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THE HYPERMETABOLISM OF TOTAL ACQUIRED LIPODYSTROPHIC DIABETES. --ETC(U)
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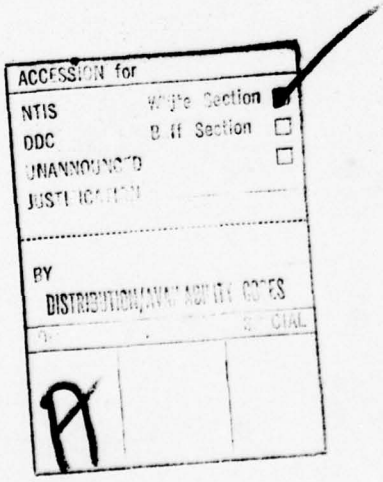
The spontaneous hypermetabolism of total acquired lipodystrophy is related to dietary intake and thyroid hormone metabolism. The elevated metabolic rate has been shown to fall with fasting and thyroidectomy and is restored with refeeding and physiologic replacement of thyroid hormones, respectively. Similar associations have been shown in normal volunteers in whom starvation is associated with a decrease in metabolic rate (MR) and 3,3',5-triiodothyronine (T_3) concentration and a rise in 3,3',5'-triiodothyronine (rT_3) concentration. Overfeeding has

produced the opposite effects. These changes may represent important physiologic adaptations and, in lipodystrophy, a response to the diminished capacity to store calories as fat. We have examined whether these associations in lipodystrophy are related to total caloric intake and the composition of the diet. An 18-year-old female with total acquired lipodystrophy and a 23-year-old normal female simultaneously took diets and supplements which varied in total caloric content and composition. 3000 cal/d and 1800 cal/d diets of identical composition (40% fat, 40% carbohydrate, 20% protein) were taken by the subjects for 4 and 6 days, respectively, to test whether metabolic rates and thyroid hormone concentrations would be higher with greater caloric intake. We then compared the effects of protein, fat or carbohydrate by adding 1200 cal/d of single dietary components to the 1800 cal/d diet for three-day intervals. The adaptation to starvation was assessed by a 72-h fast. Thyroid hormones and metabolic rates were measured several times at the conclusion of each dietary interval. The lipodystrophic subject's metabolic rates were uniformly higher than the normal value of 36.5 W/m^2 ± 10%. The mean resting metabolic rate during the initial 3000 cal/d was 63.7 W/m^2 which fell to 56.1 W/m^2 during the first 1800 cal/d dietary period. Metabolic rates were higher when supplements of protein (77.9 W/m^2), fat (62.8 W/m^2) or carbohydrate (57.8 W/m^2) were added to the 1800 cal/d diet. Dietary associated fluctuations in basal metabolic rates were less pronounced. Fasting was associated with a decline in metabolic rate to 46.5 W/m^2. T_3 concentrations in the lipodystrophic subject were within the nomral range and varied directly with caloric intake and metabolic rate. T_3 concentrations were relatively higher during the periods of higher caloric intake than during the unsupplemented 1800 cal/d intervals and the fast. The highest mean concentration of 168 ng/dl was found during the period of protein supplementation and the lowest of 98 ng/dl was during the three-day fast. ~~T_4~~ concentrations also varied with caloric intake but this was mostly due to changes in thyroid binding protein concentration or affinity. rT_3 concentrations were relatively unchanged throughout the study period. Metabolic rates in the control subject rose only with protein supplementation and fell during the three-day fast. Of the three thyroid hormones measured, only T_3 varied with caloric intake. A crude but more accurate method of expressing metabolic rate in lipodystrophy may be as Watt/kg estimated lean body mass. On this basis, the lipodystrophic subject has a more normal metabolic rate when she consumes less food. The elevation in metabolic rate seen with greater caloric intake may be a response to the inability to store excess calories as fat. It is concluded that the association between total caloric intake and metabolic rate in lipodystrophy may represent a form of dietary-induced thermogenesis. The role of thyroid hormones and in particular T_3 in this process is unclear. However, physiologic fluctuations in T_3 concentrations in response to the content and composition of the diet may be one of several mechanisms that regulate metabolic rate. Total acquired lipodystrophy may prove to be a useful model in the study of dietary-induced thermogenesis.

Thyroxine (T_4)

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.



(6) THE HYPERMETABOLISM OF TOTAL ACQUIRED LIPODYSTROPHIC DIABETES? EFFECT OF DIET ON THYROID HORMONE CONCENTRATIONS AND METABOLIC RATES,

Running Title: Hypermetabolism of total lipodystrophic diabetes

by

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ABSTRACT

The spontaneous hypermetabolism of total acquired lipodystrophy is related to dietary intake and thyroid hormone metabolism. The elevated metabolic rate has been shown to fall with fasting and thyroidectomy and is restored with refeeding and physiologic replacement of thyroid hormones, respectively. Similar associations have been shown in normal volunteers in whom starvation is associated with a decrease in metabolic rate (MR) and 3,3',5-triiodothyronine (T_3) concentration and a rise in 3,3',5'-triiodothyronine (rT_3) concentration. Overfeeding has produced the opposite effects. These changes may represent important physiologic adaptations and, in lipodystrophy, a response to the diminished capacity to store calories as fat.

