective "stress" factor is added ranging from 1.2 to 2 (102). Using this approach or that of others, the final estimate of caloric requirements can be two-fold or more than the BMR (103).

Current research has disputed the accuracy these recommendations. The actual REE of critically ill has been compared to these predictive equations using indirect calorimetry. In a study of 20 critically ill, non-mechanically ventilated surgical and medical patients, Baker et al found total daily energy expenditure to be 1,600 kcal (6,720 kJ)/day, which was not significantly different from unadjusted BMR. In a study of 50 surgical patients, it was found that the use of BMR x 1.75 to predict energy requirements overestimated actual needs by 59% (86). As for the mechanically ventilated patient without surgical stress, Liggett and colleagues found in a study of 73 patients, the unadjusted BMR (Harris-Benedict Equation)

best met the needs of all patients except for septic patients who showed a 20% increase in energy expenditure over estimated BMR. Physical and chest therapy, pain and other manipulations that frequently occur in the ICU setting have been reported to increase metabolic rate by 15% (105). In summary, the goal energy intake in the malnourished, mechanically ventilated patient is to maintain zero energy balance, which will allow for positive nitrogen balance (34) without the potential consequences of excess energy intake. Therefore, total daily energy expenditure of the stable mechanically ventilated patients can be predicted by the BMR (Harris-Benedict equationm) multiplied by a factor of 1.15 (105,106).

1.5.4 Appropriate Composition of Non-Protein Energy Intake

Once energy and protein requirements have been assessed, the best mix of non-protein energy substrates (carbohydrate and fat) must be determined. The respiratory quotient (RQ) for the oxidation of fuels can be used to evaluate the appropriate substrate mix given the clinical state and treatment goals. The RQ is the ratio of CO_2 produced to oxygen consumed. For every glucose oxidized, one molecule of CO_2 is produced per O_2 consumed yielding a RQ of 1.0. The RQ of fat is 0.7, and protein 0.8. Therefore, more CO_2 is produced when carbohydrate is oxidized than for fat or protein on a gram to gram basis. Theoretically, the RQ is approximately 8.0 during lipogenesis, however, this is never clinically observed, and instead a RQ of greater than 1.0 to 1.2 is detected (54,55). In principle, one would expect excessive carbohydrate intake or lipogenesis to impose a greater demand on the respiratory system by increasing CO_2 production. As previously described an increased $PaCO_2$ stimulates minute ventilation. When minute ventilation reaches maximum minute ventilation fatigue may ensue (107).

The effect of a high carbohydrate load on the respiratory system was first studied by Askanazi and colleagues. They found that nutritionally depleted patients on total parenteral nutrition (TPN) consisting of protein (62.5 g/day) and all the non-protein energy exclusively as dextrose, caused a 32% increase in minute

ventilation. It was a 23% elevation in $PaCO_2$ that initiated the increased minute ventilation (108). In a subsequent study, all non-protein energy was supplied as dextrose and then compared to a solution with half the non-protein energy as fat. The shift from the mixed energy source to only dextrose lead to a 20% increase in CO_2 production and a 26% increase in minute ventilation. Although the expected metabolic changes and subsequent compensatory respiratory response occurred, neither groups required assisted ventilation, nor were they noted to have respiratory impairment (109) making the clinical relevance of these findings questionable. Additionally, energy requirements were based on REE x 1.5-1.75 which may have resulted in overfeeding leading to increased $PaCO_2$. Despite this, some enteral product manufacturers began to promote specialized products containing half of the non-protein energy as fat and the other as carbohydrate. It is important to note no direct evidence to support the use of a particular mix of non-protein energy exists, only that inclusion of fat is preferable to carbohydrate as the sole source of energy.

To determine the most appropriate substrate mix for mechanically ventilated patients several factors must be considered. First, minimal carbohydrate requirements must be met which is estimated to be approximately 150 g/day. Then the maximal rate of glucose oxidation, 5 mg/kg/minute, must not be exceeded or an increase in CO_2 production will result (110). Carbohydrate intake should be between these two extremes with the remainder of non-protein energy as fat.

1.6 Effects of Protein-Energy Malnutrition on Pulmonary Status

The association between protein-energy malnutrition and the impairment of the respiratory system has been long recognized. It has been previously said that "death from starvation is frequently respiratory in origin" (12). This relationship is more complex than this statement implies.

Protein-energy malnutrition can reduce the capacity to sustain adequate levels of ventilation by exerting an effect on respiratory musculature and drive (12,111-113). Respiratory musculature is not spared during protein-energy

malnutrition (PEM). To survive semistarvation, protein stores are mobilized and the liberated amino acids are used as an energy source. The end result of this process is the loss of muscle mass. It was commonly believed that muscles critical to survival, such as the heart and diaphragm, were protected during starvation (111). However, this has been disproved by studies showing that these muscles are subject to the same catabolic conditions as is peripheral muscle mass (3,114).

The detrimental effect of PEM on diaphragmatic muscular dimensions was quantified at necropsy by comparing previously normal subjects who died suddenly to patients who died after prolonged illness (n=70) (3). Diaphragmatic muscle mass, area, and thickness were within normal limits in well-nourished subjects at the time of death. In contrast, the poorly nourished subjects, whose body weight averaged 71% ideal body weight (IBW), experienced a dramatic loss of diaphragmatic muscle mass of 43% (<0.001) with about half of the deficit resulting from thinning of the diaphragm muscle and the remaining resulting from a reduction in diaphragmatic muscular length (3). The findings of this trial confirmed that even without pulmonary disease, there is a diminution of diaphragmatic muscle mass due to PEM alone.

The relationship between diaphragmatic and body weight in emphysema was studied by Thrulbeck et al. One-hundred eighty-four subjects were classified according the severity of their disease (114). A strong correlation was found between the diaphragmatic muscle mass and body weight ($p< 0.001$) indicating that emphysema patients lose diaphragmatic muscle mass during PEM, as do patients without lung disease. Additionally, a progressive loss of diaphragmatic muscle mass was observed as emphysema worsened ($p<0.05$). Interestingly enough, in both studies diaphragmatic weight loss is greater than would be predicted by loss of body weight alone. This was shown in the latter study by comparing the ratio of diaphragmatic weight to body weight in patients with mild emphysema, ratio 4.61±0.15, to end stage emphysema patients, ratio 4.0±0.2 g/kg (114).

Protein-energy malnutrition not only weakens the diaphragm by reducing

overall muscle mass, but it also diminishes the contractile strength of the remaining muscle fibres (4). A dimensional analysis of diaphragmatic contractile force suggests that the contractile force per unit area of diaphragmatic muscle cross sectional area is about one-third normal in protein-energy malnutrition. The contractile tension of the diaphragm as calculated from transdiaphragmatic pressure (Tdi) was examined in 184 patients classified according to nutritional status. The Tdi in normal subjects was 1:26 kg/cm^2 but only 0.48 kg/cm^2 in the malnourished group. Tdi was one-third normal in the malnourished group exceeding the loss that would be predicted by a 40% loss of diaphragmatic muscle mass suggested that the remaining muscle mass is myopathic (4).

The loss of contractility can be partially explained by the preferential loss of diaphragmatic muscle fibers producing the greatest amount of force (107). The diaphragm is made of striated muscle cells containing Type 1 (slow twitch) and Type 2 (fast twitch) fibres (107). Type 1 fibres are aerobic and use both glucose and fatty acids for fuel, whereas, type 2 depends on stored glycogen as an energy source (12). The type 2 fibres generate a greater peak force than type 1. Type 2 fibres are more seriously affected by malnutrition as shown by selective atrophy of these fibres. Additionally, the remaining type 2 fibres may be limited by insufficient glycogen stores (115).

The loss of diaphragmatic muscle mass and contractility associated with poor nutritional status translates into a measurable loss of respiratory muscle strength (5,24,116). Respiratory muscle strength was measured in a group of well nourished subjects at 104% IBW (n=16) and compared to 16 poorly nourished patients (71% IBW) none of whom had a history of pulmonary disease (116). The respiratory muscle strength of the poorly nourished group (calculated % predicted PI_{max} + % predicted PE_{max} divided by two) was reduced by 63% as compared to the well nourished controls. Respiratory muscular weakness was accompanied by a 37% reduction in vital capacity and 59% reduction in maximum voluntary ventilation (116).

The relationship between inspiratory muscle strength and body composition was studied by Kelly et al in a group of 59 spontaneously breathing surgical patients receiving TPN (5). Body cell mass and extracellular body water were estimated by measuring total exchangeable potassium (K_e) and sodium (Na_e). Na_e/K_e, an index of nutritional status, was calculated. The malnourished patients with a Na_e/K_e of more than 1.22 had significantly lower PI_{max} values, 33.5+2.8 -cm H_20 than the well nourished patients, 45.3±4.3 -cm H_20 ($p<0.05$). Similar findings were made by Schols et al in the COPD patient population who found the Pi_{max} of well nourished patients (n=34) was 53.1±2.1 -cm H_2O as compared to 42±1.9 -cm H_2O in 34 poorly nourished patients (5). The data of these two studies suggests that the loss of body cell mass and/or weight adversely affects inspiratory muscle strength.

Compromised respiratory muscle strength, as the result of PEM, may not allow the body to compensate for altered gas exchange caused by the underlying disease, COPD. Briefly, one of the primary problems in COPD is maintenance of adequate levels of alveolar ventilation to match perfusion and allow for necessary gas exchange in the context of increasing airflow resistance (62). The resulting ventilation/perfusion mismatch leads to hypoxemia and eventually hypercapnia. To compensate for this chronic state, the respiratory rate is increased to replenish declining O_2. As well being required to meet the demands of an increased respiratory rate, additional force must be generated to overcome the stiffness of the lung that is characteristic of COPD. As a result increased demands are imposed on the respiratory system.

The work of breathing is the amount of energy expenditure required to perform the act of ventilation (107). Factors that can increase the work of breathing are increased respiratory rate, tidal volume, airway resistance, and decreased lung compliance (107), which are all commonly seen in COPD and often during critical illness (117). The work of breathing in critically ill patients has been found to increase daily energy expenditure by 10.2% ($p<0.05$) (117). With an augmented workload, the respiratory system will consume more O_2 and the oxygen cost of

breathing will be increased. In a normal subject breathing quietly the oxygen cost of breathing is less than 5% of total VO_2 consumption (118). The oxygen cost of breathing was assessed in 13 patients with cardiorespiratory disease. The oxygen cost of breathing was calculated as the difference between VO_2 during spontaneous ventilation and mechanical ventilation. The VO_2 respiratory, 24% of total VO_2, of patients with pulmonary disease were dramatically elevated in comparison to normal subjects (118).

COPD and/or critical illness imposes greater demands on the respiratory system due to the increased work of breathing. PEM does not affect the underlying disease, but instead it limits the available "supply". When demand exceeds supply and respiratory muscles become "fatigued", they are incapable of generating prior attainable force (62). The result is a failure of the muscles to produce the force required to support continuous gas exchange (62). In the worst case scenario, the result is a failure of the respiratory muscles to produce the force necessary to support gas exchange leading to respiratory failure.

Given that a loss of body cell mass adversely affects inspiratory muscle strength and can contribute to the development of respiratory failure, the question emerges; can the restoration of body cell mass lead to improvements in respiratory muscle performance? Kelly et al studied this in 59 patients. Of the 59, 29 received TPN and had serial measures of inspiratory muscle strength taken (5). Twenty-one of the 29 patients showed an increase in body cell mass (16.2±0.8 to 18.1±.8 kg) and a corresponding significant improvement in Pi_{max} from 39.2±4.8 to 52±4.6 -cm H_2O ($p<0.001$). This data shows that refeeding via TPN can lead to improvements in respiratory muscle strength when there is a corresponding increase in body cell mass.

The beneficial effects of refeeding on respiratory muscle strength has also been shown in the COPD patient population (5-8). In a nine-month trial, one group of poorly nourished COPD patients (80%IBW) received oral nutritional supplements to increase intake by 800 kcal (3369 kJ) per day over usual intake for 3 months

while the control group received none. During supplementation a significant improvement in peak inspiratory and expiratory pressures 45.7±3.7 to 53.1±5.2 -cm H_2O ($p<0.03$) and 78.7±9.5 to 84.0±9.5 cm H_2O ($p<0.05$) respectively was observed (119). Similar findings were reported by Whittaker et al who administered nocturnal enteral feedings to supplement the usual diet by 1000 kcal (4200 kJ)/day in hospitalized COPD patients. After 16 days of feeding, the malnourished (85%IBW) COPD patients receiving the nocturnal feedings showed a significant improvement in PE_{max}. Pi_{max} improved by 19% over the study period but did not reach statistical significance perhaps due to the small numbers of patients (n=6). Wilson and colleagues demonstrated an improvement in respiratory and peripheral muscle strength, as measured by PI_{max} and handgrip strength respectively, in six malnourished emphysema patients who gained weight ($p<0.001$) after 3 weeks of nutritional supplementation. These studies provide evidence that refeeding malnourished COPD patients restores respiratory strength (6,8).

Nutrition supplementation is only successful in promoting improvements in respiratory muscle strength if weight gain is achieved (119,120). Both Lewis (n=21) and Knowles (n=25) supplemented the diets of outpatient COPD patients for three and eight weeks respectively. The patients enrolled in these two studies reduced their food intake when given the supplement. As a result the subjects did not gain weight. No significant changes in respiratory muscle performance were detected, confirming that weight gain is a prerequisite for the improvement of these muscles.

1.7 Proposed Mechanism for Prolonged Respiratory Failure in COPD

The association between protein-energy malnutrition (PEM) and the impairment of pulmonary status has been established (12,111,112) (3,5,32,113,114,116). Protein-energy malnutrition in COPD can have serious consequences related to the limits it places on an already compromised respiratory system. PEM does not affect the underlying chronic lung disease itself, but instead respiratory muscle strength and drive. In doing so, PEM limits the "supply" or force

the pulmonary system is capable of generating. When metabolic demands exceed supply, adequate ventilation cannot be sustained resulting in respiratory failure. Therefore, this is how PEM contributes to the development of respiratory failure.

Several investigators have examined the effects of refeeding on peripheral muscle strength as well (8,9,34). Using measures of voluntary hand grip strength or adductor pollicis function in COPD patients being fed hypercaloric diets (REE x 1.5-1.7) for two to three weeks, the investigators all reported an increase in body weight, N balance, and inspiratory and/or expiratory respiratory muscle strength, but presented conflicting results regarding hand grip strength. Neither Goldstein nor Whittaker observed an increase in peripheral muscle strength over a 14 to 16 day period using hand dynamometry or adductor pollicis testing, respectively (8,34). When the duration of the refeeding period was extended to 3 weeks, Wilson observed a statistically significant improvement in hand grip strength. These results may suggest that peripheral muscle strength is not restored as rapidly in previously malnourished COPD patients as in the obese in response to refeeding.

The metabolic and physiologic conditions that commonly precipitate acute respiratory failure in COPD may further compromise respiratory muscle strength. Most events that precipitate acute respiratory failure are catabolic and increase metabolic demands that most importantly lead to acceleration of protein-wasting. The resultant protein wasting can be aggravated by inadequate dietary intake during hospitalization when attention is focused on treating the precipitating cause of respiratory failure (121). Additionally, during respiratory "disuse" atrophy of the respiratory muscles may occur due to the use of mechanical ventilation to take over the work of breathing. The cumulative effect is an accelerated deterioration of respiratory muscle performance during acute respiratory failure.

Although it has been demonstrated that refeeding improves the respiratory performance of spontaneously breathing patients, one cannot assume that the mechanically ventilated patient will respond in the same manner. There is, however, evidence that adequate nutritional support improves the respiratory status

during mechanical ventilation, and thereby, facilitates weaning. In a retrospective study of 47 patients, Bassili et al found that patients receiving adequate nutritional support (2,000-2,500 kcal; 8,400-10,500 kJ/day) were weaned from mechanical ventilation more rapidly than those given only intravenous dextrose (400 Kcal; 1,680 kJ/day) (27). Of the adequate nutritional support group, 92.8% were weaned while only 54.5% of the patients given suboptimal nutrient intake were weaned from mechanical ventilation ($p<0.05$). In another study of fourteen patients requiring prolonged mechanical ventilation, all received a similar level of nutrient intake (2,500-2,700 kcal; 10,500-11,340 kJ, and 35-38 g protein/day). Subjects were retrospectively grouped according to their ultimate ability to be weaned from mechanical ventilation. At time of entry into the study, patients of both groups had similar albumin levels. At either the time of death or weaning, the group that had been successfully weaned showed a significant increase in serum albumin and transferrin levels, whereas the unsuccessful group showed a decrease ($p<0.05$) (122). The authors concluded that patients who respond to nutritional support with an increase in protein synthesis are more likely to wean from mechanical ventilation than those who are do not. Based on the findings of these two studies, coupled with assumptions made from extrapolations of the data from spontaneously breathing patients, it is strongly suggested that PEM plays an important role in delayed weaning from mechanical ventilation and that refeeding may facilitate weaning.

Given the increased risk of morbidity and mortality associated with mechanical ventilation, there is an urgency to wean patients. Most often the status of the underlying chronic lung disease itself cannot be improved to any appreciable extent. For successful weaning, attention must be placed on those factors that both contribute to respiratory failure and are "modifiable", which includes resolution of the event that precipitated the respiratory failure, but also attention to nutritional factors.

The goal of nutritional therapy in acute respiratory is to promote nitrogen

accretion in attempt to restore or maintain respiratory muscle performance. However, under catabolic conditions, this may not be feasible for the body does not use nutrients efficiently even when given exogenously (15,123). As previously mentioned there is an acceleration of net protein breakdown during catabolic illness. The administration of adequate quantities of energy, nitrogen and other essential nutrients can suppress the rate of net protein breakdown. However, this beneficial effect is not sufficient to restore lean body mass and furthermore, it may not prevent further erosion of protein stores. The latter was demonstrated by Streat and colleagues who administered 2,750 kcal (11,550 kJ) and 127 g protein intravenously to eight critically ill, mechanically ventilated patients for ten days. Despite a hypercaloric, hypernitrogenous intake, the mean loss of body protein was 12.5% or 1.5 kg ($p=0.001$). This was accompanied by a significant gain in body fat (2.2 ± 0.8 kg, $p=0.026$) (123). This study implies that aggressive nutritional support does not prevent body protein loss during catabolic illness (15).

In summary, weaning patients from mechanical ventilation is an urgent concern. The anabolic stimulus of nutrition alone may not be sufficient to result in rapid benefits. Therefore, a potent anabolic stimulus will be combined with adequate nutritional support to see if the resulting increase in respiratory performance will hasten weaning and support the contention that nutritional factors are important in preexisting failure and in reversing it in established cases.

2. GROWTH HORMONE

2.1 Physiology of Growth Hormone Synthesis and Secretion

2.1.1 Circulating Forms of Growth Hormone

Human growth hormone (hGH) is present as a heterogenous mixture of at least 20 molecular forms (124). The major physiologic form of circulating hGH is a single-chain polypeptide composed of 191 amino acids with a molecular weight of 22,000. The second most abundant form is 20,000 molecular weight that lacks the amino acid residues 32-46. Although most plasma hGH exists in the monomeric

form, approximately 40% circulates as oligomers (68).

2.1.2 Control of Growth Hormone Secretion

2.1.2.1 Hormonal Control

Growth hormone is synthesized, stored and secreted by specialized cells of the anterior pituitary called somatotropes. It is the most abundant hormone in the human pituitary gland. Activity of these cells is regulated by the balance between two hypothalamic hormones, growth hormone releasing hormone (GHRH) and somatostatin (SS). These hormones are secreted into the hypothalamic-hypophyseal portal system for rapid and direct delivery to the pituitary gland (124).