We have examined whether these associations in lipodystrophy are related to total caloric intake and the composition of the diet. An 18-year-old female with total acquired lipodystrophy and a 23-year-old normal female simultaneously took diets and supplements which varied in total caloric content and composition. 3000 cal/d and 1800 cal/d diets of identical composition (40% fat, 40% carbohydrate, 20% protein) were taken by the subjects for 4 and 6 days, respectively, to test whether metabolic rates and thyroid hormone concentrations would be higher with greater caloric intake. We then compared the effects of protein, fat or carbohydrate by adding 1200 cal/d of single dietary components to the 1800 cal/d diet for three-day intervals. The adaptation to starvation was assessed by a 72-h fast. Thyroid hormones and metabolic rates were measured several times at the conclusion of each dietary interval.

The lipodystrophic subject's metabolic rates were uniformly higher than the normal value of 36.5 $W/m^2 \pm 10\%$. The mean resting metabolic rate

during the initial 3000 cal/d was 63.7 W/m^2 which fell to 56.1 W/m^2 during the first 1800 cal/d dietary period. Metabolic rates were higher when supplements of protein (77.9 W/m^2), fat (62.8 W/m^2) or carbohydrate (57.8 W/m^2) were added to the 1800 cal/d diet. Dietary associated fluctuations in basal metabolic rates were less pronounced. Fasting was associated with a decline in metabolic rate to 46.5 W/m^2.

T_3 concentrations in the lipodystrophic subject were within the normal range and varied directly with caloric intake and metabolic rate. T_3 concentrations were relatively higher during the periods of higher caloric intake than during the unsupplemented 1800 cal/d intervals and the fast. The highest mean concentration of 168 ng/dl was found during the period of protein supplementation and the lowest of 98 ng/dl was during the three-day fast. T_4 concentrations also varied with caloric intake but this was mostly due to changes in thyroid binding protein concentration or affinity. rT_3 concentrations were relatively unchanged throughout the study period.

Metabolic rates in the control subject rose only with protein supplementation and fell during the three-day fast. Of the three thyroid hormones measured, only T_3 varied with caloric intake.

A crude but more accurate method of expressing metabolic rate in lipodystrophy may be as Watt/kg estimated lean body mass. On this basis, the lipodystrophic subject has a more normal metabolic rate when she consumes less food. The elevation in metabolic rate seen with greater caloric intake may be a response to the inability to store excess calories as fat.

It is concluded that the association between total caloric intake and metabolic rate in lipodystrophy may represent a form of dietary-induced thermogenesis. The role of thyroid hormones and in particular T_3 in this

process is unclear. However, physiologic fluctuations in T_3 concentrations in response to the content and composition of the diet may be one of several mechanisms that regulate metabolic rate. Total acquired lipodystrophy may prove to be a useful model in the study of dietary-induced thermogenesis.

INTRODUCTION

The spontaneous hypermetabolism of total lipodystrophy has been the subject of several reports. In his classic description, Lawrence[1] found the basal metabolic rate 58-150% above normal in the absence of clinical signs of hyperthyroidism. Nevertheless, a role of thyroid hormones in maintaining the hypermetabolic state was implied when the patient underwent thyroidectomy. Signs of hypothyroidism developed, the metabolic rate fell and was then restored to elevated levels when replacement doses of 64-96 mg/d of dessicated thyroid were given. Rossini and co-workers[2] have shown that the metabolic rate was related to quantity and possibly the composition of diet. The subject in this study had basal metabolic rates of +75 to +100% above normal in the fed state which decreased to -12 to +17% after a three-day fast. A hypocaloric diet of only medium chain triglycerides also resulted in relatively lowered metabolic rates.

The apparent association of thyroid, dietary intake and metabolic rate is not unique to total acuired lipodystrophy. Portnoy and co-workers[3] showed that T_3 concentrations decreased and rT_3 increased in euthyroid obese volunteers during a three-week fast.[4] The associated decline in metabolic expenditure during starvation is well documented.[5-7] We have described opposite changes during overfeeding of normal volunteers.[8,9] T_3 concentrations increased, rT_3 concentrations decreased and basal metabolic rate was increased by the end of 2-4 weeks. These findings suggest that

even within the physiologic ranges, thyroid hormone may play a role in the day-to-day regulation of metabolic rate and a close association with dietary intake.

This report is an attempt to examine the relationship of the caloric content and composition of the diet to metabolic rate and the metabolism of thyroid hormones in a rare condition, marked by spontaneous hypermetabolism, insulin-resistant diabetes mellitus and the loss of subcutaneous fat.[10] We hypothesized that dietary related changes in metabolic rate and thyroid hormone concentrations would be more rapid and exaggerated than in normal subjects because of the decreased ability to store excess calories as fat. We have compared the effect of protein, fat or carbohydrate on metabolic rate and the metabolism of thyroid hormones by adding supplements of single components to a mixed-calorie diet. We have examined the question of whether diets of varying caloric content, but identical composition, affect the metabolic rate and thyroid hormone concentration proportional to caloric value. The association we have found between caloric intake, metabolic rate and T_3 concentrations in this study suggests, but does not prove, a role for T_3 in the day-to-day regulation of metabolic rate. Total acquired lipodystrophy is a useful model for the study of dietary-induced changes in thermogenesis and the role of thyroid hormones in the modulation of this process.