The GHRH containing cells are located in the arcuate nucleus of the hypothalamus (125). Upon reaching the somatotropes, GHRH binds to a cell membrane receptor and stimulates the immediate release of stored hGH (126). Besides controlling the release of hGH, GHRH also regulates the synthesis of hGH. GHRH signals the transcription of GH mRNA via control of cAMP levels (124). More specifically, when GHRH binds to somatotrope cell receptors it stimulates adenylate cyclase to catalyze intracellular ATP to increase cAMP levels (26). The primary hypothalamic factor opposing GHRH and thereby inhibiting hGH release is somatostatin. Although it is now known that there is a family of related SS-like peptides, the term was originally applied to a 14 amino acid cyclic peptide, somatostatin-14 (127,128). It is produced by the neuron cell bodies of the perventricular region of the hypothalamus (129). The synthetic rate of hGH is not affected by SS. This became evident from observations of rebound hGH levels after stopping exogenous SS infusions. SS decreases hGH release by down regulating exocytosis (129). If cells are exposed to GHRH and SS simultaneously, SS exerts the dominant effect (130).

Somatostatin is not only present in the hypothalamus, but it is widely distributed throughout the body. SS exerts its inhibitory effects on various hormones, including

insulin, glucagon, and gastrointestinal hormones, including gastrin and pepsin (131).

2.1.2.2 Pattern of Release

Secretion of SS and GHRH into the hypophyseal portal system is intermittent, thereby creating varying degrees of stimulatory or inhibitory tone on the GH-producing cells of the pituitary gland. As a result hGH is not secreted at a constant rate, but rather episodic pulses throughout the day. Between bursts of hGH release, serum GH concentrations are undetectable (<0.2 ug/L) (130). The highest peak of GH bursts occurs during slow wave sleep. In young adults these surges occur every three to four hours. The magnitude of the peaks varies with individuals and has been measured between 10 and 50 ng/L (132).

Due to the pulsatile nature of hGH secretion it is very difficult to measure the amount secreted in over 24 hours. Reported endogenous 24 hour hGH secretion for an adult male is reported to be from 0.25-0.52 mg/m^2 surface area (133,134). The integrated plasma hGH concentration has been found to be between 3 and 6 ng/ml (130). Five to ten mg of hGH are stored in the anterior pituitary (132).

2.1.2.3 Influence of Age and Nutritional Status

Superimposed on the basic hypothalamic control are the actions of a variety of modulating substances that further modify hGH release. The secretion of hGH is influenced by age. The greatest amount of hGH is secreted during adolescence and gradually declines after the age of 30 (135,136). This decline may be due to changes in pituitary responsiveness to GHRH and/or to increased hypothalamic SS secretion (137,138).

Nutritional influences play a major role in the regulation of growth hormone secretion. During periods of nutritional deprivation, such as starvation or anorexia nervosa, the serum concentration of hGH is increased (139-142). Conversely, obese humans have depressed circulating hGH concentrations and a decrease in

hGH response to stimulation by GHRH (143,144).

Recent studies in adults have attempted to define the influence of various nutritional states on hGH secretion. The effect of five days of fasting on hGH secretion was studied in 10 men. Fasting lead to a 3-fold increase in 24 hours integrated hGH concentrations and a 2-fold increase in the number of GH pulses per 24 hours. In another fasting study, but of only 2 days, nine men were found to have a similar increase, 3.4-fold, in GH production (145). The effects of nutritional repletion on hGH secretion after fasting have also been studied. Two days of fasting caused a predictable increase, 2.4-fold, in hGH concentrations. Upon refeeding, a six-fold reduction in GH levels occurred only 2 hours after the first meal. In fact, the response was so immediate that a significant decline in hGH occurred after only 30 minutes of refeeding (146).

2.1.3 Growth Hormone Binding Proteins and Receptors

Two forms of circulating growth hormone binding protein (GHBP) have been isolated, one of high and the other of low affinity (147,148). The high affinity GHBP is a 61 kD glycoprotein that has limited binding sites. This GHBP appears to be identical to the extracellular domain of the hepatic GH receptor (147,148). However, it is not clear if the circulating GHBP is derived from the cleavage of this extracellular fragment of tissue GH receptor or is produced through a separately regulated synthetic pathway (149). A separate, low affinity, high capacity GHBP has been identified which is not related to the GH membrane receptor and binds the 20 kD hGH preferentially (150).

The biological significance of GHBP has not been completely elucidated. However, the protein bound form of GH is metabolized differently than in its free form. Binding increases hGH half-life by ten times. Additionally, the distribution of protein bound hGH is twice greater in the intravascular compartment than is the unbound form. The binding of hGH to its binding proteins appears to enhance the biological activity of hGH (151).

2.2 Metabolic Effects of Growth Hormone

2.2.1 Glucose Metabolism

The hyperglycaemic effect of large doses of pituitary hGH was first noted in the late 1950's (152). An inhibition of muscle glucose uptake is believed to be responsible. This was demonstrated by hyperinsulinemic, euglycemic glucose clamp studies, showing a generalized insulin resistance in muscle, liver and adipose tissue in response to hGH administration (153-155). As found in pathophysiologic states of insulin resistance, a state of hyperinsulinemia coexists when serum GH levels are elevated (153,154). Pharmacologic doses of hGH are also associated with 50% reduction in glucose oxidation (156).

2.2.2 Lipid Metabolism

Growth hormone stimulates mobilization of fat stores from the adipose tissue. This process is initiated by the binding of hGH to a hGH specific receptor on the adipocyte (157). The result is an increase in plasma free fatty acid (FFA) concentration 2-3 hours after hGH administration and a decrease in the respiratory quotient indicating a shift to fat oxidation. Since FFA are converted by the liver into ketones, an increase in ketogenesis accompanies hGH administration (158). Since the rate of ketone body clearance remains unchanged with hGH administration (156) circulating ketone body concentrations increase.

The lipolytic actions of GH are stimulated only during periods of insulin deficiency (158). This was shown by creating a state of insulin deficiency with somatostatin, which alone led to an increased free fatty acid and ketone body concentrations. When GH was administered (80 ug/kg/min) there was a further elevation in FFA and ketone body concentrations. These results suggest hGH can mobilize fat stores independent of insulin. Because hGH secretion reaches its highest levels during the night, could play an important role in postabsorptive substrate metabolism by stimulating of FFA release (156).

2.2.3 Protein Metabolism

Muscle is one target tissue of the anabolic actions of GH. The result is positive nitrogen, phosphorus, potassium, magnesium, calcium, sodium and chloride which are all constituents of anabolism (159-163). Unlike the expression of its catabolic effects, adequate amounts of insulin must be present for GH to exert its anabolic effects (164).

The anabolic actions of hGH include increased body nitrogen conservation and a decrease in urea synthesis that is easily detected clinically by a drop in urea levels (165). Sixty to eighty percent of the interorgan N flux can be accounted for by the two main ureogenic precursors, alanine and glutamine, for which muscle tissue is the major source (166). During hGH therapy, the release of these two amino acids into the blood remains unchanged, but, their metabolic fate is altered. Welbourne and colleagues found that the rerouting of glutamine from urea synthesis to glutamate synthesis is responsible for the decreased urea production. In fact, the increase in liver glutamate release is equal to the amount that urea synthesis is depressed (167). This conservation of amino acids provides the building blocks necessary for protein synthesis.

It has been long recognized that hGH administration leads to improved N balance. Improved N balance can be the result of a relative increase in whole body protein synthesis and/or decrease in breakdown. Studies using labelled amino acids (isotopes) have shown that hGH increases whole body protein synthesis, but has little effect on proteolysis (168-170). Specifically, the rate of nonoxidative disappearance of labelled leucine and glycine, which has been shown to correlate well to overall skeletal protein synthetic rates (171), increases with hGH administration. The results of balances in the extremities agree with the whole body findings. Studies of the effects of hGH administration on skeletal muscle, show a stimulation of total, essential and branch chain amino acid uptake without changes in proteolysis (166). If one considers the forearm data of Fryberg et al (172) together with the whole body protein synthetic rates obtained by Haymond,

it appears that a substantial portion of the increase in whole body protein synthesis occurs in the muscle tissue (159,173).

2.2.4 Fluid Homeostasis

The early work describing the biological effects of GH showed hGH administration is associated with fluid retention and weight gain (174). Although the mechanism by which hGH causes changes in fluid homeostasis is not fully understood, it has been hypothesized that the antinatriuretic properties of GH are either the result of a direct renal effect and/or indirectly through the stimulation of mineralocorticoid secretion (175).

These initial studies focused on the relationship between GH administration and increased aldosterone secretion. The results of these studies yielded conflicting results that either aldosterone excretion was increased or not effected at all by hGH administration. The source of the hGH used for these studies was derived from the pituitary of cadavers. The possibility existed that these preparations were contaminated and that the contaminants of the GH were responsible for these effects (175). When recombinant hGH became available further studies were undertaken.

The administration of rhGH in pharmacologic doses has been shown to result in significant sodium retention. Over five days, normal volunteers received 5 mg rhGH/day. By the fifth day, 24 hour urinary sodium excretion fell from 197±38 mmol to 42±20 mmol and this was associated with a decrease in urine volume from 1652±182 mL to 848±348 mL. There was a concomitant increase in body weight. Significant increases in plasma renin activity ($p<0.005$) and plasma aldosterone concentrations ($p<0.001$) were detected providing evidence that rhGH administration stimulates the renin-angiotensin system (176). The exact mechanism for this effect remains unknown. This evidence, however, does not rule out the possibility that rhGH also acts on the kidney directly.

2.2.5 Energy Expenditure

Growth hormone administration has a stimulatory effect on energy expenditure (EE). This has been reported in GH deficient children (177) along with being well known that EE is elevated in acromegaly. This effect is not acute. Moller and colleagues gave 4 hour infusions of 20 ng rhGH/kg/min to six normal volunteers and found no significant change in EE over this brief time period (178). The stimulatory effects of GH administration on EE have been observed during administration over a longer time period. In normal subjects receiving 12 U rhGH/day for 14 days, total daily EE (TDEE) increased from 1990±310 to 2073±392 kcal (8358±1302 kJ to 8706±1642 kJ)/24 hours (p=0.01) (179). In post surgical patients receiving rhGH, the findings have been conflicting. Lehmann et al reported no significant difference in TDEE of rhGH treated versus control patients, whereas Azanknazi and colleagues detected a significant increase in TDEE but not until the third day.

The mechanism controlling the hGH induced elevation in EE has not been elucidated. It has been suggested that this may be the effect mediated by an increase in thyroid hormone action. rhGH therapy has been known to increase circulating T3 levels in GH deficient children (180,181) and adults (182). After 14 days of GH administration, a significant difference in T3/T4 ratio was noted in the rhGH treated group as compared to the controls, 1.84±0.12 vs. 1.37±0.06, respectively.

2.3 Insulin-Like Growth Factors

Growth hormone stimulates the synthesis and release of insulin-like growth factor-1 (IGF-1), which has been thought to mediate the anabolic effects of hGH (130,183). In man, there are two types of Insulin-Like Growth Factors. Insulin-like Growth Factor-1 (IGF-1) is a 70 amino acid peptide, previously known as Somatomedin-C. This hormone is structurally related to proinsulin, as the name suggests. In fact 43% of the amino acid sequence of IGF-1 is identical to

proinsulin. The other type of IGF, IF-2, is more abundant and has serum concentration three to four times that of IGF-1. IGF-1 concentrations in the serum of normal adults is about 200 ug/L whereas IGF-2 concentrations are around 600 ug/L (130).

The rate of IGF-1 synthesis in tissues and its secretion into systemic circulation is dependent not only on hGH but also on adequate nutritional intake and age (184). During nutrient deprivation, when hGH plasma concentrations are high, IGF-1 levels are resistant to hGH influence and remain depressed (159,175). Conversely, plasma IGF-2 levels are not GH dependent and are virtually refractory to extreme nutrient deprivation (132).

The original hypothesis linking IGF-1 to hGH suggested that hGH secreted from the pituitary exerted its effects by stimulating IGF-1 release from the liver which would then act on target specific tissues. Recent research has shown that the liver is not the only site of IGF-1 synthesis (185,186). Many cells have been shown to have the capacity to secrete IGF-1. As a result the original hypothesis has been revised. Growth hormone is now thought to stimulate IGF-1 synthesis not only in hepatic tissues but also in other target tissues throughout the body (152,187).

2.3.1 Insulin-like Growth Factor Binding Proteins (IGFBP)

Insulin-like growth factors-1 and -2 are carried through the body by binding proteins (IGFBP) which may play an important role in the cellular actions of IGF. To date five classes of IGFBPs have been isolated (188). Of the five, relatively little is known about the most recently discovered IGFBPs, 4 and 5, and therefore, they will not be included in this discussion.

2.3.1.1 IGFBP-3

The most abundant of the IGFBPs is IGFBP-3. The plasma concentration of IGFBP-3 in the serum is typically 5 mg/L that is twenty times the concentration of IGFBP-2 and fifty times that of IGFBP-1 (188,189). IGFBP-3 is a large complex

(150 kD) composed of two subunits, an acid labile non-binding and binding unit, which together with IGF-1 or -2 forms a ternary complex. It binds with IGF-1 and -2 with the same affinity (188).

The majority of circulating IGF is bound to plasma IGFBPs, probably accounted for by the abundancy of IGFBP-3, so that only 1% is free (190). In the ternary complex with IGFBP-3, IF is unable to exert any considerable insulin-like activity (188). Coupled with the fact that IGFs are not stored in an endocrine gland as are other hormones, this suggests that one of the roles of IGFBP-3 may be as a stable, inactive reservoir for IGFs.

The plasma concentrations of IGFBP-3 are regulated by hGH. In states of diminished hGH secretion or when there is an abberation in the interaction of GH with its receptors, there is a decrease in IGFBP-3 (191). For example, in Laron Drawfism, a genetic defect leads to a reduction in GHBP, one finds low levels of plasma IGFBP-3 (188).

2.3.1.2. IGFBP-1

IGFBP-1 is present in the serum in lower concentrations than IGFBP-3 and binds with both IGF-1 and -2 with equal affinity. The plasma concentrations of IGFBP-1 are acutely regulated by food intake and by fluctuations in plasma insulin and glucose concentrations (132). IGFBP-1 plasma levels have an inverse relationship with serum insulin levels are suppressed by as much as four to five fold after a meal.

2.3.1.3 IGFBP-2

Much less is known about IGFBP-2 than the previously discussed IGFBPs. Studies of bovine IGFBP-2 have suggested a strong preferential affinity for IGF-2 (190). IGFBP-2 may play an important role in the regulation of IGF concentrations when there are insufficient levels of IGFBP-3. For example, hypopituitary adults

with low IGFBP-3 levels have a two-fold increase in IGFBP-2 concentrations.

2.4 Influence of Critical Illness on Growth Hormone and IGF-1

As seen in starvation, hGH levels are elevated and IGF-1depressed during critical illness (192). This effect cannot be accounted for by inadequate nutrient intake, as is often seen in the intensive care setting (121,192). In a study of six critically ill, mechanically ventilated patients, a significant depression of hGH binding activity was detected both before and after nutritional repletion. Levels of high affinity hGH binding protein are believed to reflect hGH receptor status. Since critically ill patients are hGH-resistant with respect to stimulation of IGF-1 levels, these low levels may be related to reduced hGH receptor activity. The administration of pharmacologic doses of rhGH can overcome this hGH resistance and lead to an elevation plasma IGF-1 levels. The elevation of IGF-1 concentrations is associated with an anabolic response in critical illness.

2.5 Historical Use of Growth Hormone

The objective of hGH therapy has traditionally been to increase the growth rate and adult height of short stature GH-deficient children. It was in 1958 that the first successful therapeutic use of hGH was reported by Raben (193). Raben showed an increase in linear height of a pituitary drawf following hGH administration. This finding was confirmed in several subsequent case reports. In 1964, Soyka et al. studied the effects of hGH therapy for up to 2.5 years in 34 patients with short stature. The reported growth response in these patients was convincing (194). Administration of pituitary hGH became an accepted therapy, however, because of its scarcity this therapy was reserved for children of short stature with documented growth hormone deficiency.

For the next twenty five years, hGH deficient children received hGH extracted from human cadaver pituitary glands. However, the distribution of hGH was halted in 1985 after several recipients of cadaveric hGH developed Creutzfeld-

Jakob disease (132). Fortunately, through the development of recombinant methods, large scale production of rhGH became feasible. The biosynthetic preparation of rhGH initially had an additional methionine residue at the N-terminal end. Subsequently, rhGH with an amino acid sequence identical to the natural hormone became available. Recombinant hGH (rhGH) has been proven to be equally as effective as pituitary hGH in increasing growth velocity in growth hormone deficient children.

The production of recombinant hGH has lead to wide availability of the hormone, meeting the needs of all GH-deficient children, but also making it available for expanded uses.

2.6 Clinical Trials using Pharmacologic Doses of rhGH

The initial trials using pharmacologic doses of exogenously administered human growth hormone in severe burn injury demonstrated an attenuation of N and mineral losses (195,196). In 1961, Liljedahl found that the administration of pituitary hGH to burn patients led to an improvement in N balance. The improvement in N balance resulted from a decrease in N excretion coupled with an increase in N intake attributed to a stimulated appetite. Phosphorous and potassium balances were also improved.

In 1974 Wilmore et al administered hGH to patients with severe burns covering 35-75% of their total body surface area during the early post burn period (195). While being fed a hypercaloric diet providing a daily average intake of 4025 kcal (16865 kJ) and 28.5 g N, hGH therapy was shown to improve N and mineral retention, thus confirming the results of Liljedahl. The lipolytic effects of hGH therapy were also observed in this study as evidenced by an increase in free fatty acid levels, from 1.0±0.4 to 2.2±0.5 mEq/L ($p<0.05$).

These early studies focused on the effects of hGH therapy on changes in N and mineral balance in severe catabolic illness when hypercaloric, hypernitrogenous diets were administered. The effectiveness of hGH therapy to

exert an anabolic effect under varying conditions of energy intake was first studied by Manson et al. Eight normal volunteers received total parenteral nutrition (TPN) for 2 six-day periods. Pharmacologic doses of rhGH were administered during the treatment period and a placebo during the control period. For six days patients received adequate levels of N (1 g protein/kg/day), vitamins and minerals while energy intake was varied to provide 30%, 60% and 100% of measured resting energy expenditure plus 25% for activity in the hospital. N balance was negative at every level of energy intake when the placebo was given. In contrast, when growth hormone was administered positive N balance was achieved at all energy intakes even at the 30% level (197). This data suggests that the ability of rhGH therapy to elicit an anabolic effect is resilient to hypocaloric conditions.

The effects of growth hormone therapy on N losses in protein-energy malnourished, stable subjects given hypocaloric diets (60% of total energy requirements) were studied by Ziegler and colleagues (160). The protein intake for both groups, rhGH-treated and control patients, was 1.3 g protein/day. Interestingly enough, both groups were in positive N balance despite the hypocaloric intake. However, the difference between groups was statistically significant being greater in the rhGH treated group, +3.4±0.5 g N/day, versus the control group, +0.5±0.9 g N/day. This study verifies that rhGH therapy promotes whole body N conservation, in the order of 2.9 g N/day, the equivalent 90 g of lean body mass per day. A comparison of the effects of rhGH treatment in these malnourished patients versus normal volunteers on the same level of energy intake (60% of estimated requirements) and rhGH dose, but a lower protein intake (1.0 g protein/day) (197), shows that the anabolic response to rhGH therapy appears greater in malnourished individuals.