METHODS

The experimental subject of this study is a female Caucasian only-child whose birth weight was 3.8 kg after an uncomplicated full-term pregnancy and delivery. Early growth and development was apparently normal until age 6, when there was an unspecified weight loss and a striking change in the physiognomy (see Figure 1). She was referred to the care of Dr. David Brown

at the Albany Medical Center, Albany, New York where the diagnosis of total acquired lipodystrophy was made. There was absence of subcutaneous fat, minimal lymphadenopathy and hepatosplenomegaly. Hepatic enzymes were elevated and percutaneous liver biopsy revelaed fatty infiltration. Fasting blood sugar was 148 mg/dl and a two-hour postprandial blood glucose was 300 mg/dl. She was given 20 units of NPH insulin daily.

At the age of 14 years, she was first admitted to the Medical Center Hospital of Vermont in March Of 1974 for evaluation of the diabetes. She weighed 46.6 kg and was 157 cm tall. There had been oligomenorrhea and early pubertal changes were present. The typical features of lipodystrophy were apparent. In addition, the skin was coarse and thickened. There were psoriatic lesions over the extensor surfaces and partial vitiligo of the hands and feet. Lesions of acanthosis nigricans were along the base of the neck, axillae and groin. The liver was percussable over 14 cm in the mid-clavicular line and the spleen tip was palpable. There were no signs of diabetic retinopathy or neuropathy. Standard liver function tests were normal. The insulin dose was increased to 80 units NPH/d. Postprandial blood sugars were no lower than 230 mg/dl. The patient had an excessive appetite, which was apparent when the staff nurses found her eating other patients' meals in addition to her own.

At age 17, there were several spontaneous episodes of nausea, vomiting, dehydration, ketonemia and acidosis. On one occasion, when admitted to the Medical Center Hospital of Vermont, the arterial pH was 7.22, total venous CO_2 content 4 meq/l, beta-hydroxybutyrate 3.21 mM (normal 0.03 - 0.06)

and acetoacetate 0.71 mM (normal 0.01 - 0.04). She responded to treatment with electrolyte solutions and was given no additional insulin.

When first admitted to the Clinical Research Center at the Medical Center Hospital of Vermont in July, 1977, she was 18 years old, weighed 50.7 kg and was 160 cm tall. The liver dullness extended 12 cm to percussion and there was no lymphadenopathy, neuropathy, retinopathy, ascites or adnexal mass. The average 24-h creatinine excretion was 1.08 g/d (range: 0.86 - 1.77 g/d) and the creatinine clearance was 182 ml/min. Fasting serum triglycerides were 996 mg/dl, cholesterol 188 mg/dl and there was an increase in beta and pre-beta bands on lipoprotein electrophoresis. Postprandial blood glucoses were 318-594 mg/dl, insulin C-peptide assayed without separation of pro-insulin was 4.4 ng/ml (normal 0.9 - 4.4) fasting and 6.2 ng/ml 1 h post-prandial (kindly performed by Bioscience Laboratories, Van Nuys, CA). A test for serum antibodies to insulin receptors was performed by Dr. C.R. Kahn of Bethesda MD by the methods of Flier et al[11] and none were found. Body fat determined by the method of Buskirk and Goldman[12] from underwater weighings was calculated as less than 0, probably due to methodologic inaccuracies when applying the formula to subjects of such low total fat content.

When readmitted to the Clinical Research Center in September, 1977 at the age of 18, she was given the various diets shown in Figure 2. An open quadriceps muscle biopsy (kindly evaluated by Drs. Brian Little and Patricia Krupp, University of Vermont Departments of Pathology and Anatomy) showed occasional type I fibers with increased amounts of neutral (oil red O positive) lipid, associated with increased subsarcolemmal NADH-tetrazolium

reductase activity. No other pathological features were observed with either light or electron microscopy. Previously described[13] muscle fiber degeneration, mitochondrial aggregation and dilatation of the sarcoplasmic reticulum was not seen. Size, shape and numbers of mitochondria were normal. Muscle glycogen content in the fed state was 1.16 g/100 g wet tissue (normal 0.21 - 1.73) and muscle protein was 0.190 mg/mg wet tissue (normal 0.13 - 1.17).

The subject had taken no medications other than insulin during the three weeks prior to the study. Except during the fast, when insulin was withheld, she was given 30 units of NPH insulin subcutaneously at 0700 h and 5 units at 2300 h.

A 23-year-old normal female volunteer simultaneously underwent the same dietary program and testing protocol as the lipodystrophic subject. The control was 165 cm tall, weighed 66.5 kg and had a fat compartment of 24% determined by the underwater weight technique. Mean 24-h urinary creatinine excretion was 1.42.g.

The study had the approval of the Institutional Human Research Committee. Informed consent was obtained from the subject, control, the New York State Human Services Agency and the subject's legal guardian.

Meals were given at 0700, 1200 and 1800 h (Figure 2). The diet was free of caffeine-containing beverages. The diet on the first 4 days of the study contained 40% fat, 40% carbohydrate and 20% protein by calories and contained 3000 cal/d. On study days 5-26, an 1800 cal/d diet of the same composition was taken. 30% of the daily meal calories were each included in breakfast and lunch and the remainder at dinner.

Supplements of 1200 cal/d as protein, fat or carbohydrate were taken on study days 11-13, 17-19 and 24-26, respectively. The supplements were

divided and given with meals at 0900 h and 1400 h. The protein was given as hydrolyzed collagen with added tryptophan, EMF^{R} (Control Drug, Port Reading, NJ) and natural food sources, the fat as Lipomul^{R} (Upjohn Co., Kalamazoo, MI) and the carbohydrate as a mixture of Polycose^{R} (Ross Co., Columbus, OH) and Dextromaltose^{R} (Mead-Johnson, Evansville, IND).

On study days 27-29, the subject and control fasted and took only water.

In measuring the thermic effect of a previous diet or supplement, a liquid formula breakfast was given in place of the usual breakfast on the morning following each supplemented or unsupplemented dietary period. The formula contained 400 cal, 20% protein, 40% fat and 40% carbohydrate by calories.

Neither the subject nor the control had difficulty in tolerating any diet or supplement except the fat. On the third day of the fat supplemented period the lipodystrophic subject complained of mild abdominal distension, flatulence and fatigue. The rectal temperature was 38.1 C. She was, nevertheless, cooperative. Reliable collections of expired air were obtained. The symptoms subsided spontaneously the next day.

During the July 1977 admission, metabolic rates were determined by closed circuit analysis (Metabulator, Sanforn Co., Cambridge, MA).

During the September 1977 admission, non-exercising metabolic rates were tested in a "thermoneutral" room where the temperature was 24-26 C and the relative humidity 40-50%. The subject and control were supine and at rest. Expired air was collected and the volume determined in a Tissot spirometer. The oxygen and CO_2 content of the room and expired air were measured with a Beckman E2 and LB-1 (Beckman Instruments, Palo Alto, CA), respectively. The instruments were frequently calibrated against compressed gases which had previously been analyzed by the micro-Scholander technique.[14] Work of exercise was measured while walking on a level treadmill at 1.34 m/sec.

Testing began on the final afternoon of each dietary interval with a three-minute collection of expired air while resting and was followed by three 1-minute collections during a 15-minute period of exercise. After about 1 h of rest, two pre-supper resting determinations were made. The supper was given and metabolic rates were then tested every half hour for 4 h. The subject and control slept undisturbed in the "thermo-neutral" room. At 0600 h, they were aroused just enough for duplicate "basal" expired air collections to be made. They were allowed to leave the room briefly and returned for a pre-formula breakfast measurement of resting metabolic rate. The breakfast of liquid formula was taken, and resting collections were obtained every half h for 3½ h. Calculations of the metabolic rate were by the Weir method.[15]

Venopuncture was done at 2300 h on the final day of each diet or supplemented dietary period and again at 0700 h the next morning. The subject and control were supine for at least 1 h prior to blood collection to minimize hemoconcentration.[16] Analyses of T_3,[17] thyroxine (T_4)[18] and rT_3[19] concentrations were performed by modifications of previously published techniques using polyethylene glycol to separate bound from free hormones. Samples were analyzed in triplicate, non-specific binding for each sample in duplicate, and samples from the subject and control were each analyzed in a single assay to minimize inter-assay variability. The intra-assay variability for T_3, rT_3 and T_4 in the physiologic ranges was 1.7%, 4.3% and 2.8%, respectively. Antibodies for thyroid hormone assays were kindly provided by Dr. Albert Burger, Geneva, Switzerland. T_3 resin uptakes were determined with the Abbott Trisorb M^{125} Kit^R (Abbott Laboratories, North Chicago, IL).

Certain technical problems were encountered in the thyroid hormone assays and we have attempted to account for these difficulties. There were

wide variations in serum protein concentrations which reflect hemoconcentration or dilution. Since T_3 and T_4 are predominantly protein bound, it is necessary to be cognizant of these changes. Variations in T_4 concentrations were expressed as the free thyroxine index (% T_3 resin uptake $\div$ 100 X T_4 ug/dl). Variations in T_3 concentration due to hemoconcentration were accounted for by adjusting the T_3 relative to a constant serum protein content by the formula: "corrected" T_3 = T_3 ng/dl X $\left(\frac{8.0\ g/dl}{\text{measured serum protein, g/dl}}\right)$. Other errors in the measurement of thyroid hormone could be due to high concentrations of serum lipids. Lipid occupied from 2-5% of the serum space in the most severely lipemic samples (from the period of fat supplementation) and would dilute thyroid hormone concentrations. This souce of error is small and was neglected. Very high lipid levels did, however, interfere in the radioimmunoassays of thyroid hormone in samples from the lipodystrophic subject taken during the fat supplemented dietary period. The poorly formed and slippery precipitate of antibody bond thyroid which resulted on the addition of polyethylene glycol might result in spurious measurements of thyroid hormone concentrations in these samples.