The accelerated net breakdown of protein characteristic of catabolic illness can be attenuated by the administration of pharmacologic doses of rhGH (35,168,170). This was first demonstrated by Ward et al who gave 0.10 rhGH mg/kg/day during severe dietary restriction following major gastrointestinal (GI)

surgery (168). In this controlled study, the subjects (n=14) received only intravenously administered dextrose (400 kcal;1680 kJ/day) with zero N intake for the first six post-operative days. The mean total N excretion in the rhGH-treated group was significantly lower than the control group, 31.5±2.4 and 42.7±3.1 g N/day, respectively. Kinetic studies revealed that rhGH accelerated the rate of both protein synthesis and breakdown. However, compared to the controls, the rhGH-treated group showed an increase in synthesis to breakdown of 39% ($p<0.05$). These results demonstrate that even under conditions of severe nutrient deprivation, pharmacologic doses of rhGH can alleviate the nitrogen losses induced by surgical stress by increasing the protein synthetic rate relative to the rate of breakdown.

Ponting and colleagues also studied the effects of rhGH therapy following major GI surgery, but with less severe dietary restriction. In this study, eleven patients received 950 kcal (4000 kJ) and 42 g protein/day. The rhGH-treated group had a mean nitrogen balance of +1.8±0.4 g N/day while the placebo group remained in negative nitrogen balance, -0.9±0.7 g N/day (170). Using N^{15} glycine, the rhGH-treated group were found to have a relative increase in protein synthesis to breakdown as compared to the controls. The net rate of breakdown minus synthesis was +0.29 g protein/kg BW/day in the treatment group and -0.23 g protein/kg BW/day in the controls representing a difference of 18.9 g N or roughly 500 g of lean body mass.

In 1989, Jiang et al studied the effects of a lower dose of rhGH (0.06 mg/kg/day) and an increased dietary intake in the same population, immediate post-operative GI surgery patients. In this controlled study, all patients received TPN providing 20 non-protein kcal (84 kJ)/kg and 1.0 g protein/kg/day. The rhGH treated group did not achieve positive nitrogen balance until postoperative day 5 and were positive 17 mg N/kg/day two days later. Over eight days, the control group had significantly greater nitrogen losses of 32.6 g N versus 7.1 g N in the rhGH-treated group ($p<0.001$) translating into an impressive preservation of 790 g lean body mass.

Kinetic studies using N^{15} glycine enrichment demonstrated that the anabolic effects of rhGH were associated with an increase in protein synthesis (2.19±0.30 vs. 3.65±0.47g N/kg/day, $p<0.05$) while the rate of protein breakdown remained unchanged Additionally, the uptake of amino acid across the forearm was measured on Day 7 and illustrated the effectiveness of growth hormone in reversing the erosion of lean body mass as measured by the flux of amino acids across the forearm. On day 7 the release of amino acids persisted in the control group while this well-known reaction to surgical stress was reversed in the growth hormone treated group. Body composition studies showed that the rhGH treated patients did in fact maintain their lean body mass despite a major surgical intervention, while the control group lost 2.8 kg of LBM ($p<0.05$). RhGH administration also preserved handgrip strength, while the control group experienced a 10% decline in strength ($p<0.05$) (35).

The effects of rhGH on wound repair after post-operative GI surgery has not been studied. However, the effect on wound repair was examined in severely burned children (n=40) given either 0.1 or 0.2 mg rhGH/kg/ day throughout their hospitalization. The patients receiving the higher rhGH dose had reduced healing time of donor sites by 2 to 4 days as compared to the placebo group. Additionally, the length of stay was reduced for 46 to 32 days with rhGH administration ($p<0.05$) (198).

In malnourished COPD patients, free of metabolic stress, rhGH can lead to prompt repletion of lean body muscle mass. Positive nitrogen balance can be promoted by GH administration in spontaneously breathing patients with moderate to severe COPD (101,199). In a study of 6 volunteers receiving 12 days of TPN at 130% RMR with concomitant administration of 30 ug GH/kg/day for four days and 60 ug/kg/day for the last four days, demonstrated a significant improvement in nitrogen balance on the last four days only. The lower dose was not sufficient to elicit a significant change in nitrogen balance. Similar to nitrogen balance, changes in REE also appear to be dose related. Although not statistically significant an

increase in REE was observed from 121.8 to 125 kJ/kg with the higher dose of GH (199). The positive nitrogen balance of the last four days was 34 mg/kg/day which is equal to the value observed by Goldstein et al in a similarly malnourished patient population given TPN at 175% REE. This suggests that it is possible to achieve positive nitrogen balance in malnourished COPD patients with rhGH therapy that would otherwise require a marked increase in energy intake. Despite the attainment of a positive nitrogen balance for the last four days respiratory muscle strength did not improve.

Longer periods of sustained positive nitrogen balance may be required to improve the respiratory muscle strength of COPD patients. Pape and colleagues studied a group of 7 malnourished (78% IBW) patients with moderate to severe COPD admitted to an inpatient metabolic unit for a four week period. The subjects consumed 35 kcal (140 kJ)/kg and 1 g protein/kg plus GH (0.05 mg/kg/day) for three weeks. For the duration of the rhGH treatment there was a significant improvement in nitrogen balance as compared to diet alone. Respiratory muscle strength as measured by PI_{max} improved by 27±8% ($p<0.02$) over the study period (101). The longer study period (21 v. 8 days) plus a higher average daily dose of rhGH was sufficient to lead to improvements in respiratory muscle strength that were not observed in the earlier study.

In conclusion, pharmacologic doses of rhGH elicit an anabolic response even under conditions of severe catabolic stress. As a result, the lean body mass of rhGH treated subjects is not only attenuated but restored by as much as 500- 700 g per week. The restoration of lean body mass leads to improvements in respiratory muscle strength in spontaneously breathing patients. In the malnourished mechanically ventilated COPD patient, it is an urgent concern to withdraw this support. The administration of pharmacologic doses of growth hormone with the background of adequate nutritional support is expected to stimulate an accelerated restoration of lean body mass. It is anticipated that the increase in lean body mass will benefit the exercising muscles, which are the

respiratory muscles in the case of the critically ill, and hence, improve strength and facilitate weaning from mechanical ventilation.

3.0 RESEARCH RATIONALE AND HYPOTHESES

3.1 Rationale

1. There is a high incidence of PEM in the COPD patient population. PEM is associated with a decrease in respiratory muscle performance.

2. Since most of the precipitating causes of acute respiratory failure in COPD are catabolic as well as being associated with decreased voluntary food consumption, it is predictable they will be accompanied by nutritional deterioration,and hence a decline in respiratory muscle mass and performance. During rehabilitation, when the catabolic illnesses have resolved, yet respiratory failure persists, the limiting factor preventing successful weaning may be compromised respiratory muscle performance resulting from a prior decline in nutritional status.

3. Since the anabolic response to nutritional support alone in patients with prolonged respiratory failure is likely to be slow and variable, even under nonstressed conditions, a practical and convincing test of this hypothesis may be best carried out by administering a potent anabolic stimulus. Pharmacologic doses of rhGH induce a prompt and uniform increase in net muscle protein synthesis.

4. Since it is normal medical practice to provide nutrition to all patients, the appropriate comparison group is one that is being fed adequate nutritional support alone.

3.2 Hypotheses

1. It was hypothesized that the anabolic response of patients in prolonged

respiratory failure supplemented with pharmacologic doses of recombinant human growth hormone (rhGH) will be greater than those receiving the equivalent nutritional support alone when patients have been selected in whom factors well-known to impede or limit weanibility have already been stabilized. These factors include severe heart failure, sepsis, hemodynamic instability, and excessive bronchial secretions. To test for such an effect, pharmacologic doses of rhGH (5 mg/day, Humatrope, Eli Lily, Canada) known to exert an anabolic effect were administered. Since the anabolic effect of rhGH is mediated through hormonal mechanisms, blood levels of total circulating IGF-1, and insulin were measured. Daily N balance and weekly serum concentrations of circulating "visceral" proteins (albumin, transferrin, prealbumin, and retinol binding protein) were measured to learn about the effects of rhGH on protein metabolism and changes in lean body mass.

2. It was hypothesized that accelerated nutritional rehabilitation, accomplished through the administration of pharmacologic doses of rhGH would increase respiratory and peripheral muscle strength and endurance and, hence, facilitate weaning from mechanical ventilatory support more rapidly than equivalent nutritional support alone. Specifically, it was hypothesized that:

(A) Maximal inspiratory pressure (PI_{max}) would be greater and the level of ventilatory support less in the rhGH-treated group as measured daily.

(B) RhGH-treated group would be weaned from ventilatory support sooner than the control group. This comparison was made realizing that a significantly large sample size to rule out a false negative result would not be feasible; and therefore a finding of a favourable trend, even if it failed to reach a significance level of $P < 0.05$, would still be regarded as a valuable finding for the planning and design of a future, larger and more comprehensive trial.

(C) It was hypothesized that voluntary handgrip strength would increase in the rhGH-treated group, but not in the control group.

4.0 Materials and Methods

4.1 Experimental Design

1. Pre-Study Period. All patients meeting the selection criteria (See Section 4.3) started on a 3-day trial of nutritional support. The enteral route of administration was preferred. If 80% of estimated nutritional requirements (See section 4.7) were not tolerated enterally, then total parenteral nutrition (TPN) was initiated to either supplement or replace enteral feedings. Also, during the prestudy period patients on a mode of ventilatory support other than pressure support ventilation (PSV) were switched to this mode. The procedure for this transition was standardized (See Appendix 1).

2. Baseline Measurements. Baseline measurements were taken on Day 0 to assess nutritional and metabolic status. These baseline measurements included selected serum protein concentrations, vitamin (serum B_{12}, and RBC folate) and mineral status (serum iron, and ferritin), body weight, serum electrolytes (including magnesium), blood hormone levels (IGF-1, insulin, cortisol), resting metabolic rate and respiratory quotient. Tests of peripheral muscle strength (hand grip dynamometry) and the severity of respiratory failure (weaning trial; See Section 4.8), were conducted on Day 0.

3. Study Period. The study period was 14 days or 24 hours after weaning from mechanical ventilation; whichever came first. On Day 1 and throughout the study period at 9:00 a.m. daily either rhGH (5 mg) or the placebo was administered subcutaneously. All enrolled patients remained on the nutritional support regimen initiated during the prestudy period (See section 4.7). Serum electrolytes were monitored every one to three days to assess the metabolic response to the protocol. Twenty-four hour urine collections were started daily at 7:00 a.m. for N balance studies, and for determinations of urinary creatinine and sodium. The level of pressure support ventilation required and adherence to a standardized weaning

protocol was judged daily along with measures of respiratory status; PI_{max}, respiratory rate, FiO_2 compliance, resistance, and tidal volume.

On Days 7, 14 and/or the last day of the study period, several analyses were conducted. On Day 7, the RMR and RQ measurements were repeated to determine the effects of rhGH therapy on energy expenditure and substrate utilization. Weaning trials were repeated to detect changes in respiratory status. To monitor hormonal and nutritional responses to the treatment, selected plasma protein concentrations, hormone levels, hand grip dynamometry and body weight were measured. Serum B12, folate, ferritin, and iron levels were drawn on day 14 or the last study day.

4.2 Recombinant Human Growth Hormone

4.2.1. Dosage and Administration

The treatment group received 5 mg daily of rhGH (Humatrope, Eli Lily, Canada) for a maximum of 70 mg rhGH, while the control group received a placebo (dibasic sodium phosphate crystals, mannitol, and glycine). The rhGH or placebo was administered subcutaneously at 9:00 a.m. daily by the nursing staff.

The daily dose was selected based on evidence that it was sufficient to safely exert an anabolic response in hospitalized patients (160-162,168,200,201). The daily administration of doses as little as 0.05 mg/kg body weights (3.5 mg/70 kg/day) to 10 mg/day has been shown to elicit an anabolic response with few adverse effects.

4.2.2. Blinding

This was a double blind study. The rhGH was supplied in vials containing 5 mg each. The vials containing the placebo appeared visually identical to those containing the rhGH and were reconstituted with the same amount of diluent. All vials were labelled "Effects of GH replacement in adults." The rhGH or placebo was reconstituted with 1.5 mL diluent (Diluent for Humatrope, Eli Lily, Canada) by the

RVH Pharmacy staff and by the nurses at the MCH. Neither the research personnel, nursing staff, treating physician, nor the patient knew identity of the vials' contents. With a suspected adverse reaction, the blinding was to be broken. This decision would be made by L. John Hoffer, M.D. If the blinding was broken, the patient would have been automatically disqualified. However, such a situation never arose.

4.3. Subjects

All patients admitted to the Intensive Care Units (ICU) of the Royal Victoria and Montreal Chest Hospital's Intensive Care Units were assessed for eligibility from January 2, 1994 to October 1, 1994. Additionally, patients in the Intensive Care Units at several other Montreal hospitals, including the Montreal General and Reddy Memorial Hospitals, were also evaluated for eligibility. The eligibility of potential subjects was determined through careful review of physical exam, past medical history, nutritional history, current illness, respiratory status, prognosis, haematological, and blood chemistries by the graduate student and a study physician. The selection criteria were as follows:

Inclusion Criteria

- Protein and energy intake meeting 80% or more of estimated requirements (See Section 4.7)
- Informed consent obtained from patient
- Age 18-85 years old
- Requiring mechanical ventilatory support for 3 days or more
- Has failed at least 1 previous attempt to wean from mechanical ventilation
- On pressure support ventilation
- Hemodynamically stable
- Alert and competent to give or withhold informed consent

Exclusion Criteria

- Respiratory status sufficient to sustain more than one and a half hour of spontaneous, unassisted breathing while on 6 cm water of pressure support ventilation
- Airway obstruction including that produced by excessive tracheal secretions
- pO_2 < 60 mm Hg with F_iO_2 of 0.4
- Suspected sepsis or uncontrolled infection in lungs or elsewhere (Clinical evidence of same includes suggestive leucocytosis, positive blood cultures, increased cardiac output, rectal temperature of > 38.5°C)
- Advanced cancer
- Severe congestive heart failure
- Renal failure (Serum Creatinine > 300)
- Clinically significant hepatic failure
- Insulin-dependent diabetes mellitus

Patient Termination Criteria

The following circumstances would result in termination from the protocol before the completion of the full 14 days: request of the patient, severe adverse reaction to treatment, request of "treating" physician, change in medical status making the patient ineligible and/or extubation. At the time of termination, the administration of rhGH or placebo was immediately halted with the exception being in the case of extubation. Patients had to be free of ventilatory support for more than 24 hours to be considered successfully weaned. For this reason, these patients received one additional dose of rhGH during this 24 hour period. If 24 hours passed without need of ventilatory support, the study was terminated at that point. The decision to continue or stop the nutritional support regimen and/or weaning protocol was made by the "treating" physician.

4.4. Sample Size

A minimum sample size of 4.9 subjects per treatment group was estimated, based on a power calculation for a two-tailed test with the alpha and beta set at 0.05, given an expected difference between groups of 2.5 g N/day and an anticipated standard deviation of 1.0 g N/day. The expected difference between groups and standard deviation was based on the findings of previous research using pharmacologic doses of rhGH (35,101,162,197,202,203). Since this was the first study to look at the response of respiratory parameters in mechanically ventilated patients given pharmacologic doses of rhGH, data was not available to determine the expected differences between groups and the standard deviation. Therefore, the sample size calculation was based soley upon N balance. Based on this power calculation, a sample size of six in each group was proposed.

Having said this, and while concluding that it was anticipated that significant improvements in nitrogen balance in the rhGH-treated patients would be shown, we were aware that a small sample size left open the possibility of false negative findings regarding respiratory or weaning parameters; i.e. no significant difference found despite a true beneficial effect. Our philosophy in designing in this trial was to anticipate this would likely occur, but to regard the experiment as a pilot project. If sufficiently interesting trends were observed, this would provide sufficient motivation to enter into a larger, multi-centre trial using the techniques validated in this smaller experience.

4.5 Patient Assignment and Randomization Procedure

A consecutive, nonprobability sampling design was used meaning that all patients meeting the selection criteria from January 2 to October 1, 1994 were enrolled in the study. All patients meeting the selection criteria underwent at least one formal pre-study period weaning trial. The weaning trial procedure involved decreasing the level of pressure support to 6 cm water (which is enough pressure to overcome the resistance of the endotracheal tube) and then observing the

patient for signs of failure (See Section 4.8 for definition of failure). The time elapsed from the beginning of the trial until failure was measured. Patients who failed at 1-30 minutes were classified as the "severe" respiratory failure group, and failure between 31-90 minutes were classified as "moderate to severe" and "moderate" failure was defined as 91-180 minutes. If spontaneous respirations were maintained without signs of "failure" for more than one and a half hour (see Section 4.8), he or she was excluded from the study because of the likelihood of weaning soon independent of any therapy.

Eligible subjects were assigned at random to either the rhGH treated or control groups by a statistician from the Department of Medicine, McGill University who prepared a list of patient assignment numbers from one to twelve. The results of the weaning trials were used during randomization to ensure that the patients were matched for baseline respiratory status. To do so the twelve patient numbers were divided into 3 subgroups according to classifications for severity of respiratory failure used in the weaning trials. The first patient enrolled in each subgroup were assigned the smallest number in that group. Since it was desirable to maximize the numbers of patients with similar severity of respiratory failure, if one group became filled one or more of the remaining groups would be deleted.

4.6. Research Facility

The subjects were admitted to the Intensive Care Units at the Royal Victoria and Montreal Chest Hospitals. Inservice education was conducted by the graduate student for all members of the nursing and respiratory therapy staff at both hospitals. The educational materials used for the inservices were prepared in both English and French. The inservice training provided information regarding the general goals of the study, rhGH administration, rhGH side effects, nutritional support regimen, weaning protocol and procedures for sample collections (See Appendix 1).

4.7. Nutritional Support Protocol

Treatment and control groups received equivalent levels of nutritional support targeted to meet their maintenance energy and protein requirements. There is a medical obligation to meet the nutritional needs of all patients when this can be safely accomplished, since there is no doubt that starvation is counterproductive to health. Energy intake was designed to meet total daily energy expenditure so that the patients were in zero energy balance. Resting energy expenditure (REE) was measured using the indirect calorimetry method. To obtain total daily energy expenditure, REE was multiplied by a factor of 1.15 to account for the increase in metabolic rate in response to physical and chest therapy, pain and other manipulations that occur frequently in the ICU setting (105). When either the indirect calorimeter was not operable or the results were judged to be unreliable, total daily energy expenditure was assessed as basal metabolic rate per Harris-Benedict equation times a factor of 1.2. The Harris-Benedict equation is as follows:

BMR(males)= 66.4730 + (13.7516W) + (5.0033H) - (6.7550A)

BMR(females)= 665.095 + (9.563W) + (1.8496H) - (4.6745A)

where W = weight in kg

H = height in cm

A = Age in years

Protein requirements were assessed at 1.2 g/kg IBW (100). Of the non-protein energy, 65% was provided as carbohydrate and the remaining as fat.

The preferred route of administration was enteral. Patients were fed either by nasogastric tubes or with small bore (8 Fr) nasoduodenal tubes depending on patient tolerance and/or preference of "treating" physician. Commercially prepared enteral products were used (Jevity, Ross Laboratories, Montreal, Quebec and Nutrisource, Sandoz. See Table 1). Of the non-protein energy, 65% was carbohydrate and 35% fat. If the protein content of the enteral feeding was not sufficient, a protein modular was used (Promod, Ross Laboratories, Montreal, Quebec). The enteral feeding was continuous over 24 hours. To determine total

TABLE 1: COMPARISON OF JEVITY (ROSS) VS. NUTRISOURCE (SANDOZ)

Characteristic	Jevity	Nutrisource
KJ/mL	4.45	5.02
Protein Source	Ca & Na Caseinate	Ca & Na Caseinate soy protein isolate
g protein/L	44	43
Carbohydrate source	Hydrolyzed cornstarch	Maltodextrin corn syrup solids
g CHO/L	152	170
non-protein energy as CHO	65%	64%
Fat source	Corn Oil MCT	Canola MCT
g fat/L	37	42
Non-protein energy as fat	35%	36%
Fiber source	Soy polysaccharides	Soy polysaccharides
g fiber/L	13.6	10
g fiber/4184KJ	12.8	12.0

daily nutrient intake, all enteral and/or intravenously (TPN, dextrose, or saline) administered solutions were figured out from the nursing observation records.

Patients on enteral feedings were to receive a minimum of 80% of their estimated requirements from the enteral feedings. If patient tolerance did not allow the targeted goal to be attained or enteral nutrition was contraindicated, total parenteral nutrition (TPN) was used to either supplement or to replace enteral feedings to achieve prescribed level of intake. The protein source in the TPN was crystalline amino acids in the usual concentration of 2.75% or 5% and dextrose concentration of usually 25%. The fat was provided as a soy-based intravenous (IV) fat emulsion (Intralipid, 10 or 20%). IV fat emulsions were provided only twice per week as is standard clinical practice in these hospitals. Therefore, except for these two days, carbohydrate served as 100% of the non-protein energy. Infusion of TPN was also over twenty-four hours.

4.8. Weaning Protocol

The procedure for weaning from mechanical ventilation was standardized for this research project. Any patient meeting the selection criteria, but on any other mode of mechanical ventilatory support was switched to pressure support ventilation (PSV) during the prestudy period. Since all patients received pressure support ventilation, comparisons of respiratory status between groups were made. The transition to this mode of support was the same for all participants; peak pressure developed on a tidal volume of 10 cc/kg and a flow rate of 60 litres/minute was determined. The peak end expiratory pressure (PEEP) was set at 5 cm water and for the remaining of the weaning process when possible. Once on PSV, the level of support was decreased by 5 cm of water every 60 minutes until the patient "failed."

Weaning failure was stringently defined as any one of the following: respiratory rate of >30 bpm, tidal volume of <5 mL/kg, PCO_2 change >10 mm Hg on ABG (to be checked 15-30 minutes after change in pressure support), desaturation

(SaO_2 <90%), a change in heart rate of 25% and a heart rate of 60 or >120 bpm, systolic blood pressure increases or decreases by 25% of baseline, or agitation and/or distress. The respiratory rate and tidal volume were measured by the ventilator.

Once a patient failed the PSV was increased by 5 cm water and the patient rested until next day. At 6:00 a.m. on study Day 1 and on each subsequent day, the level of PSV was set at the lowest level tolerated the previous day. Attempts to further decrease the PSV by 2 cm water were made at 12:00 and then again at 6:00 p.m. daily. When a patient did not tolerate the decreased PSV, it was increased to the previously tolerated level. After failure, attempts to decrease pressure support further were abandoned for that particular day. Each night at 10:00 p.m. until 6:00 a.m. the next morning the patients were "rested" by increasing the level of PSV to the original level tolerated at the beginning of the study and which was modified according to patient progress over the course of the study. When a patient sustained adequate ventilation on 6 cm water for five continuous hours, mechanical ventilatory support was withdrawn. To be considered successfully weaned, a patient had to sustain spontaneous respiration for 24 hours or more.

4.9. Respiratory Muscle Strength

Maximal inspiratory pressure (PI_{max}) was measured to assess respiratory muscle strength. PI_{max} is measured at the end of expiration against an obstructed uni-directional mouthpiece with a small leak to minimize oral pressure artifacts. After being sure the endotracheal cuff was fully inflated, three consecutive measurements of PI_{max} were taken allowing for a short rest between each trial by a respiratory therapist. To ensure a maximal effort, the mouthpiece was occluded for 20 seconds. The highest measure was used for analysis.

4.10. Peripheral Muscle Strength

Peripheral muscle strength was measured by voluntary hand dynamometry.

The grip size was adjusted for comfort but kept constant throughout the study. To assess handgrip strength, force was measured in both hands three times each using a Smedley-type hand dynamometry (Jamar, Jackson, MI). The dominant hand was noted. Patients were instructed regarding the purpose and procedure of this test. Measurements of hand dynamometry are usually taken standing with one's arm at a 90-degree angle, but not touching the body. Because these patients were bedridden, a standard position was used in which the hand dynamometry rested on the bed not touching their body. Once in proper position the patients were encouraged to apply maximal force. The hand grip strength was measured in kg of force with an accuracy of ± 1 kg. The average of the three measurements in the dominant hand was used for analysis.

4.11 Nitrogen Balance Studies

Complete 24 hour urine collections were made for every study day. The time of the collections was from 7:00 a.m. to 6:59 a.m. the next day. All patients had Foley catheters that served to reduce urine losses. Nursing staff was instructed to record any losses of urine, due to spillage, being sent to biochemistry or other reasons, on the nursing observation flow sheets. Urine was collected in containers without acid preservative. Each container was labelled "Growth Hormone Study" with the patient's name, date, and time of collection. For the 24 hours of the collection the urine was stored at the bedside at room temperature with the top tightly secured.

Once complete the 24 hour urine collections were weighed using an electronic scale (Mettler PE) with precision to 0.01 g. The collection was then agitated and the specific gravity was determined (Squibb Urinometer, Parsippany, NJ). Using the weight and specific gravity, the adjusted volume was calculated. The urine was then put into 5 ml plastic vials and stored in a freezer at -30 degrees Celsius until analysis. The urinary excretion of urea N and total urinary N was determined for N balance calculations.

A modified Jaffe method (204) on the Beckman Syncorn CX4 and CX5

systems (Brea, California) was used to determine urinary creatinine. The automated Beckman systems were also used for urea N determination (Ion Selective Electrode Methodology). The Royal Victoria Hospital (RVH) laboratory did these analyses. Total urinary N was determined by the Kjeldahl method (205) followed by colorimetric determination with Technicon Autoanalyzer II (Chauncey, New York).

N balance was calculated as N intake minus output (sum of urinary, faecal and miscellaneous losses). N intake was determined from enteral and parenteral solutions. Faecal N losses were assumed to be 0.6 g/day based on reported faecal losses with a similar enteral feeding (206). Miscellaneous losses were assumed to be 8 N mg/kg/day (60). Urinary nitrogen was determined from the daily 24 hour urine collections. Urinary creatinine was measured daily to assess if the urine collections were complete. Urine collections were judged incomplete if the daily urinary creatinine level was more than one SD from the mean. The urine volume for incomplete collections was adjusted by multiplying actual urine volume by the sum of mean urinary creatinine divided by that day's urinary creatinine.

Changes in lean body mass were estimated from changes in N balance assuming 1 g N is equivalent to 6.25 g protein and 31.25 g LBM (207).

4.12. Laboratory Indices

Postabsorptive venous blood samples were drawn on Days 0, 7, 14 and or the last day of the study protocol.

Insulin, IGF-1: 10 millilitres of blood was collected in a 2-10 ml test "lavender top" tube containing 0.07 ml (0.34 M) EDTA K_3 and was stored on ice during transportation. The blood-EDTA K_3 solution was centrifuged at 3000 rpm for 15 minutes at 4 degrees Celsius. The plasma portion was retrieved and separated into ten equal portions, placed in 2 ml plastic test tubes, labelled and stored at -30 degrees Celsius. RIA was used to measure IGF-1 (Standard prepared by McGill University, Polypeptide Hormone Laboratory under the supervision of Dr. Barry I.

Posner) and insulin (Human Insulin Specific RIA kit, Linco, St. Louis, MO) levels using a Gamma Counter (LKB Wallac-1271 Riagamma Automatic Gamma Counter).

Transferrin, retinol binding protein, prealbumin: 5-7 millilitres of blood was collected in a 10 ml red top tube (no additive) and was kept at room temperature. The blood was allowed to coagulate and then spun for 15 minutes at 3000 rpm at room temperature. The serum portion of the blood was retained and placed in four 2 ml plastic test tubes, labelled and stored at -30 degrees Celsius. These measurements were determined at the Clinical Biochemistry laboratory at the Hotel Dieu Hospital (Montreal, Quebec) using the nephelometry technique (Nephelometer, Behring, Germany).

Cortisol: Blood was collected in a 10 ml green top tube containing 143 USD units of Na Heparin and were stored on ice during transportation. The blood-EDTA K_3 solution was centrifuged at 3000 rpm for 15 minutes at 4 degrees Celsius. The plasma was placed into 2 ml plastic test tube. Cortisol concentrations were determined by RIA using the "Serono Cortisol MAIA kit" (Serono Diagnostics).

Serum iron, ferritin, erythrocyte folate, and vitamin B_{12}: (Collected on days 0 and 14 only): Serum iron was collected in a 7 ml navy top tube without additives. This test was completed using a Miles Technicon Random Access Analyzer set at 560 nm wavelength (Tarrytown, NY). The vitamin B_{12}, RBC folate, and ferritin samples were collected in a 10-ml red top tube without additives. An ACS:18 Automated Chemiluminesce System (Corning, NY) was used for these determinations. All of these tests were conducted by the Haematology Division at the Royal Victoria Hospital.

The following venous blood samples were drawn every 1 to 3 days. The frequency of the drawing of these samples was determined by the "treating" physician:

SMAC-16 and Serum Magnesium: (208) Blood was drawn by the nursing staff in red top tubes (no additives) for determinations of serum sodium, potassium,

chloride, bicarbonate, urea, creatinine, glucose, uric acid, calcium, phosphorus, total protein, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), cholesterol, and triglyceride. The SMAC-16 and serum magnesium was determined by the RVH clinical biochemistry laboratory using standard automated methods (Technicon SMAC II).

Complete Blood Cell Count: (208) Using a lavender top tube 7 ml of blood was collected for determination of haemoglobin, haematocrit, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils and placarders. These tests were completed using a Technicon H-I System (Tarrytown, New York) at the RVH clinical biochemistry laboratory.

4.13 Indirect Calorimetry

Resting metabolic rate was measured by indirect calorimetry using a Deltatrac ™ metabolic monitor (SensorMedics, Yorba Linda, California). The respirator mode was used for all measurements. In the respirator measurements, the expiratory air coming from the respirator is first led into a 4-litre mixing chamber from which the fraction of expired O_2 and CO_2, FEO_2 and $FECO_2$, respectively, are determined. The calculation of VO_2 and VCO_2 also requires the measurement of respiratory flow.

The fixed airflow through the system was 39.2 L/minute. The flow rate was calibrated by combusting 5 ml of absolute ethanol in a calibration burner unit every month. The ethanol used for calibration was carefully sealed with paraffin to protect it from ambient moisture. During the combustion test the total amount of CO_2 produced was used to determine the flow rate by this equation:

$$\text{New Flow Rate (L/min)} = \frac{1.03 \times 3820 \times \text{Current Flow Rate (l/min)}}{\text{total } CO_2 \text{ produced (ml)}}$$

The alcohol combustion also served to verify the accuracy of the O_2 consumption and CO_2 production measurements by comparing to the actual to the theoretical

yield, along with checking the accuracy of the respiratory quotient ($RQ_{alcohol}$=0.667).

The analyzer measured oxygen with a differential paramagnetic sensor and carbon dioxide with an infrared sensor. The gas analyzers were calibrated before each measurement using a calibration gas of 96% O_2 and 4% CO_2. The VO_2 and VCO_2 measurements were made under ambient conditions, however, the Delatrac™ corrected O_2 consumption and CO_2 production for standard conditions (STPD); dry gas at 0 degrees Celsius and 760-mm Hg. To find out the resting metabolic rate from gas measurements the Weir equation was used.

Resting metabolic rate (RMR) was measured on Days 0, 7, and 14 by the same operator. The tests were conducted between 8:00-8:30 a.m. after several hours of sleep prior to physical or chest therapy (105), dressing changes, X-Rays and during continuous administration of nutritional support. After connecting the expiratory limb of the ventilator to the indirect calorimeter, the patient was allowed to rest for five minutes. During the test the curtains were drawn and no manipulations were done to the patient. The first five minutes was collected but not included in analysis. Measurements would last for 15-20 minutes. To be considered a "steady state" study the coefficient of variability for the VO_2 and VCO_2 had to be 5-10% of the mean. If the study did not meet this criterion it was repeated the next day.

4.14 Hazards to Subjects and Informed Consent

The reported potential deleterious side effects of short term administration of pharmacologic doses of growth hormone are hyperglycaemia and fluid volume overload (153-155,174,175). Arthralgias have also been described. To ensure that the administration of rhGH did not further exacerbate these problems to a clinically unacceptable level, serum glucose were monitored daily. To guard against fluid overload, intake/output records were reviewed daily and patients weighed weekly.

Prior to enrolling the first subject, the proposed research protocol was approved by several external and internal review boards. The protocol was

reviewed and approved by Health and Welfare Canada. Their approval of the protocol was necessary because the use of pharmacologic doses of rhGH in adults without growth hormone deficiency is not yet an approved indication for the drug. Additionally, the protocol was accepted by the Eli Lily Co., the manufacturer of rhGH (Humatrope).

An internal review board was the Ethics Committee of the Royal Victoria Hospital. The proposed research protocol and informed consent document was presented to this committee by Dr. L. John Hoffer and Candace Hinze on May 17, 1993. After review of these materials, the committee approved the protocol and informed consent form without revision. Dr. Peter Goldberg presented the same materials to the Ethics Committee at the Montreal Chest Hospital. This committee approved the protocol, but asked for revisions to the informed consent to make it easier to read (larger lettering) and gave approval pending these changes. The research proposal and informed consent form were resubmitted to the Ethics Committee at the Royal Victoria again one year later May 2, 1994 according to their policies. Minor revisions were made to the protocol at this time and were approved without delay. A sample copy of the informed consent is appended (Appendix 3).

When a patient meeting the selection criteria was identified, the graduate student would briefly describe the basic information regarding the research to the patient. If the patient requested further information, then the details of the study design and the possible side effects were carefully explained. This information was shared with family members when requested. After this explanation, each patient was asked if he/she would like to speak with one of the study physicians regarding this matter. All prospective patients opted to speak with a physician. Dr. Peter Goldberg discussed the study protocol and answered all questions. When a patient remained interested in the study, the informed consent form was reviewed and the patient was given time to make their final decision to participate in the study. At the time of signing the consent form, all patients had to be deemed alert and competent by the treating physician. Two people were witnesses to the signing of this

consent. The signed consent form was then placed in the medical record.

4.15 Statistical Analysis

The measured variables fall into three categories; (1) outcome variables, which are the dependent variables that were measured to test the primary hypotheses relating to respiratory function and muscle strength, (2) confirmatory variables used to confirm that the treatment had its expected physiologic effects, (3) other measures to test for the comparability of the two subject groups and for the presence of factors that might impinge on the expected results. Specifically, the outcome variables were: PI_{max}, level of PSV, hand grip strength, and days to successful weaning. The confirmatory variables included N balance, blood glucose, fluid balance, and sodium excretion. The measurements to confirm compatibility and to identify possible confounding variables were weaning trials, admitting diagnoses, number of days on ventilator, age, sex, height, weight, BMI, energy/protein intake, hormonal levels (IGF-1, insulin, cortisol), plasma protein concentrations, serum magnesium, B_{12}, folate, and iron status.

The statistical analyses for the outcome and three of the confirmatory (blood glucose, sodium excretion, and fluid balance) variables were handled similarly. A plot of each of the variables against time was completed for each subject. The purpose of plotting the data was to display the nature of the change in each outcome variable over time. If rhGH had the hypothesized effects, one would observe an increase in the measured outcome and confirmatory variables with time under the effect of the drug, but little or no change in the measured variables for the placebo group. Changes in these variables might occur steadily with time, or after a short initial delay, increase to a steady-state maximal effect, thus demonstrating a "sigmoidal" time relationship. Previous trials have shown the anabolic effect of rhGH to be almost instantaneous (160,162,170). Therefore, the lag phase would be expected to be short and since we argued that patients are likely to be weaned either before or shortly after the maximum effect is obtained, the simplest model for

hypothesis testing was chosen, namely that the outcome variable y(t) would increase approximately linearly and show the relationship of $y(t)= a + b.t$ where a is the value of y at baseline and b is the rate of increase in y with time. The units are "unit time^{-1}". The statistical hypothesis then is that a will be equal for the two groups (to show they were comparable at baseline) and that b will be significantly greater for the rhGH group. This was tested by calculating b for each subject, then calculating the mean ± SD for each b in the rhGH and placebo groups and testing whether the means were statistically significantly different by two-tailed two-sample t-test. The two tailed t-test allows that the differences between the two groups may be either in the direction of the hypothesis or in the opposite direction. A p-value of 0.05 or less was considered statistically significant. A p-value of 0.05 means that when the null hypothesis is rejected there is only a 5% chance that the null hypothesis is indeed true in the population. The computer software package "Primer" was used to perform this test of significance.

A mathematical method, the method of least squares, was used to determine the linear relationship of the data points. When a line fits a set of data there will be some points that fall above and below this line. The least squares line is the line that will make the sum of the squares of the deviations of the data points that form the line in the vertical (y) direction as small as possible. The line of least squares is a powerful tool to measure the association between two variables. Specifically, in this study it was used to define the response of the forementioned variables over time. The least squares line was determined using the computer software package entitled InPlot.

5. RESULTS

5.1 Patient Recruitment

The intended sample size was 12. Over a ten month period all patients admitted to the Intensive Care Units (ICU) at the Royal Victoria (RVH) and Montreal

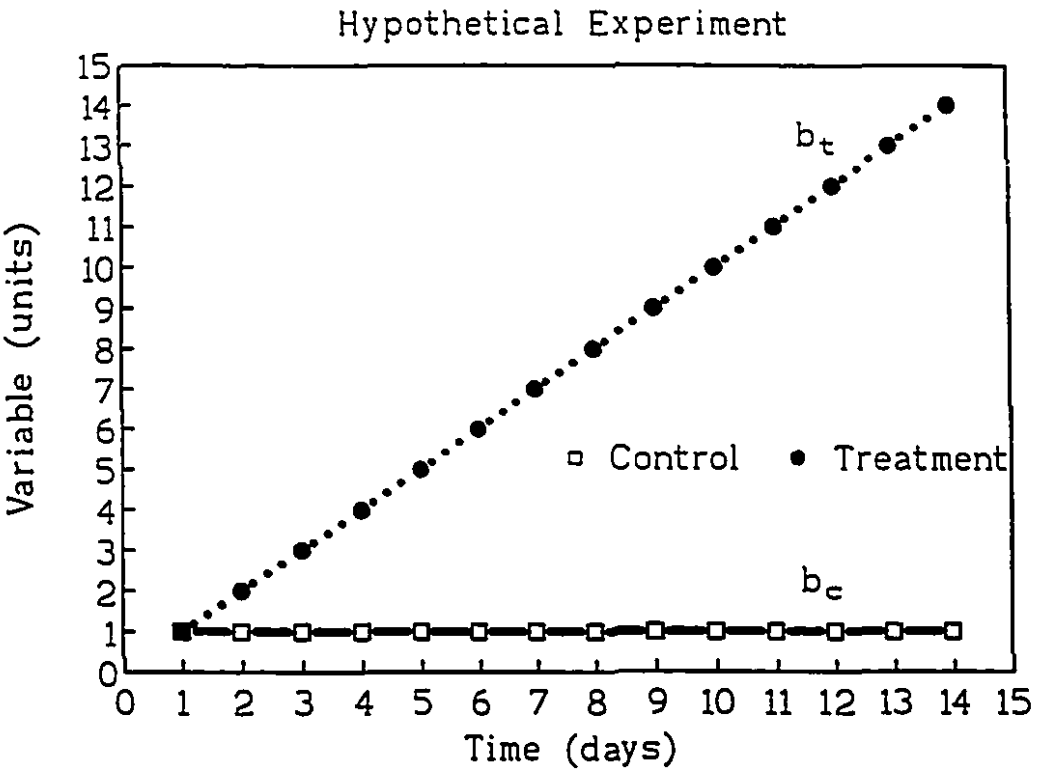

Figure 1. Hypothetical Experiment to illustrate planned statistical analysis with b_t representing slope of rhGH-treated group and b_c the slope for the control group.