Glucoses were determined by automated analysis (Technicon-SMAC, Terrytown, NY) using the glucose oxidase method. Cholesterol and triglycerides were measured by autoanalyzer suing routine procedures. High density lipoprotein cholesterol was determined by the method of Bachorik.[20] Serum protein concentrations were measured by the Biuret reaction.[21] Lipemic samples were cleared prior to analysis with ether extraction.

RESULTS

The consequences of allowing the lipodystrophic subject free access to food and a 68-h fast are shown in Table I. Some dietary restraint prior to

this first Clinical Research Center admission in July 1977 was evident by the rapidly worsening hyperlipidemia and hyperglycemia during hospital days 1-2 which improved with the 68-h fast. On refeeding with a diet identical to the one she had self-selected on the first two days of the admission, the metabolic rate, blood lipids and glucose returned toward previously elevated levels.

In order to study the effect of caloric intake and composition of the diet on the metabolic rate the subject was readmitted in September, 1977. She took the diets and supplements shown in Figure 2. A significant amount of food energy was lost as urinary glucose, and this was greatest during the initial 3000 cal/d diet and somewhat less while taking the protein and carbohydrate supplemented diets. Excretion of urinary glucose diminished during the three-day fast despite the abrupt withdrawal of insulin, and this reduction demonstrated the subject's ability to control gluconeogenesis during the fast. The weight was 48.8 to 47.4 kg during the various diets and supplemented dietary periods. Change in weight did not seem to correlate with measured fluid balance or caloric intake except during the three-day fast where the weight fell to 45.1 kg. Most of this weight loss was accounted for by fluid loss (data not shown).

Plasma triglyceride and glucose concentrations (Table 2) rose with increased caloric intake and fell to near normal values during the fast. Trigylceride concentrations were greatest during the period of supplementation with fat, and, along with the appearance of chylomicrons, demonstrate the subject's difficulty in storing and metabolizing dietary fat.

Metabolic rates measured on the final day and next morning of each dietary interval are shown in Table 3. The lipodystrophic subject's metabolic rates were uniformly higher than normal[22] when expressed as W/m^2 calculated body surface area. Only during the basal metabolic rate

determination following the third 1800 cal/d dietary interval does the metabolic rate fall just within the predicted range of 36.5 $\pm$ 3.7 Watt/m^2.

The metabolic rates were relatively higher when the subject took the initial 3000 cal/d mixed composition diet and each of the supplemental diets than they were during each of the 1800 cal/d dietary intervals. The association between caloric intake and metabolic rate is most evident in the mean resting determinations. The resting metabolic rates were consistently higher during each period of higher caloric ingestion than during the 1800 cal/d intervals and lowest during the fast. The pattern is less evident in the basal determinations of metabolic rate which followed a 16-h overnight fast and probably are subject to more variability than the resting determinations. In some instances, the effect of a diet or supplement may have diminished by the following morning.

Protein supplementation was clearly associated with the greatest increment in metabolic rate, despite greater excretion of urinary glucose during this interval than the periods of fat or carbohydrate supplementation. The resting determination of metabolic rate during the third day of the protein supplemented diet of 77.9 W/m^2 is 123% above the expected value. The highest basal determination of metabolic rate was also found on the morning after the period of protein supplementation and reflected the persistent effect of this supplemented diet. It is, however, puzzling that the evening meals supplemented with protein, fat or carbohydrate had about the same effect on the post-supper metabolic rate determinations. The additional effect of the so-called "specific dynamic action" of the supplemented suppers was minimal.

The adaptation to the fast is best seen in the mean resting metabolic rate of 46.5 W/m which is still 25% above the normal basal value. The basal determination measured on the final morning of the fast was higher than expected and may reflect the subject's complaint of restlessness during those collections.

The work of exercise, expressed as the increment above the basal measurement of metabolic rate, varied little and inconsistently with the diets and supplements. The lowest measurement was seen during the three-day fast where the subject had an unexpectedly high basal metabolic rate. This relatively low value for the work of exercise of 3.97 W/kg may reflect a spuriously elevated basal determiantion rather than a true decrement in the work of exercise.

The respiratory quotients (RQs) shown in Table 3 are generally within the expected range and show some variation with the time of day, exercise and the supplement taken. The RQs are generally lower during the basal collections than the afternoon resting values. The lowest ratios were observed during the priod of fat supplementation and the highest during carbohydrate supplementation. The subject adapted to the composition of the diet by using relatively more of the supplemented dietary component. It is of interest to compare the lipodystrophic subject's RQs at the conclusion of the three-day fast with those of the control subject's values shown in Table VI. The higher values of the lipodystrophic subject reflects generally a greater use of carbohydrate fuels.

Mean T_3 concentrations obtained at the conclusion of each dietary interval are shown in Table 4. Uncorrected T_3 concentrations were consistently higher during the periods of higher caloric intake than they were during the

unsupplemented 1800 cal/d diet intervals or after the fast. The highest value was seen during the period of protein supplementation, where the highest metabolic rates were also found. Correcting the T_3 concentrations for changes in serum protein content tended to diminish the magnitude of the fluctuations, and, in the case of the first two dietary periods, reversed the pattern seen in the uncorrected T_3 concentrations. Nevertheless, "corrected" T_3 concentrations were relatively higher during the periods of dietary supplementation than during each previous 1800 cal/d unsupplemented interval and lowest after the three-day fast. The highest mean "corrected" T_3 concentration was found during the period of protein supplementation.