Chest (MCH) Hospitals were evaluated for eligibility. The total number of patients admitted to the ICUs from January 2, 1994 to October 1, 1994 was 1,723. Of these patients 106, or 6% had prolonged respiratory failure as defined by requiring mechanical ventilatory assistance for more than three days. Of the patients in prolonged respiratory failure, 94% were excluded. The excluded patients had unresolved medical and surgical problems making them ineligible for participation in this study as defined by the selection criteria. Specifically, recent surgical intervention accounted for 20% of the excluded patients, followed by 11% for both sepsis and cancer. The diagnoses of all patients excluded from this study are listed on Table 2. Eight patients met the selection criteria and were randomized. Two patients became unstable and were withdrawn after randomization. One of the two patients was discontinued on Day 1 prior to the administration of rhGH or placebo. The other patient, who had been randomized to the rhGH-treated group, was terminated after three days on the protocol. The data of these two patients is excluded from all analysis. This made the attrition rate 25%. Thus the final sample size was six, which represents 0.3% of the total ICU admissions for the ten-month period. Three patients were randomized to the treatment and three to the control group (See Figure 2). Two of these patients were admitted to the MCH ICU and the remaining 4 to the RVH ICU.

Due to the small sample size the appropriateness of the statistical analysis (as outlined in Section 4.15) was reevaluated. With a sample size of six, the power of the proposed statistical tests was too low to provide meaningful results. The power of a statistical test is the probability of accepting the null hypothesis when in the population there is truly an association (Type II error). The data for each patient was plotted with the variable (y) against time (x) for the outcome, confirmatory and a comparability (cortisol) variables. Therefore, the statistical testing strategy that had been planned at the onset of this study (Section 4.15) had to be abandoned. Instead, individual patient data is provided for most of the results presented here. The mean$\pm$SD was calculated for several confirmatory and

TABLE 2: REASONS FOR EXCLUSION FROM STUDY

Pneumothorax	1
Esophagopleural fistual	1
Chest wal dehiscence	1
Hemodynomically unstable	1
Supraglottic stenosis	1
Neurologic deficits	1
Necrotizing pneumonitis	1
Lung emboli	1
Severe kyphoscoliosis	1
Ischemic heart failure	1
Pancuatitis	1
Gullian Barré disease	1
Wegner's granulomatosis	1
Meningitis	1
Tuberculosis	1
Refused consent	1
Cystic fibrosis	2
Gastrointestinal bleeding	2
Pulmonary edema	2
Cartiogenic shock	2
Muscular dystrophy	2
IDDM	2
Multiorgan failure	2
Thick tracheal secretions	3
Unable to give informed consent	3
CVA	3
Liver cirrhosis	5
Renal failure	5
Congestive heart failure	7
Sepsis	11
Cancer	11
S/p surgery (ACBP, lung liver transplant, splenectomy, bowel resection, cholestectomy, AAA)	20
Total:	98

outcome variables along with the baseline subject characteristics to describe the data and its variability.

5.2 Study Period

The study period ended at 14 days or 24 hours after successful weaning from mechanical ventilation, whichever came first. Therefore, the length of the study period varied among participants ranging from four to 14 study days. The total number of study days was 48 with 26 days for the control group and 22 days for the treatment group.

5.3 Comparability Variables

Comparability variables were measured to ensure that the control and treatment group were well matched.

5.3.1 Subject Baseline Characteristics

The baseline characteristics of the six subjects are shown in Table 3 and four. Weaning trials were used during the randomization process to ensure that the baseline respiratory status of the two groups was well-matched. Time until failure ranged from one second to six minutes showing that all six subjects had severe respiratory failure.

The ages of the patients ranged from 49 to 77 years old. All patients were females except one male in the rhGH-treated group. The treatment group had a mean weight of 83.8±7.7 kg as compared to 50.6±9.2 kg for the controls. Mean height for subjects in the control group was 156±3.5 cm and 163 ±5.7 cm for the treatment group. The body mass index (BMI) of the patients ranged from 14 to 42. The obese patient (BMI=42) was in the rhGH-treated group.

Four of the six patients had a confirmed history of COPD with equal numbers in each group. The mean number of days on mechanical ventilatory support before the beginning of the study period ranged from four to 62 days with the mean days

FIGURE 2:

Subject recruitment at Royal Victoria and Montreal Chest Hospitals' Intensive Care Units (ICU) from January 2, 1994 to October 1, 1994:

Total Number of ICU Admissions
1723
↓

Total Number of ICU Admissions
for more than 3 days
106
↓

Number of Patients in Prolonged Respiratory meeting selection criteria
8→
↓ → 2 became unstable

6 Patients Completed Study Protocol

3 Patients
Control Group

3 Patients
Treatment Group

TABLE 3: PATIENT ASSIGNMENT AND ADMITTING DIAGNOSIS

Patient Number	Patient Assignment	Sex	Body Mass Index	Diagnoses
1	Control	F	14	Acute Respiratory Distress Syndrome (ARDS), Pneumonia
2	rhGH	M	28	Coronary Heart Disease s/p Coronary Artery Bypass Graft, Emphysema
3*	Control	F	24	Pulmonary Edema, Congestive Heart Failure, COPD Exacerbation
4	rhGH	F	25	Acute Respiratory Failure Pulmonary Edema, Pneumonia
5	Control	F	24	COPD Exacerbation
6	rhGH	F	42	Acute Respiratory Failure COPD

* On glucocorticoid therapy during study period.

TABLE 4: BASELINE CHARACTERISTICS OF PATIENTS (Mean±SEM)

CHARACTERISTIC/VALUES	CONTROL	TREATMENT
N=	3	3
Weight (kg)	50.6±9.22	83.8±7.7*
Height (cm)	156±3.5	163±5.7
# of Days on Ventilator	30.6±16.9	23.3±11.6
Weaning Trial (seconds)	120±34.6	30.3±17
PI_{max} (cm H_20)	38.3±16.4	32.6±6.4
Transferrin (gm/L)	1.85±.27	2.56±.59
Prealbumin (gm/L)	0.20±0.04	0.19±0.04
RBP (gm/L)	0.05±0.01	0.05±0.01
Serum Magnesium	0.97±0.15	0.82±0.04

* $p<0.05$ when compared to control by nonpaired t-test

of 30.6±16.9 and 23.3± 11.6 for the control and treatment group, respectively. The mean number of days on mechanical ventilation far exceeded the 3-day minimum. The mean maximal inspiratory pressure (PI_{max}) for the control group was 38.3±16.4 -cm H_2O and 32.6±6.4 -cm H_2O for the treatment group. For normal, healthy women aged 70-74, a PI_{max} of 65±26 -cm H_2O is expected and -103±32 cm H_2O for men aged 55-74 years old (209). Therefore, the mean baseline respiratory muscle strength of the enrolled patients was approximately one-third to one-half of that expected in normal, healthy patients the same age.

Serum protein concentrations, transferrin, prealbumin and retinol binding protein, were measured at baseline to assess visceral protein stores. The mean serum protein concentrations for both groups were all within normal limits.

5.3.2 Serum Cortisol

Serum cortisol levels were measured to compare the degree of physiologic stress in the two groups. Morning serum cortisol levels were measured at baseline and at the conclusion of the study (See Figure 3). Normal cortisol levels are 248-690 nmol/L. Control patient #3 and 5 received glucocorticoid therapy during the study period. Since the cortisol radioimmunoassay reacts with glucocorticoids these measurements do not accurately reflect serum cortisol levels.

5.3.3 Serum Magnesium

Serum magnesium levels were measured at baseline, every one to three days, and at the conclusion of the study (See Table 5). All measures of serum magnesium for both groups throughout the study period were within normal limits (0.75-1.25 mmol/L).

5.3.4 Serum Protein Concentrations

The serum concentrations of selected proteins were measured (transferrin,

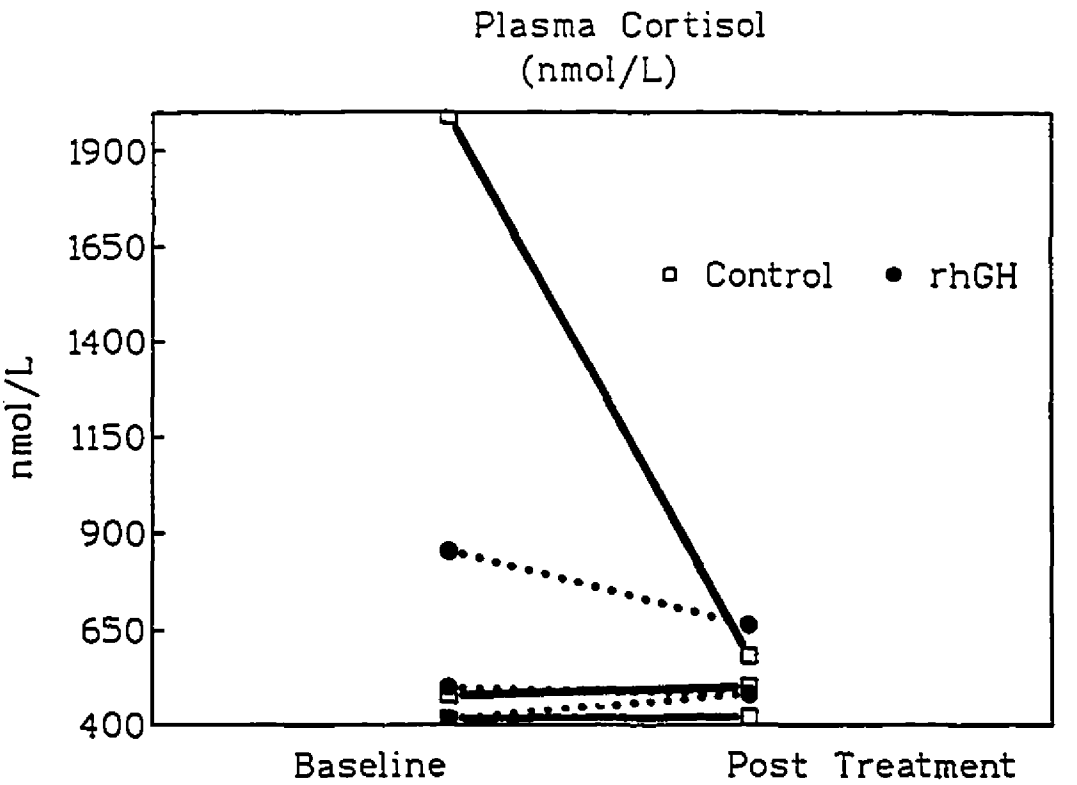

Figure 3. Serum cortisol concentrations (nmol/L) at baseline and post treatment in controls (❑) and rhGH-treated (●) subjects.

TABLE 5: SERUM MAGNESIUM LEVELS mmol/L

1. Control Group				2. Treatment Group			
Patient Number	Baseline	Day 1	Post	Patient Number	Baseline	Day 1	Post
1	0.92	0.87	0.85	2	0.80	0.83	0.93
3	1.14	0.78	0.77	4	0.92	0.89	0.83
5	0.85	0.85	0.83	6	1.12	0.91	1.10
Mean ± SD	0.97 0.15	-	0.82 ± 0.04	Mean ± SD	0.95 ± 0.16	-	0.95 ± 0.14

prealbumin, and retinol binding protein) at baseline and post-treatment to look for the effects of this intervention on visceral protein stores. Figures 4, 5, and 6 display the individual subject data at baseline and post-treatment for all three serum proteins.

Normal transferrin levels range from 1.8-3.6 g/L. The baseline transferrin levels ranged from 1.45-3.48 g/L. Two controls and 1 rhGH-treated patient had baseline transferrin levels below normal limits. All patients had prealbumin levels within normal limits (0.1-0.4 g/L) at baseline. The serum concentrations of RBP ranged from 0.025-0.07 g/L. One patient from each group had slightly depressed baseline RBP levels.

When comparing the individual patient data, a clear pattern in the change of serum concentrations from baseline to post-treatment for all three proteins is not evident.

5.3.5. Vitamin B_{12}, Folate, and Iron

Serum vitamin B_{12}, RBC folate, serum iron and ferritin levels were measured at baseline to obtain a measure of general nutritional status. The results for two patients are missing. The blood sample for a patient was lost after delivery to the laboratory and for the other patient the blood was not drawn due to difficulties with venous access. Due to the missing data, the results of these tests are not reported.

5.4 Nutritional Support Protocol

All patients were fed enterally with the exception of one control patient (R.R.) on TPN during the pre study and study period. The enterally fed patients tolerated feedings without diarrhea, emesis, abdominal distension, nausea, vomiting, or other signs of intolerance.

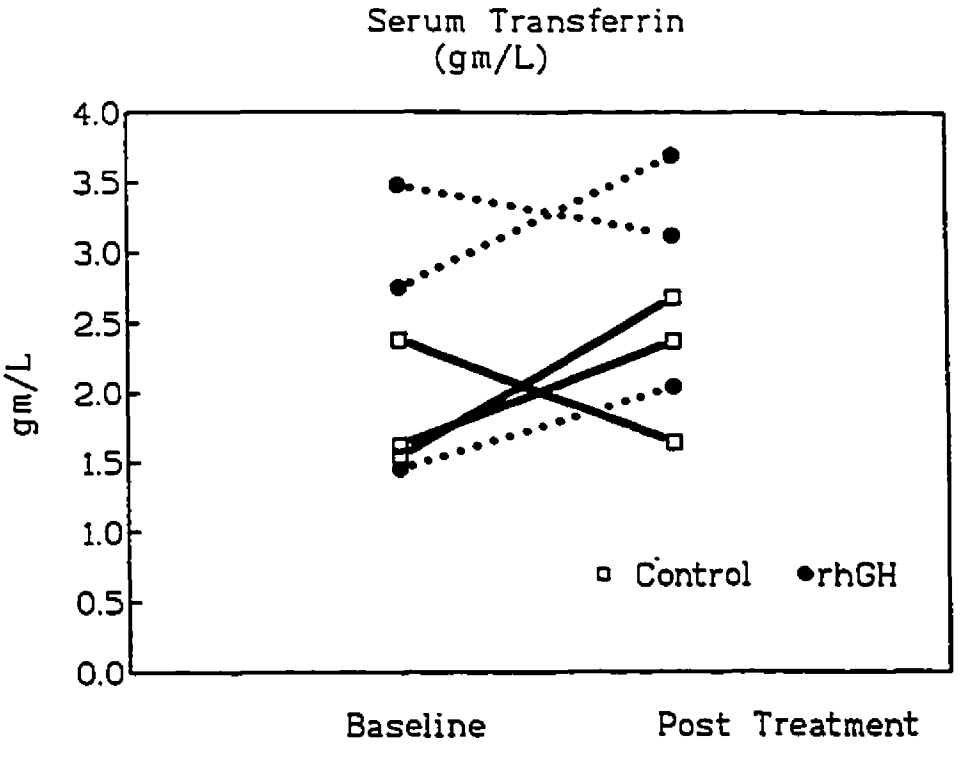

Figure 4. Serum transferrin concentrations (gm/L) at baseline and post treatment in controls (□) and rhGH-treated (●) subjects.

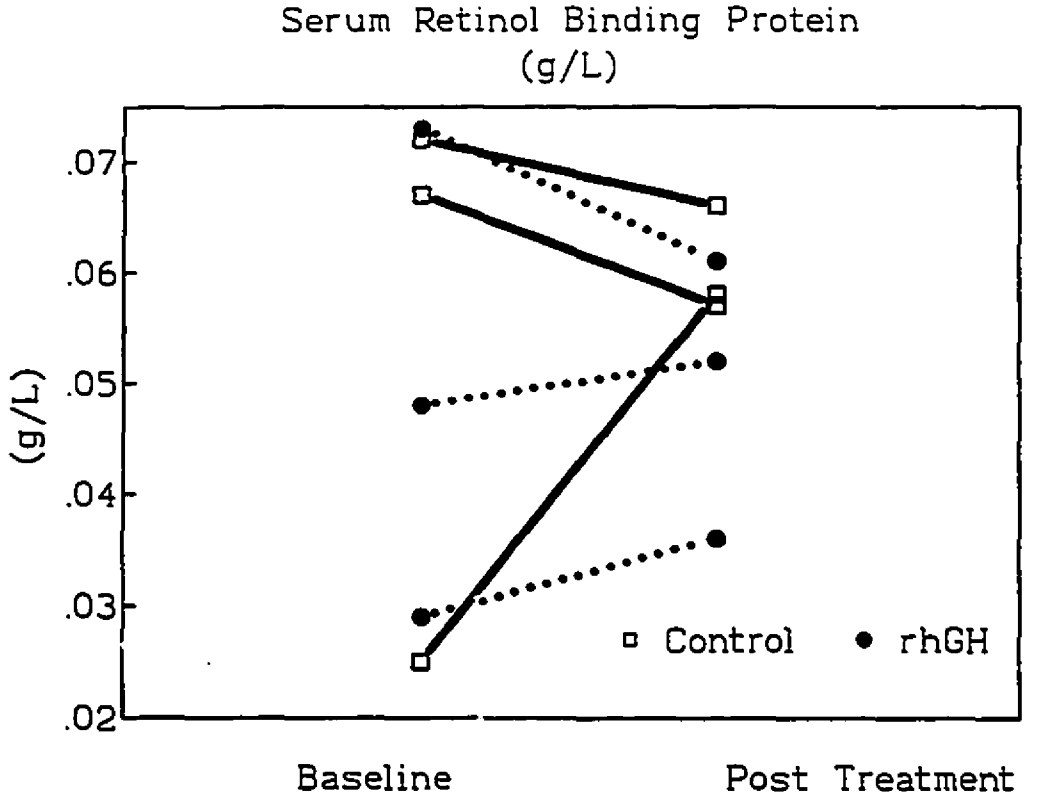

Figure 5. Serum retinol binding protein concentrations (gm/L) for controls (❑) and rhGH-treated (●) subjects at baseline and post treatment.