T_4 concentrations also appeared to vary with the caloric intake and were greatest during the period of fat supplementation. The free thyroxine indices account for most of the fluctuation due to changes in thyroid binding proteins rather than a physiologic change in T_4 concentration. The relatively higher free thyroxine index seen during the period of fat supplementation may reflect problems introduced into the radioimmunoassay by the very high concentration of serum lipids during this dietary interval.

The rT_3 concentrations were relatively stable throughout the study period, except for a near doubling during the period of fat supplementation. Although this rise may reflect an increased production of rT_3, it may also reflect an effect of the lipemia in the radioimmunoassay. The expected rise in rT_3 concentrations with fasting was not seen despite the diminished concentration of T_3, suggesting that the production or clearance of these two hormones may be independent. 72-h of fasting may also have been insufficient to produce the expected rise in rT_3 concentrations.

The 23-year-old control subject who was closely matched in estimated lean body mass simultaneously underwent the same dietary and testing protocol as the lipodystrophic subject. Except for the measurements during the period of protein supplementation, the metabolic rates were within the normal range[22] of 41.3 $\pm$ 4.1 W/m^2 and did not vary with the caloric intake (Table 5). The mean resting metabolic rate of 59.7 W/m^2 during the period of protein supplementation was 42% greater than normal. Contrary to the response of the lipodystrophic subject, this effect did not persist the next morning as an elevation in the basal metabolic rate. The lowest resting metabolic rate was seen after the three-day fast, and, as had been the case with the lipodystrophic subject, the basal metabolic rate at the conclusion of the fast was unexpectedly high. The control subject also complained of restlessness.

Of the three thyroid hormones measured, only T_3 varied with caloric intake (Table 6). This is most evident in the "corrected" T_3 concentrations. The lowest T_3 value was observed at the termination of the three-day fast. Variations in T_4 concentrations were mainly explained by alterations in thyroid binding proteins as reflected in the relatively stable free thyroxine indices. The rT_3 concentrations, as expected, rose during the three-day fast.

DISCUSSION

The metabolic rates of this lipodystrophic subject are abnormally high and rise with increased caloric intake. However, at least two characteristics of total lipodystrophy could give an apparent elevation in the metabolic rate when it is expressed as energy consumed per calculated body surface area (W/m^2). The absence of subcutaneous fat causes a relative

decrease in the ratio of calculated surface area to lean body mass. Adipose tissue contributes relatively little to metabolic expenditure but usually adds 10-20% to the body surface area. It is also apparent by the Herculean appearance of the lipodystrophic subject that there is an absolute increase in muscle mass, and on this basis alone, energy consumption would be elevated. These factors would lead the investigator to find an increased metabolic rate as Watt/m^2, but would not indicate whether the subject's tissue consumes more energy than a comparable amount of normal tissue.

Comparison of the lipodystrophic subject with the control on the basis of energy consumption per kg of estimated lean body mass may provide a crude, but more accurate means of judging the relative rates of energy expenditure. The control subject's estimated lean body mass of 48 kg is compared with the lipodystrophic subject whose body weight of 48-49 kg was assumed to be entirely lean. This comparison is shown if Figure 3. It can be appreciated that, in each comparison, the lipodystrophic subject has a higher metabolic rate per kg estimated lean body mass. It should be noted, however, that the difference between the two subjects is much larger during the 3000 cal/d diet and each of the periods of supplementation than during the fast and each 1800 cal/d intervals where the difference is negligible.

The interpretation of this comparison is consistent with the hypothesis that the hypermetabolism of lipodystrophy is a result of a disorder in the ability to store excess calories. When the lipodystrophic subject is consuming normal or less than normal amounts, the metabolic rate per kg lean body mass is more normal. When excess calories are taken they are expended as heat in response to the inability to store energy in the form of fat. This may represent a true form of dietary-induced thermogenesis.

The mechanisms that regulate thermogenesis are speculative and a number of reviews of this subject are available.[23-26] Thyroid hormones and T_3 in particular may regulate metabolic expenditure by several mechanisms. Among them are increased numbers or activity of the membrane associated $Na^+ - K^+$ ATPase pumps,[27] increased sensitivity to catecholamines[28] or indirect stimulation of metabolic rate through accelerated protein synthesis.[29,30]

In this study, we have examined changes in thyroid hormone concentrations and found in the lipodystrophic subject that T_3 concentrations increased when there was increased caloric intake (Figure 4). The correlation between T_3 concentrations and metabolic rates is significant ($r = 0.92$ $p < 0.005$), but this does not prove that physiologic fluctuations in T_3 concentrations alter the rate of energy expenditure. T_3 concentrations may simply rise and fall in concert with dietary intake and have no role in the regulation of metabolic rate.

It is noteworthy that protein supplementation was associated with the greatest rise in metabolic rates in both subjects. In a careful study of normal male volunteers, Swift et al.[31] also found a significant increase in the metabolic rate when the protein content of equicaloric diets was changed from 34 g/d to 122 g/d. We have shown that 14 days of overfeeding with 496 cal/d of protein in normal male volunteers resulted in a 17% increase in the basal metabolic rates.[32] Significant but less marked increases in metabolic expenditure were seen with fat and carbohydrate overfeeding.

The mechanisms by which protein increases the metabolic rate is unclear. Increased blood glucose concentrations and glucosuria in the lipodystrophic subject suggests that the cost of accelerated gluconeogenesis contributed to the increase in rate of energy expenditure. Cissik[33] has pointed out that at least some of the protein-stimulated increase in metabolic rate may be

spurious when measured by indirect calorimetry. Endogenous nitrogen production from gut flora could dilute expired oxygen and cause up to a 13% overestimation of the metabolic rate. Swift in his study,[31] however, observed the increase in the protein-stimulated metabolic rate both by direct and indirect calorimetry. Even if this source of error exists, it would not explain the increment in the metabolic rates we observed in both the lipodystrophic subject and the control.

The period of protein supplementation was preceded by the longest interval of the relatively hypocaloric 1800 cal/d diet. It is possible that the period of protein supplementation was analogous, in an accelerated form, to the hypermetabolic response observed in the refeeding of malnourished children. Brooke and Ashworth,[34] however, described this phenomena not as an increment in resting metabolic rate but in the postprandial effect of a meal on the metabolic rate. Because the effect of protein in our study was seen both in the resting and basal metabolic rates and not in the effect of the meal, it is less likely that a refeeding phenomena was being observed.

This study may have some relevance to the dietary treatment of total acquired lipodystrophy. Since metabolic abnormalities were worsened with increased caloric intake regardless of the composition of the diet, it would be prudent to advise limitation of total caloric intake. It is difficult to set an ideal level, since the metabolic expenditure seems to parallel changes in intake. Small, frequent feedings would probably be helpful, since storage capacity for unused calories is so limited. And, finally, excess dietary fat is poorly handled and should be avoided.

There are inherent difficulties in the study of this rare disease and problems in drawing conclusions from the behavior of a single patient. Further study of this bizarre and unfortunate condition may increase our knowledge of thermogenesis and the physiologic mechanisms that regulate it.

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TABLE 1
Summary of July 1977 Admission

Hospital Day	1	2	3	4	5	6
Total Calories (cal/d)	5622	2558*	0	0	5622	2429
Urinary glucose (g/d)	277	364	21	1.2	158	-
Calories retained	4514	1102	0	0	4990	-
Urinary ketones	moderate	moderate	neg.-small	large	small	moderate
Serum ketones	absent	absent	absent	absent	absent	absent
Fasting cholesterol (mg/dl)	188	330	-	200	196	175
Fasting triglycerides (mg/dl)	996	2490	-	720	391	1090
Metabolic rate 0700 h	>100	55	55	32	20	62
(% above normal) 1900 h	-	>100	33	28	30	-

TABLE 2

Serum lipids and glucose, lipodystrophic subject

	Mixed 3000 cal/d	1800 CAL/D					Fast
			+protein		+fat	+CHO	
Serum glucose (mg/dl)	352	295	318	250	299	207	322	109
Cholesterol (mg/dl)	181	169	176	152	178	112	133	152
Triglycerides (mg/dl)	648	335	441	380	1290	389	520	185
HDL Cholesterol (mg/dl)	19	18	22	16	13	17	20	

TABLE 3
Metabolic rates and RQ's: Lipodystrophic subject

	Mixed 3000 cal/d	1800 CAL/D DIET						Fast
			+protein		+fat		+CHO	
Resting MR (W/m^2)	63.7	56.1	77.9	54.6	62.8	54.5	57.8	46.5
Exercise MR (W/kg)	4.86	4.37	4.71	4.43	4.66	4.80	4.43	3.97
Pre-supper MR (W/m^2)	61.5	55.0	77.5	52.0	61.3	54.7	58.7	50.0
Post-supper MR (W/m^2)	70.1	62.2	80.7	58.9	64.1	60.6	57.3	-
Basal MR (W/m^2)	49.0	45.2	65.9	49.5	40.7	38.1	49.5	45.7
Resting RQ	.749	.790	.835	.808	.730	.784	.861	.766
Exercise RQ	.848	.810	.874	.886	.772	.887	.917	.844
Basal RQ	.797	.794	.798	.811	.700	.775	.841	.796

TABLE 4
Thyroid hormone concentrations; Lipodystrophic subject

	Mixed 3000 cal/d	1800 CAL/D						Fast
			+protein		+fat		+CHO	
Total T3 (ng/dl)	137	121	168	103	150	108	138	98
Corrected T3 (ng/dl per 8g/dl serum protein)	125	130	152	106	130	123	139	104
Reverse T3 (ng/dl)	31	29	28	25	48	28	23	29
T3 resin uptake (%)	28	29	26	31	31	33	31	31
Total T4 (ug/dl)	6.2	5.5	6.2	5.6	8.4	6.0	6.5	5.9
Free Thyroxine index	1.7	1.6	1.7	1.7	2.6	2.0	2.0	1.8