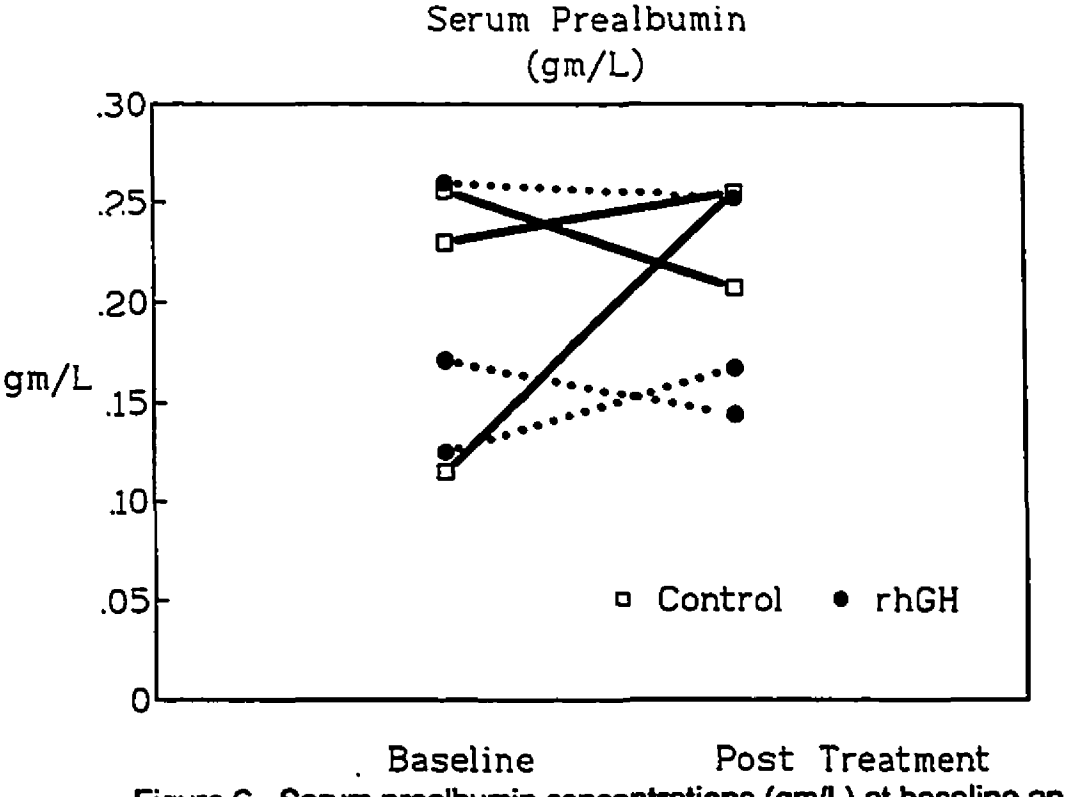

Figure 6. Serum prealbumin concentrations (gm/L) at baseline and post treatment in controls (□) and rhGH-treated (●) subjects.

5.4.1 Energy Intake

Indirect calorimetry measured resting energy expenditure for half the patients, all of whom were in the control group (see Table 6). Although resting energy expenditure was measured for two of the three rhGH patients, these studies were not steady state and were not accurate measures of REE. Instead, the energy requirements for three rhGH-treated patients were estimated using the Harris-Benedict equation to determine the BMR, which was then multiplied by a factor of 1.2 (see Section 4.7). The energy requirements for the obese subject (BMI=42) were calculated by substituting ideal body weight (IBW) plus 10% for actual body weight in the HB equation. As shown in Table 7, the mean energy requirements for the control group 5795±439 kJ/day and 6748±749 kJ/day for the treatment group. The mean actual energy intake was 6265±402 kJ/day for the control group and 5907±1019 kJ/day for the treatment group.

5.4.2 Protein Intake

Estimated protein requirements and mean actual protein intakes are summarized on Table 8. Protein requirements were calculated as 1.2 g protein/kg ideal body weights. The mean calculated protein requirements of the treatment group were 82±12 g protein/day and 63±4.6 g protein/day for the control group. The mean protein intake of the control group was 63±1.7 g protein/day and 73±6.1 g protein/day for the treatment group. Although not statistically significant, the treatment group consumed a lower percentage of protein and energy requirements than the controls because enteral feedings were held in anticipation of weaning from mechanical ventilation. This is a commnon clinical practice to reduce the risk of aspiration.

5.5 Confirmatory Variables

Confirmatory variables were measured to ensure rhGH exerted its expected physiologic effects.

Table 6: Indirect Calorimetry (kJ/day)

Patient #	Day	Resting Energy Expenditure [1] (REE)	Total Daily Energy Expenditure [2] (TDEE)	Respiratory Quotient [3] (RQ)	Predicted Total Daily Energy Requirements [4]
1	0 7	4452 4200	5124 4830	0.75 0.89	5338 5338
2	0 14	3557 7774	3977 8938	0.99 0.80	7841 7841
3	0	3998	4586	0.84	5691
4	No	Data			6080
5	0	5544	6376	0.83	5817
6	0	2734	3142	1.35	5326

[1] REE as measured by indirect calorimetry
[2] TDEE=REEx1.15
[3] RQ as measured by indirect calorimetry
[4] Predicted Total Daily Energy Requirements=Basal Metabolic Rate (Harris-Benedict Equation)x1.2

TABLE 7: DETAILS OF ENERGY INTAKE (kJ/day)

1. TREATMENT GROUP

Patient Number	Calculated Energy Requirements	Mean Intake (±SEM)
2	7812	7790±234
4	7125	5645±1276
6	5305	4289±1277
Mean±SEM	6748±749	5907±1019

2. PLACEBO GROUP

Patient Number	Calculated Energy Requirements	Mean Intake (±SEM)
1	5104	5473±117
3	5669	6535±151
5	6611	6786±171
Mean±SEM	5795±439	6265±402

TABLE 8: CALCULATED PROTEIN REQUIREMENTS AND MEAN INTAKE (g/day)

1. TREATMENT GROUP

Patient Number	Calculated Protein Requirements	Mean Intake
2	100	89
4	86	57.5
6	60	34
Mean±SEM	82±12	73±17

2. PLACEBO GROUP

Patient Number	Calculated Protein Requirements	Mean Intake
1	54	52
3	66	68
5	69	68
Mean±SEM	63±4.6	62.5±1.65

5.5.1 Insulin-like Growth Factor-1 (IGF-1)

HGH stimulates the liver and other tissues to synthesize and release IGF-1 (130,183). Pharmacologic doses of rhGH have been shown to increase serum IGF-1 levels three to five fold (35,162,197,203).

The serum IGF-1 levels were measured at baseline and 22-24 hours after the last injection of rhGH or placebo. These results are shown on Figure 7. The baseline IGF-1 levels of the two groups were similar, however, by the end of the study the mean IGF-1 levels of the rhGH-treated were significantly higher than the control group ($p=0.015$). The mean baseline IGF-1 level for the treatment was 0.13 ± 0.23 u/mL and by the conclusion of the study was 0.58 ± 0.15 u/mL.

5.5.2 Nitrogen Balance Studies

N balance results are summarized in Figures 8 and 9. The N balance results varied from +1.22 g N/day to -13.48 g N/day on Day 1. The mean daily N balance for each individual patient is summarized in Figure 8. As is evident from this figure, a distinguishable difference between the N balance data of the two groups does not emerge. Figure 9 shows the mean daily N balances of rhGH-treated Patient #4 are strongly negative. Representation of data in this manner, however, does not reflect the increase in N balance observed over the course of the study. This patient started with an -13.48 g N/day balance on Day 1, which climbed to -2.68 g N/day by Day 3.

The mean daily N balance for each group was determined. The control group had a mean daily N balance of 0.35+2.55 g N/day and 1.32 5.03 g N/day for the treatment group. The standard deviations of 2.55 g N/day and 5.03 g N/day for the control and treatment groups respectively, reflect the variable response of patients in both the control and treatment groups to either rhGH treatment and/or nutritional support.

A sample size calculation for a two-tailed t-test was completed taking into consideration the difference in mean daily N balance of the two groups, 0.97 g

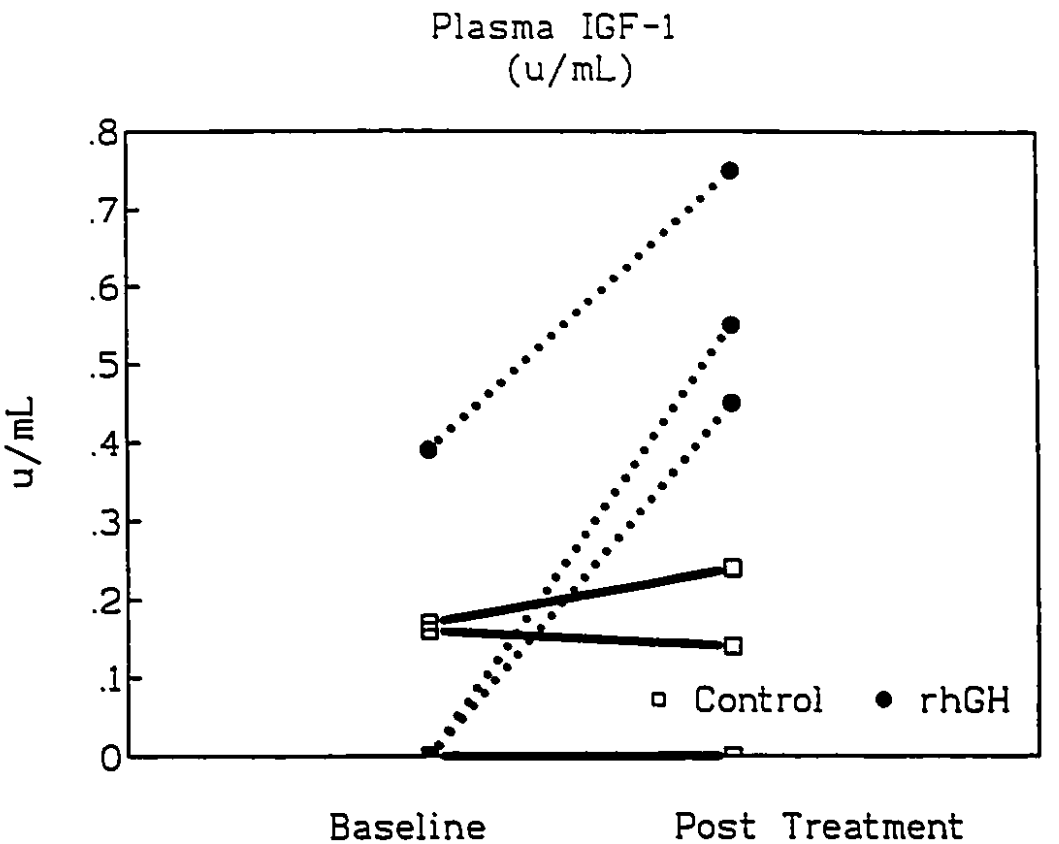

Figure 7. Plasma insulin-like growth factor-1(IGF-1) concentrations (u/mL) at baseline and post treatment in controls (□) and rhGH-treated (●) subjects.

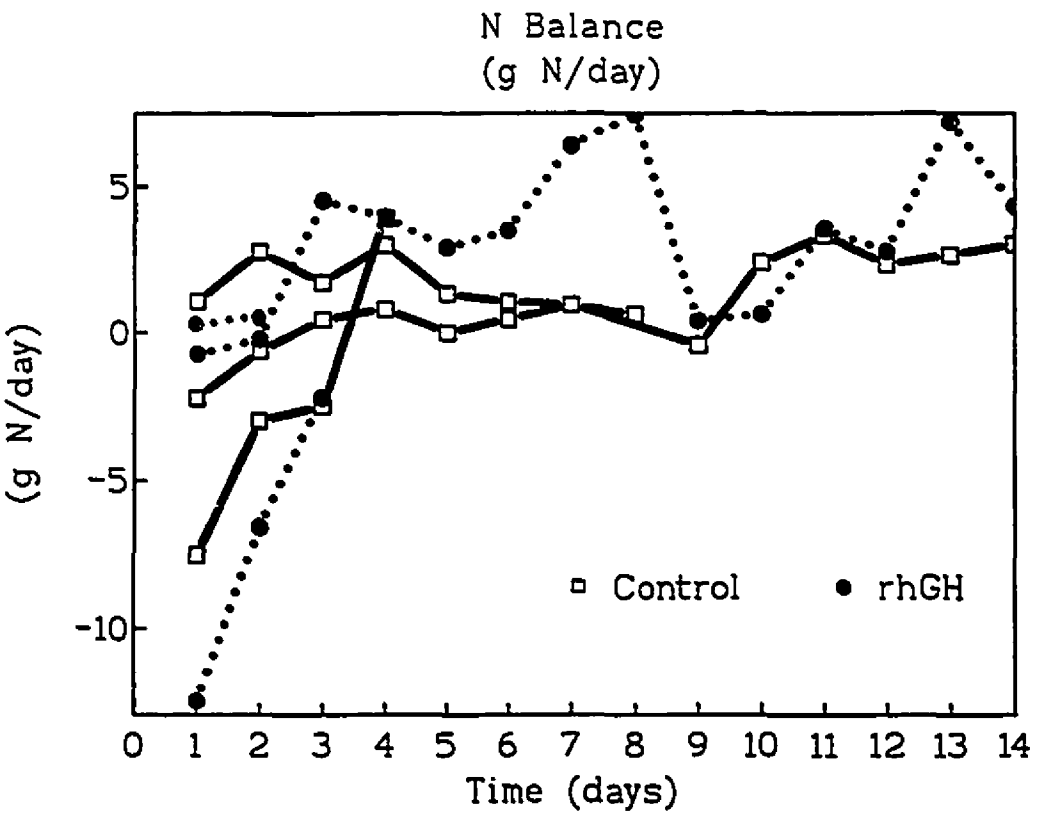

Figure 8. Daily N balance data for controls (□) and rhGH-treated (●) subjects over the study period.

Average Daily Nitrogen Balance (g N)

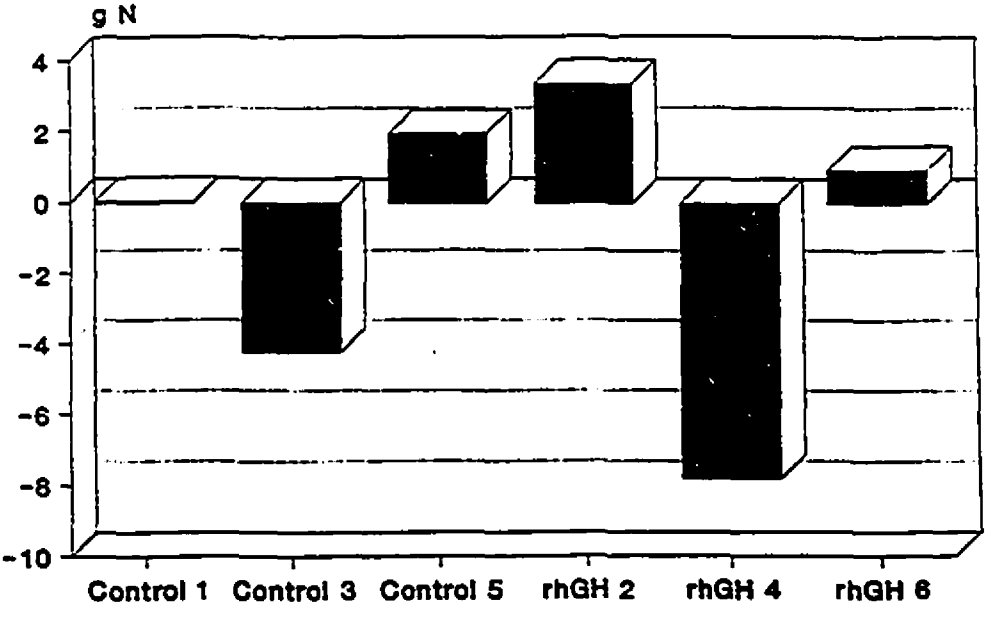

Figure 9: Average daily N balance for the control group (N=3) and the rhGH-treated group (N=3).

N/day, and the standard deviation(SD) of 3.8 g N/day observed in this study. Setting the α and β at 0.05, there is a one in 20 chance of a false positive or a false-negative, a sample size of 938 (469 per group) subjects would required to detect a significant difference.

5.5.3 Blood Glucose Levels

Pharmacologic doses of rhGH have been reported to induce hyperglycaemia (153-155). To monitor for this side effect, blood glucose levels were measured every 1 to 3 days. The mean daily blood glucose levels for each patient over the study period is shown on Table 9.

One patient in each group (Control 3 and rhGH 2) received exogenous insulin therapy during the study period. The control patient requiring insulin therapy was on total parenteral nutrition and glucocorticoid therapy both of which are known to increase blood glucose levels (210). The measured blood glucose levels of these two patients did not solely reflect the effects of pharmacologic doses of rhGH and/or nutritional support, but it also the effects of exogenous insulin therapy.

5.5.4 Fluid Balance

The mean daily fluid balance of the treatment group was +749±856 ml/day. The control group also had a positive fluid balance, but only about one quarter of that of the treatment group (199±531 ml/day; refer to Table 10). This difference was not statistically different (p=0.384).

Although the mean daily fluid balances of the two groups were not statistically different, it may have been clinically significant. The 3 rhGH-treated patients required diuretic therapy (fursemide) during the study period. Fursemide increases urine output (210). . As a result of the fursemide therapy it is impossible to evaluate the influence of pharmacologic doses of rhGH vs fursemide on the fluid balance data of the treatment patients.

TABLE 9: MEAN BLOOD GLUCOSE LEVELS ± SD (mmol/L)

1. Control Group		2. Treatment Group	
Patient Number	Mean Blood Glucose Level	Patient Number	Mean Blood Glucose Level
1	6.9±0.6	2	11.2±4.9
3	9.7±1.3	4	11.2±5.1
5	7.5±0.8	6	6.6±0.3
Mean±SD	7.8±1.4	Mean±SD	10.5±4.6

TABLE 10: MEAN FLUID BALANCE ± SD (mL/day)

1. Control Group		2. Treatment Group	
Patient Number	Mean±SD	Patient Number	Mean±SD
1	212±284	2	912±841
3	420±581	4	541±956
5	124±401	6	269±872
Mean±SD	181±531	Mean±SD	749±856

5.5.5 Urinary Sodium Excretion

As mentioned in the previous section, the three treatment patients were treated with fursemide. This makes comparisons of urinary sodium excretion between the two groups meaningless.

5.5.6 Insulin

Pharmacologic doses of rhGH are known to induce a hyperinsulinemic state (153,154). Baseline and post-treatment insulin levels were measured in all subjects and are presented on Figure 10. Normal plasma insulin levels are 35-145 pmol/L. The baseline plasma insulin levels of the control group were within normal limits. The three patients in the rhGH-treated had elevated baseline plasma insulin levels. By the end of the study, two patients in each group were hyperinsulinemic. As mentioned in Section 5.6.1, Control Patient 3 and rhGH Patient 2 received exogenous insulin therapy and it was their plasma insulin levels that were well above normal limits, at 993 pmol/L and 734 pmol/L respectively. The data of these two patients cannot be interpreted because it would be impossible to describe the influence of pharmacologic doses of rhGH and/or nutritional support vs exogenously administered insulin on plasma insulin levels. The post-treatment plasma insulin levels of patients not on insulin therapy ranged from 132 to 180 pmol/L.

5.6 Standardization of Respiratory Care

5.6.1 Adherence to Weaning Protocol

All patients enrolled in this study were on a standardized weaning protocol. The purpose of developing a standardized protocol was to ensure that all patients were weaned from mechanical ventilation in a similar manner and so that comparisons could be made between the two groups. Adherence to the protocol was defined as implementation of changes in ventilator settings within one hour of

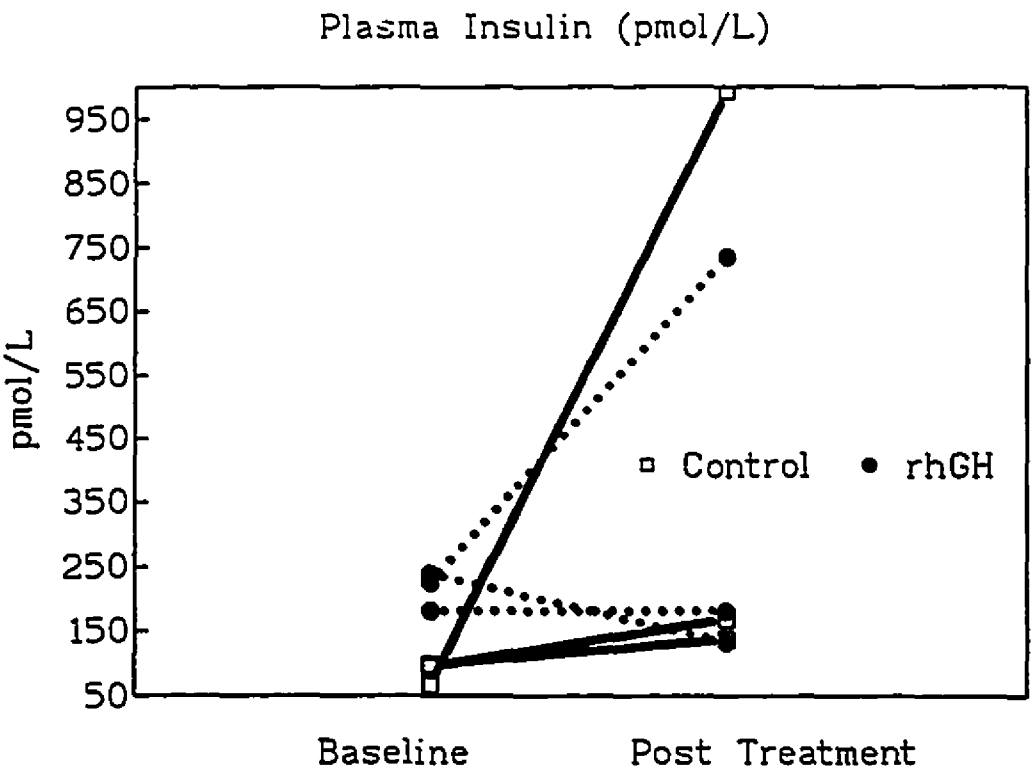

Figure 10. Baseline and post treatment plasma insulin concentrations (pmol/L) for the control group (❑) and the rhGH-treated group (●).

being ordered. The results of this study reveal that compliance to the weaning protocol was 76%.

5.6.2 Weaning Trials

Weaning trials were used to assess the baseline respiratory status of eligible patients. All patients failed within one second to six minutes, thereby, classifying their degree of respiratory failure as severe. The average time until failure in the treatment group was 120±34.6 seconds and in the control group was 30.3±17 seconds. The first sign of failure in all six patients was an increase in respiratory rate to more than 30 breaths per minute or 0.5 breaths per second (See definition of failure Section 4.8).

5.7 Outcome Variables

Outcome variables were the dependent variables measured to examine the effects of pharmacologic doses of rhGH on respiratory muscle strength, level of ventilatory assistance required, number of days to successful weaning, and peripheral muscle strength.

5.7.1 Maximal Inspiratory Pressure

Maximal inspiratory force (PI_{max}) is an important clinical method used to measure respiratory muscle strength (71,209,211). PI_{max} (y) against time (y) was plotted for each individual patient is shown on Figure 11. The baseline PI_{max} ranged from 15 -cm H_2O to 70 -cm H_2O. A of PI_{max} -65 ±26 -cm H_2O is considered normal for women 70-74 years old and for men 55-74 years old 103±32 (209). The baseline PI_{max} measurements for these six patients varied from approximately one-quarter to expected in normal, healthy persons the same age. This illustrates the tremendous variability in the baseline respiratory muscle strength of this patient group. Also, from this figure there is no apparent difference in the PI_{max} data of the two groups. Instead, the tremendous variability in the response of both groups to

pharmacologic doses of rhGH and/or nutritional support is illustrated well by this figure. Respiratory muscle strength of the two patients not weaned from mechanical ventilation during this two-week study is lower than the patients who were weaned. The PI_{max} data from one control patient showed that respiratory strength was not compromised and in fact, was even greater than expected by the end of the study period.

A sample size calculation for a two-tailed t-test was determined using the difference in mean daily PI_{max} of the two groups, 10.3 -cm H_2O/day and the standard deviation (SD) of 21.4 -cm H_2O/day observed in this study. Setting the α and β at 0.05, a sample size of 938 (469 per group) patients would be needed to detect a significant difference.

5.7.2 Pressure Support Ventilation

All subjects were on pressure support ventilation (PSV). The level of PSV was decreased systematically as defined by the standardized weaning protocol. A lower level of PSV suggested that less mechanical ventilatory assistance was required. Figure 12 summarizes the rate of change in level of pressure support ventilation for the six enrolled patients. The rate of change is the slope of the line of least squares. The two patients (Control Patient 5 and rhGH 2) who did not wean during the 14-day study period and had the slowest rate of change in level of PSV. From this figure, a difference in the level of PSV required by the two groups is not apparent. This was confirmed by a two tailed t-test which compared the mean(SD) of the control group -2.65±0.71 -cm H_2O/day to the treatment group, -3.57± 0.99 -cm H_2O/day finding that p=0.88.

A sample size calculation for a two-tailed t-test was completed using the difference in mean daily level of PSI of 0.88 -cm H_2O/day and a standard deviation (SD) of 5.9 -cm H_2O/day observed in this study (212). Setting the α and β at 0.05, a sample size of 2820 (1410 per group) patients would be needed to detect a statistically significant difference.

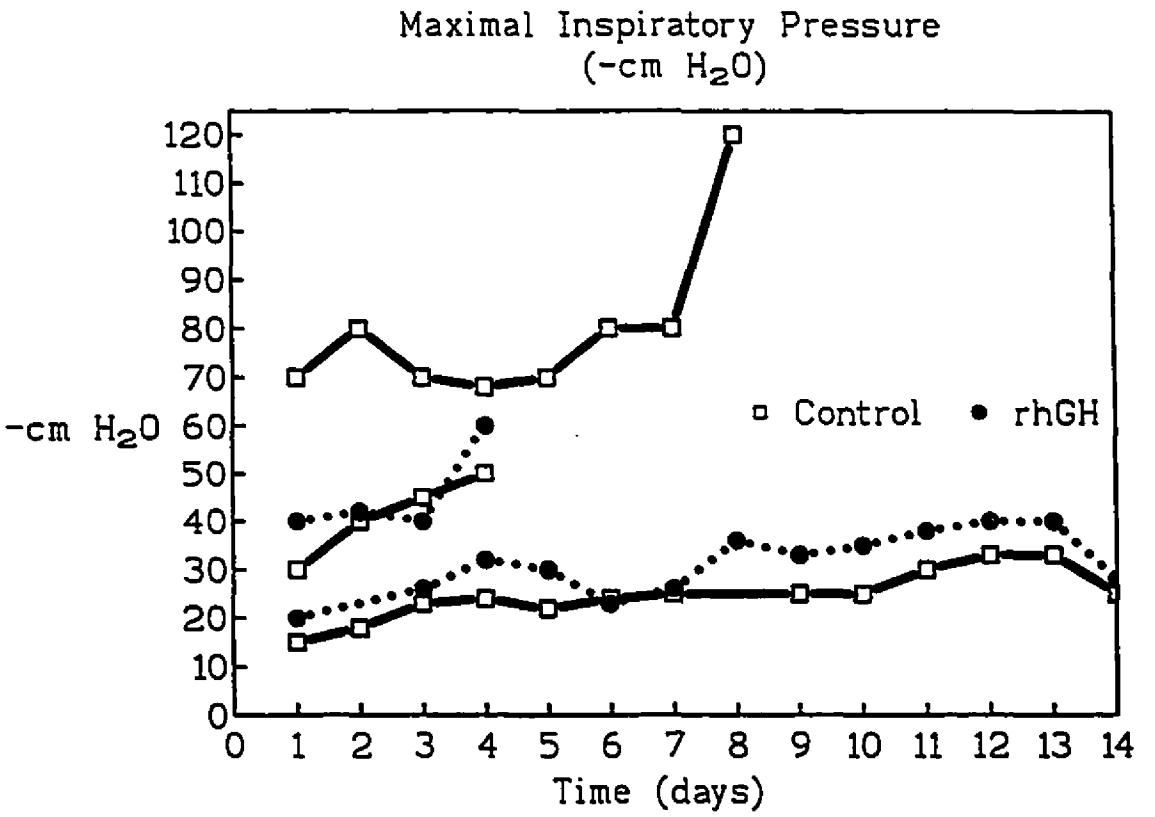

Figure 11. Daily maximal inspiratory pressures (PI_{max}) -cm H_2O for controls (❑) and rhGH-treated (●) subjects over the study period.

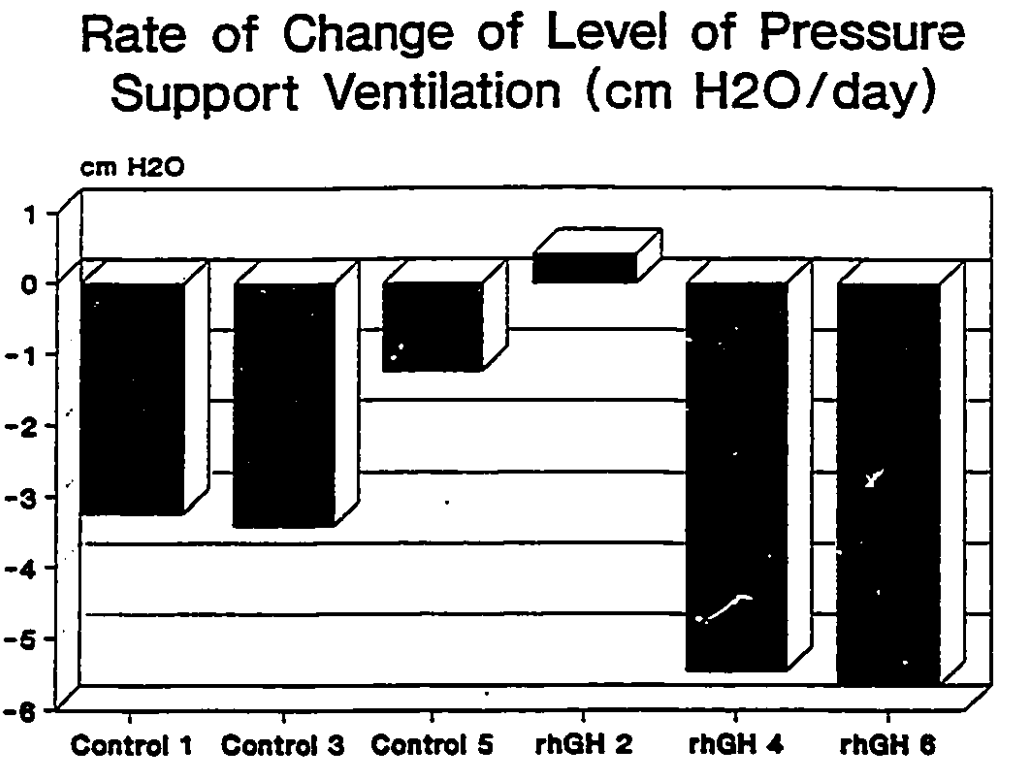

Figure 12: Rate of change of level of pressure support ventilation (-cm H_2O/day) for the control group (N=3) and the rhGH-treated group (N=3).

5.7.3 Time to Successful Weaning

The risks associated with prolonged mechanical ventilation make weaning patients an urgent concern. The number of days to wean for each patient is shown on Table 11. Mean time to successful weaning for the control group was 8.9±2.8 days as compared to 6.4±3.8 days for the treatment group. This difference was not statistically significant (p=0.635)

Given the observed difference in the days to weaning between the two groups of 2.4 days and the SD of 5.3 days, sample size calculation was done for a two-tailed t-test.

Setting the α and β at 0.05, a sample size of 300 (or 150 per group) subjects would be needed to find this data statistically significant.

5.7.4 Peripheral Muscle Strength

Hand dyanometry is a simple, non-invasive measure of peripheral muscle strength. All subjects agreed to this testing. A treatment group patient was not able to follow commands and therefore his data is excluded for analysis. Hand grip strength was measured at baseline and at the conclusion of the study. Only the results for the dominant hand are displayed on Figure 13.

The change in hand grip strength over the study period was determined for each subject. Over the study period, the change in hand grip strength for the control group was 22% for the control group and 37% for the two patients measured in the treatment group. A sample size calculation for a two-tailed t-test was conducted using difference in % change in hand grip strength between the two groups (15%) and a standard deviation (SD) of 24.8% observed in this study (212). Setting the α and β at 0.05, a sample size of 168 (84 per group) patients would required to detect a statistically significant difference.

TABLE 11: TIME UNTIL SUCCESSFUL WEANING (DAYS)

1. Control Group		2. Treatment Group	
Patient Number	Time	Patient Number	Time
1	8.09	2	14
3	4.46	4	3.23
5	14	6	2.08
Mean±SD	6.44±3.8	Mean±SD	8.85±2.78

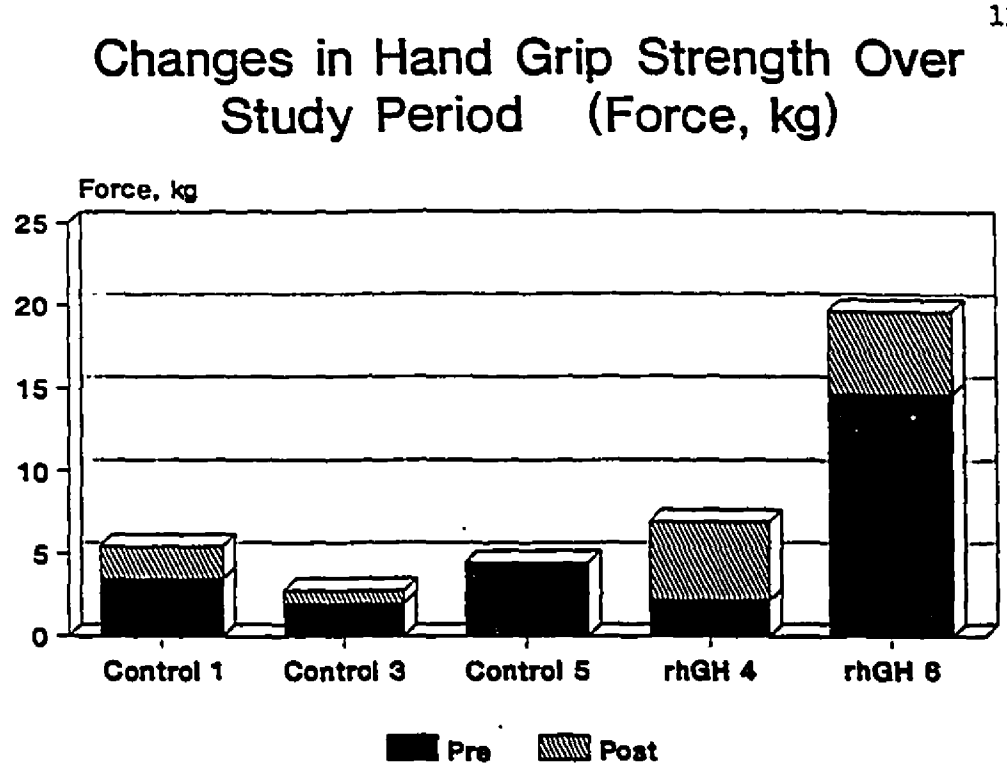

Figure 13: Changes in hand grip strength (kg) from baseline to post treatment for the control group (N=3) and the rhGH-treated group (N=2).

6. DISCUSSION

The main question addressed by this research was whether nutrition plays a role in prolonging respiratory failure. Specifically, it was hypothesized that nutritional depletion of the respiratory muscles leading to compromised respiratory muscle strength could be rate limiting in weaning patients from mechanical ventilation. To test this hypothesis a potent anabolic agent was used, pharmacologic doses of rhGH. Pharmacologic doses of rhGH elicit a strong anabolic response. By comparing patients in prolonged respiratory failure treated with rhGH to those receiving standard nutritional support alone, which stimulates a weak anabolic response at best, the role of nutrition in this disease state could be assessed.

6.1 Patient Recruitment

Many factors are known to prevent the weaning of patients from mechanical ventilation, including severe congestive heart failure, airway obstruction and sepsis among others. It would be unreasonable to think that in the face of these dominating factors that nutrition would be the rate limiting factor in weaning from mechanical ventilation. Therefore, only patients appearing clinically stable and in whom these other factors known to prolong respiratory failure were optimized, were selected for this study. During this phase of illness, it was hypothesized that depletion of the respiratory muscles if important, could emerge as an important factor that delays weaning from mechanical ventilation.

Over ten months 6% (102) of the patients admitted to the ICUs of the RVH and MCH had prolonged respiratory failure (n=1,723). Of the patients with prolonged respiratory failure, 94% did not meet the selection criteria for this study. These patients were excluded for being clinically unstable and/or factors known to limit weaning from mechanical ventilation were present (See Table 2). As a result the number of eligible patients was severely limited. The final sample size was six, with three in each group, representing only 6% of patients with prolonged

respiratory failure and 0.3% of total ICU admissions.

Subject recruitment was recognized as a potential problem prior to the onset of this study. However, it was the clinical impression of our collaborators in the Critical Care Division that most of the patients in prolonged respiratory failure were stable. The findings are this study clearly do not support this impression, since the overwhelming majority of patients in prolonged respiratory failure were unstable and/or factors known to limit weaning from mechanical ventilation were present. A retrospective analysis of patients admitted to the ICU to confirm the clinical impression of our collaborators may have alerted us to the forthcoming problems with patient recruitment.

6.2 Baseline Subject Characteristics

Despite the strict selection criteria, the baseline characteristics of the six enrolled patients were divergent. Given an adequate sample size, the use of an experimental design that involves randomization will promote the equal distribution of characteristics that could confound an observation. However, the small sample size in this study did not allow for proper randomization of characteristics. First, the respiratory muscle strength of subjects ranged from extreme weakness up to a level expected in normal, healthy adults, as indicated by maximal inspiratory pressures (PI_{max}), ranged from 15 to 70 -cm H_2O. Secondly, cortisol levels were measured to compare the degree of physiologic stress. Two patients were found to have elevated serum cortisol levels. The elevated serum cortisol levels suggested the presence of physiologic stress, although this was not apparent from their clinical condition or course in the ICU. Additionally, two patients in the control group were on glucocorticoid therapy, which is known to increase protein breakdown (126). The decision to enroll patients on glucocorticoid therapy was based on the findings that the pharmacologic doses of rhGH blunt the catabolic effects of glucocorticoids when administered simultaneously (93).

The presence of overt protein-energy malnutrition was not necessary to meet

the selection criteria for this study. If it had been, even fewer subjects would have met the inclusion criteria. It was hypothesized that the role of nutrition in prolonging respiratory failure was linked to the depletion of the respiratory muscles. Since most of the precipitating causes of acute respiratory failure are catabolic, we predicted that the mass and strength of the respiratory muscle would be adversely affected even in patients without overt malnutrition. Additionally, during mechanical ventilation a machine performs the work of breathing and disuse atrophy might ensue, which would further compromise the respiratory muscles. There was a significant difference in the weight of the two groups (p=0.05). One control subject had severely compromised energy stores (BMI=14) and one rhGH was obese (BMI=42).

Since obesity has an effect on GH and secretion the response of this patient may have been altered. Specifically, endogenous GH production is reduced to one-fourth that of the normal weight controls (6.7±1.7 vs. 27.6±9.3 ug/L. Secondly, the half life of endogenous GH is significantly shorter in the obese (11.7±1.6 minutes) when compared to normal weight controls (15.5 ± 0.81; p=0.01) (213). Since the amino acid sequence of rhGH is identical to that of endogenously produced GH the potency of this drug many have been diminished in the obese subject.

Baseline visceral protein stores were evaluated by serum concentrations of selected proteins; transferrin, prealbumin, and RBP. Normal transferrin levels range from 1.8 to 3.6 gm/L. Three patients, 2 controls and 1 rhGH treated patient, had baseline transferrin levels lower than normal. With a half life of 8 to 10 days, this may reflect inadequate intake before the initiation of this study's nutritional support protocol. All patients had normal prealbumin levels. One patient from each group had depressed plasma levels at baseline (0.25 gm/L for the control patient and 0.029 for a rhGH treated patient). The RBP results may have been influenced by non-nutritional factors because the half life of an RBP is 10-12 hours and all patients received full nutritional support for at least three days before the baseline measurements. As was seen with the RBP, these protein concentrations are

affected by many factors not related to changes in nutritonal status, such as liver function and hydration status (2,31).

The overall respiratory status of the six patients was evaluated by weaning trials before randomization to ensure that the two groups were well matched at baseline. These trials confirmed that all patients had baseline severe respiratory failure for patients failed in one second to six minutes.

The incidence of hypomagnesemia in ICU patients has been reported to be from 9.5% to as high as 65% (80-82). Magnesium has several roles in pulmonary function one of which is to inhibit vasoconstriction by competing with calcium. Serum magnesium levels were measured at baseline and then every 1-3 days and were within the normal range for every time ruling out hypomagnesemia as a confounding variable.

6.3 Confirmatory Variables

GH stimulates the synthesis and release of IGF-1 from the liver and other tissues. IGF-1 levels were measured at baseline and again at the conclusion of the study. At baseline the IGF-1 levels of the two groups were indistinguishable, however, by the end of the study the IGF-1 levels of the treatment group were significantly higher than those of the control group ($p=0.015$). The serum concentrations of the treatment group rose four and a half fold, consistent with the findings in other trials (162,197).

The anabolic effects of GH are believed to be mediated through IGF-1 (130,183). In previous studies, a rise in IGF-1 levels of this magnitude has been associated with the stimulation of a strong anabolic response, manifested by a significant increase in N retention (35,168,170). The average daily N balance data of the six enrolled patients is summarized on Figure 12. Despite the significant rise in IGF-1 levels, the mean average daily N balances of the treatment group are indistinguishable from those of the control group. This data give the impression that the anabolic response of the rhGH treated group was less than was expected

based on the findings of others. As has been previously mentioned pharmacologic doses of rhGH have improved N balances by 1-3 g N/day when compared to controls receiving the same nutritional support. But, because this data is so inadequate it is impossible to conclude that the N balance data is less than expected.

The N balance data for individual subjects is shown in Figure 11. The N balance data of the subjects on Day 1 varied greatly from -13.48 to 1.22 g N/day. Since all patients were on the nutritional support protocol at this time, the divergent Day 1 N balance data most likely reflects that these six patients were under varying degrees of physiologic stress that effect N balance (15). Also looking at the individual patient data on Figure, it becomes evident that rhGH 4, who had the most negative mean daily N balance, started out at with a N balance of -13.48 g N/day which rose to -2.68 g N/day 4 days later.

There are several conditions that may have confounded the N balance results. One is the inclusion of an obese patient in the rhGH-treated group. The IGF-1 levels of the obese patient rose over the study period from 0.39 u/mL to 0.75 u/ml representing a two fold increase. Whether or not obesity affected this patient's response to pharmacologic doses of rhGH, cannot be properly evaluated given the inadequate N balance data. However, the two fold increase in IGF-1 levels appears to be less than expected given the dose of rhGH administered along with adequate nutritional support. Secondly, the N balance data of the two patients in the control group may have been influenced by glucocorticoid administration during the study period (10 mg solumedrol, 30 mg prednisone). Since glucocorticoid therapy increases proteolysis (126,128), the N balance data of these two patients may have been adversely affected by this drug.

Hyperglycaemia and fluid retention, secondary to decreased sodium excretion, are well known side effects of pharmacologic doses of rhGH. In this study, blood glucose, fluid balance and urinary sodium excretion were measured to confirm rhGH had its expected physiologic effects. More importantly, because

hyperglycaemia and positive fluid balance can have potentially deleterious effects, these variables were monitored to ensure the safe administration of this drug. However, the concomitant administration of other drugs known to strongly affect blood glucose (insulin) and both fluid balance and sodium excretion (fursemide), the effects of rhGH on these variables cannot be isolated from the influence of these other drugs.

Figures 4, 5, and 6 depict the changes in serum protein concentrations from baseline to the conclusion of the study for all patients. From these figures it is evident that no clear pattern in change over the study period arises, illustrating the variability in the responses of the six patients. Therefore, there was no apparent effect on visceral protein stores.

6.4 Outcome Variables

Outcomes variables were measured to determine the effects of accelerated nutritional anabolism on respiratory parameters; respiratory muscle strength, level of ventilatory assistance required, and time until successful weaning; and on peripheral muscle strength.

Maximal inspiratory pressure (PI_{max}) is an important clinical measure of respiratory muscle strength, which was measured daily during this study. The individual patient data for daily PI_{max} are shown on Figure 11. A distinguishable difference between the PI_{max} data of the treatment and control group is not evident. The variable response of both patient groups to either pharmacologic doses of rhGH and/or nutritional support is illustrated by this figure. The PI_{max} of the two patients that did not wean during the study period hovered around 10 to 30 -cm H_2O throughout the study period. A PI_{max} of -30 cm H_2O or less is felt to predict weaning failure, which was the case of these two patients. The remaining 4 patients had stronger respiratory muscles (PI_{max} greater than 30 -cm H_2O) and were successfully weaned from mechanical ventilation.

To make comparisons regarding the degree of mechanical ventilatory

assistance required, all patients were on PSV. A higher level of PSV indicated higher needs for ventilatory assistance. The rate of change of level of PSV (cm H_2O/day) are shown on Figure 12. As with the other measured parameters, the response of patients is variable without a difference in the rate of change of level of PSV between the two groups being detectable. The smallest rate of change in leave of PSV required are seen in control patient 5 and rhGH-treated patient 2, the two patients who were not weaned. It had been hypothesized that the treatment group would wean faster from mechanical ventilation. However, when comparing the days to weaning in the treatment to control groups there is no apparent difference (See Table 11). One patient in both groups did not wean during the study period. The mean number of days to wean for the control group was 6.4±3.8 days as compared to 8.85±2.8 days in the control group. This difference was not statistically significant.

Peripheral muscle strength was measured by hand dynamometry. Patients receiving pharmacologic doses of rhGH after major gastrointestinal surgery have been reported to maintain their hand grip strength during the immediate postoperative period while untreated ones had a significant decrease in hand grip strength. We had hypothesized that in this more stable patient population we would seen an increase in hand grip strength in the treatment group while the control group would not. From baseline to post-treatment, the hand grip strength of the of the control group increased by 22%. The hand grip strength of two patients in the treatment group increased by 37%. Although this difference is not statistically significant does provide a hint that the 2 rhGH patients responded with an increase in effort or peripheral muscle strength.

7. Conclusions

Six percent of the patients admitted to the ICU of the RVH and MCH had prolonged respiratory failure. Of the patients in prolonged respiratory failure, 94% were excluded. These patients were excluded because factors that are well known

to limit weaning were present. In the face of these dominating factors, it would be unreasonable to think that nutrition would be the rate limiting factor in weaning from mechanical ventilation. Therefore, for this study patients were selected whose clinical course appeared to be optimized. Through these efforts to recruit potential subjects, we learned that the failure of the vast number of patients in prolonged respiratory failure to be promptly weaned from the ventilator can be attributed to well-recognized factors that would be expected to dominate their course.

Despite the strict selection criteria, the six patients enrolled were heterogenous. This was demonstrated by their divergent baseline characteristics (weight, PImax), clinical course, and variable response to pharmacologic doses of rhGH and/or nutritional support. In fact, we are not convinced that their clinical conditions had been sufficiently stabilized. This would account for some of the variability observed in their response to rhGH and/or nutritional support.

The research question this study addressed was whether nutrition plays a role in prolonging respiratory failure. Despite a significant rise in IGF-1 levels of the treatment group, the divergent baseline characteristics, the clinical complexity, and tremendous variability in their response to this intervention, coupled with the small sample size made it impossible to either rule in or rule out our hypothesis.

To assess the feasibility of conducting a large scale trial to look into the role of nutrition in prolonging respiratory failure, sample calculations for a two-tailed t-test were performed given the observed difference between the two groups and the standard deviations for N balance and the outcome variables. The sample size required to find significant differences ranged from 168 for sample size to 2,820 for level of pressure support ventilation. Taking into consideration the difficulties encountered with patient recruitment, such large sample size requirements may make testing of this hypothesis impractical.

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Appendix 1.

ROLE OF MALNUTRITION IN PROLONGED RESPIRATORY FAILURE: EFFECTS OF PHARMACOLOGIC DOSES OF GROWTH HORMONE TO ACCELERATE NUTRITIONAL REHABILITATION

INVESTIGATORS Dr. L. John Hoffer, Dr. Peter Goldberg, Dr. Sheldon Magder, Candace Hinze

BACKGROUND INFORMATION

Pharmacologic doses of human growth hormone when added to adequate nutritional support have been found to:

- Improve nitrogen balance and mineral retention
- Increase protein synthesis
- Improve respiratory muscle strength in spontaneously breathing COPD patients

HYPOTHESIS

Patients receiving adequate nutritional support plus growth hormone will have a greater anabolic response rate as compared to those receiving nutritional support alone. This will lead to improvements in respiratory muscle strength and endurance, therefore, facilitating weaning from mechanical ventilation.

SUBJECTS

- 12 in total
- Male or Female
- 18-65 years old
- Require mechanical ventilation for more than three days and have failed previous attempts to wean
- Hemodynamically stable

EXCLUDED FROM STUDY

- Sepsis
- Advanced cancer
- Severe congestive heart failure
- Renal and hepatic failure
- Insulin dependent Diabetes Mellitus

LENGTH OF STUDY

14 consecutive days

GROWTH HORMONE ADMINISTRATION

- The growth hormone and the placebo (normal saline) will appear visually identical.
- First dose will be administered by a physician and all subsequent doses by nursing
- Dose: 5 mg human growth hormone daily for entire length of study
- Route of administration: Subcutaneously
- Time: 09:00 a.m.

RESPIRATORY CARE

Mode of mechanical ventilation: Pressure support ventilation
All patients will be actively weaned per a standardized weaning protocol

NUTRITIONAL SUPPORT PROTOCOL

Nutritional assessment will be completed by study personnel. All patients will receive goal intake for duration of study
Enteral nutrition is preferred, but if patient cannot tolerate TPN will be started
Ready to hang Osmolite HN will be used so that intake can be measured precisely. **These containers must be saved, not discarded,** so that the amount administered can be calculated. Study personnel will pick them up daily.
If gastric residuals are discarded, record exact amount on the "Observation Chart" under output "Nasogastric" or "NG"
If patient is on **TPN, please save TPN bags and Intralipid bottles daily.**
Keep all nutritional containers at the bedside in basket marked "Malnutrition in Prolonged Respiratory Failure".

24 HOUR URINE COLLECTIONS

Purpose: To measure the amount of lean body mass (muscle) the patient is losing or retaining. Complete collection (all urine from 24 hour period) is necessary.
Procedure For every patient enroled in the study, a 24 hour complete urine collection will be completed daily for **all 14 days.** The 24 hour urine collections will begin at 07:00 a.m. and end at 06:59 a.m. the next day. At 06:59 a.m. all urine should be emptied into currently used collection bottle. After this all subsequent urine should be collected in the new day's bottle. Urine will be collected in 3 litre brown bottles. The completed 24 hour urine collection should be left at the bedside in basket marked "Malnutrition in Prolonged Respiratory Failure" and will be picked up that morning by study personnel.
Do not send to Biochemistry.

Documentation If any urine is lost, record the exact amount lost "Observation Chart" under output in a column headed "Wastage"

PROCEDURE FOR ADVERSE REACTION

Growth hormone can cause hyperglycaemia and mild fluid retention (in 2.5% of patients). Serum glucose and fluid balance will be monitored daily. Any concerns about possible side effects should be directed to Candace Hinze, McGill Nutrition Centre, 843-1665 or x5025. If an acute adverse reaction is suspected, contact attending physician.

Appendix 2.

WEANING PROTOCOL

Transition of Pressure Support Ventilation

1. If a patient is on any other mode than pressure support ventilation, switch to pressure support ventilation at the peak pressure developed on a tidal volume of 10 cc/kg and flow of 60 L/minute. PEEP should be set at 5 cm water and for the remainder of the weaning process.

2. Once on pressure support, decrease by 5 cm water every 60 minutes until patient "fails" (see below for definition of failure).

3. Increase pressure support by 5 cm water over level at which patient failed. Leave pressure support at this level until 6:00 a.m. the next day.

Nocturnal Ventilatory Support

1. "Rest" every night from 10:00 p.m. to 6:00 a.m. by increasing level of pressure support to the level required by the patient at the start of the weaning process (See #3 above).

Day 1 and all Subsequent Days

1. At 6:00 a.m. start off on lowest pressure support level tolerated on the previous day.

2. Attempt to decrease pressure support by 2 cm water at 2:00 and 18:00 until patient fails. Increase support to previously tolerated level if patient fails. Do not attempt do decrease pressure support for remainder of day after failure.

3. Extubate when patient has tolerated pressure support of 6 cm water for 5 continuous hours.

WEANING FAILURE WILL BE DEFINED AS ANY ONE OF THE FOLLOWING:

1. Respiratory rate of >30 bpm
2. Tidal volume of <5 ml/kg
3. PCO_2 change >10 mm Hg on ABG (to be checked 15-30 minutes after change in pressure support)
4. Desaturation (SaO_2 <90%)
5. A change in heart rate of 25% and a heart rate of 60 or>120 bpm
6. Systolic blood pressure increases or decreases by 25% of baseline
7. Agitation or distress

Appendix 3.

DEPARTMENT OF MEDICINE

ROYAL VICTORIA HOSPITAL
CONSENT FORM: HUMAN GROWTH HORMONE AND RESPIRATORY FAILURE STUDY

You are asked to be in a study to learn if injections of human growth hormone will improve the ability of your lungs to breathe on their own. If this treatment works you might get off the ventilator sooner. If you agree to participate, you will be given one injection of growth hormone each morning until you are able to breathe on your own, or for 21 days, whichever is shorter. There is a 50% chance the injection will contain growth hormone and a 50% chance it will be a placebo that contains no hormone. Neither you nor your nurses or doctors will know whether you received the drug or the placebo until the study has been completed.

Human growth hormone is a natural hormone produced by the body. Growth hormone is sold in pharmacies under prescription to treat diseases in which the body does not produce enough of its own. In this study, however, growth hormone will be given in a very large dose (5 mg per day) that is likely to increase the amount of muscles in your body. It is possible that the use of growth hormone, together with nutrition, will improve the muscular strength of your lungs and make it easier to breathe on your own, but this is not certain. We believe it is very unlikely growth hormone will cause you any harm, but it is possible. Known side effects of growth hormone include increased retention of water by the body, increased blood sugar, and joint pains. These effects do not occur often, and always disappear when the hormone treatment is stopped, but any of them could occur in your case. We will watch for these side effects. If they occur they will be corrected by treatment. If there is any evidence that the use of growth hormone is endangering your health the study will be stopped. If you develop any new illnesses or cannot be given nutrition at the same time as the growth hormone, the study will be stopped.

If you are included in the study your treatment will be the same as if you were being normally treated, except for the injections and for the need to take extra blood samples to measure the effects of the growth hormone treatment. The extra amount of blood taken will not be more than 4 ounces.

You may freely refuse to participate in this study without any effect on your regular treatment. Once in the study, you are free to change your mind and withdraw for any reason at all. All information obtained from this study will be confidential. You should satisfy yourself that all your questions about this study have been answered before you consent to participate. If you have any questions now or during the study you may speak with Dr. Peter Goldberg or Dr. Sheldon Magder.

I, (PRINT NAME) _____, consent to participate in the growth hormone study described here.

Dated at Montreal, this _____day of _____, 199____.

PARTICIPANT_____

WITNESS_____

WITNESS (PRINT NAME AND OCCUPATION)_____

FORMULAIRE DE CONSENTEMENT: ÉTUDE SUR L'HORMONE DE CROISSANCE ET L'INSUFFISANCE RESPIRATOIRE

Vous êtes invité(e) à participer à une étude visant à déterminer si des injections d'hormone de croissance peuvent améliorer votre autonomie respiratoire. Si ce traitement réussissait, le respirateur auquel vous êtes relié(e) pourrait être débranché plus rapidement. Si vous acceptez de participer à l'étude, on vous fera une injection d'hormone de croissance tous les matins jusqu'à ce que vous puissiez respirer par vous-même, ou pendant 21 jours, selon la plus rapprochée de ces échéances. Il y a une chance sur deux que l'injection contienne de l'hormone de croissance et donc une chance sur deux qu'elle consiste en un placebo ne contenant aucune hormone. Ni vous, ni le personnel infirmier ni les médecins ne saurez avant la fin de l'étude si vous avez reçu le médicament ou le placebo.

L'hormone de croissance humaine est une hormone naturelle produite par l'organisme. Ce médicament est actuellement vendu sur ordonnance dans les pharmacies; il sert à traiter les maladies où l'organisme est incapable de produire lui-même l'hormone de croissance. Dans cette étude, l'hormone de croissance sera administrée à des doses très fortes (5 mg par jour) susceptibles d'accroître le volume de vos muscles. Il est possible, mais non certain, que l'hormone de croissance et l'alimentation provoquent une augmentation de la force musculaire de votre cage thoracique et qu'il vous soit plus facile de respirer par vous-même. Nous croyons très peu probable que l'hormone de croissance vous fasse du tort, mais cette éventualité reste possible. On sait que l'hormone de croissance peut notamment provoquer une plus forte rétention d'eau dans l'organisme et une augmentation de la glycémie. Cet effets sont rares et disparaissent toujours lorsqu'on corrigera, s'il y a lieu, au moyen d'un traitement. On mettra fin à l'étude au moindre signe que l'administration de l'hormone de croissance menace votre santé. On interrompra également l'étude si vous êtes atteint(e) d'une autre maladie ou si l'on ne peut vous alimenter en même temps que l'on vous administre l'hormone de croissance.

Si vous participez à l'étude, vous recevrez un traitement qui sera identique au traitement normal, à ceci près que vous recevrez des injections et que nous devrons prélever des échantillons supplémentaires de sang afin de mesurer les effets du traitement à l'hormone de croissance. La quantité supplémentaire de sang ainsi prélevée sera faible.

Il vous est loisible de refuser de participer à cette étude sans que votre refus n'affecte les soins auxquels vous avez normalement droit. Une fois l'étude commencée, il vous sera possible de revenir sur votre décision et de mettre fin à votre participation pour quelque raison que ce soit. Toutes les données recueillies dans le cadre de cette étude seront confidentielles. Veuillez vous assurer qu'on répondu à toutes vos questions relativement à cette étude avant de donner votre consentement. Pour toute question, maintenant ou pendant l'étude, veuillez vous adresser au Docteur Peter Goldberg ou au Docteur Sheldon Magder.

JE SOUSSIGNÉ(E) (EN CARACTERES D'IMPRIMERIE)_____, accepte de participer à l'étude sur l'hormone de croissance décrite dans le présent formulaire.

Fait à Montreal, ce _____ jour de _____ 199___.

PARTICIPANT(E) _____

TÉMOIN _____

TÉMOIN _____

(NOM ET PROFESSION EN CARACTERES D'IMPRIMERIE)