TABLE 5
Metabolic rates and respiratory quotients: control subject

	Mixed 3000 cal/d	1800 CAL/D						Fast
			+protein		+fat		+CHO	
Resting MR (W/m^2)	40.6	45.5	59.7	42.6	42.9	44.3	45.6	39.3
Exercise MR (W/kg)	3.22	3.50	3.72	3.46	3.39	3.50	3.16	3.28
Pre-supper MR (W/m^2)	40.6	46.2	58.5	43.5	42.8	44.3	44.7	37.1
Post-supper MR (W/m^2)	37.2	58.7	62.2	46.0	51.8	47.8	57.7	45.1
Basal MR (W/m^2)	33.1	37.1	42.3	37.5	42.1	38.3	40.1	46.4
Resting RQ	.840	.820	.825	.790	.740	.790	.823	.731
Exercise RQ	.862	.813	.888	.882	.831	.871	.908	.686
Basal RQ	.870	.785	.848	.768	.795	.784	.855	.762

TABLE 6
Thyroid hormone concentrations: control subject

	Mixed 3000 cal/d	1800 CAL/D					Fast
			+protein		+fat	+CHO	
Total T3 (ng/dl)	117	93	122	103	106	124	75
Corrected T3 (ng/dl per 8 g/dl serum protein)	108	88	107	100	115	105	117	70
Reverse T3 (ng/dl)	19	19	20	18	17	28	22	38
T3 resin uptake (%)	30	32	29	32	33	32	30	31
Total T4 (ug/dl)	4.8	4.3	4.5	4.3	4.3	4.2	4.7	5.1
Free Thyroxine index	1.4	1.4	1.3	1.4	1.4	1.4	1.4	1.6

LEGENDS

Figure 1: Photographs of the lipodystrophic subject: Age 5 years, before the development of lipodystrophy (upper right) and shortly after the marked change in appearance at age 6 years (lower right, upper left) when the striking loss of fat, hepatomegaly and hypermuscularity became apparent. The subject at age 18 is shown in the lower left.

Figure 2: Dietary protocol and caloric balance for the lipodystrophic subject during the September 1977 admission. Sequence of diets and supplements is shown at the top. Line graph represents the lipodystrophic subject's weight on the final day of each dietary interval. Bar graphs show the total daily caloric intake and composition of the diet during each of the intervals. Arrows to the right of each bar graph represent the total daily caloric retention of the lipodystrophic subject (total calories consumed minus calories lost as fecal fat and urinary glucose).

Figure 3: Comparison of the control and lipodystrophic subject on the basis of Watt/kg estimated lean body mass. Note that the difference between the subjects is greatest during the periods of greater caloric intake.

Figure 4: T3 concentrations and metabolic rates for the lipodystrophic subject during each of the dietary intervals. There is a significant correlation.

Table 1: Summary of July 1977 admission when the lipodystrophic subject was allowed free access to food during the first 1½ d. A total caloric fast followed before the subject was refed.

Table 2 : Summary of serum lipids and glucose in the lipodystrophic subject during the various diets and supplements taken in September, 1977. Values are the mean of two determinations from the final 12 hours of each dietary interval.

Table 3 : Summary of metabolic rates and respiratory quotients of the lipodystrophic subject. Resting metabolic rates are the means of three afternoon determinations obtained during the final day of each dietary interval. Exercise metabolic rate is the mean of three determinations and expressed as an increment above the basal metabolic rate from the same study day. Pre-supper metabolic rates are the means of two determinations. Post-supper metabolic rates are the means of three determinations taken 30, 60 and 90 minutes after the completion of the meal. Basal metabolic rate is the lowest of two determinations. RQ's are the means of the same measurements used in the respective metabolic rate determinations.

Table 4 : Summary of thyroid hormone measurements of the lipodystrophic subject. Values are the means of two samples, one drawn at 2300 h on the final evening of each dietary interval and another from 0700 h the following morning.

Table 5: Summary of metabolic rates and RQ's in the control subject. See legend in table 3 for explanation.

Table 6 : Summary of thyroid hormone measurements of the control subject. Values are the mean of two samples, one drawn at 2300 h on the final evening of each dietary interval and another from 0700 h the following morning.

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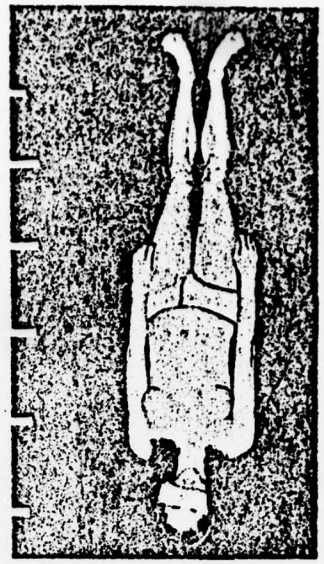
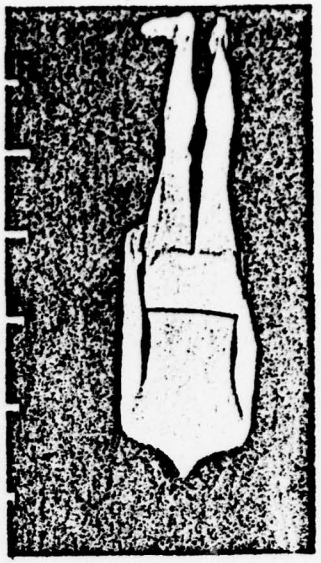
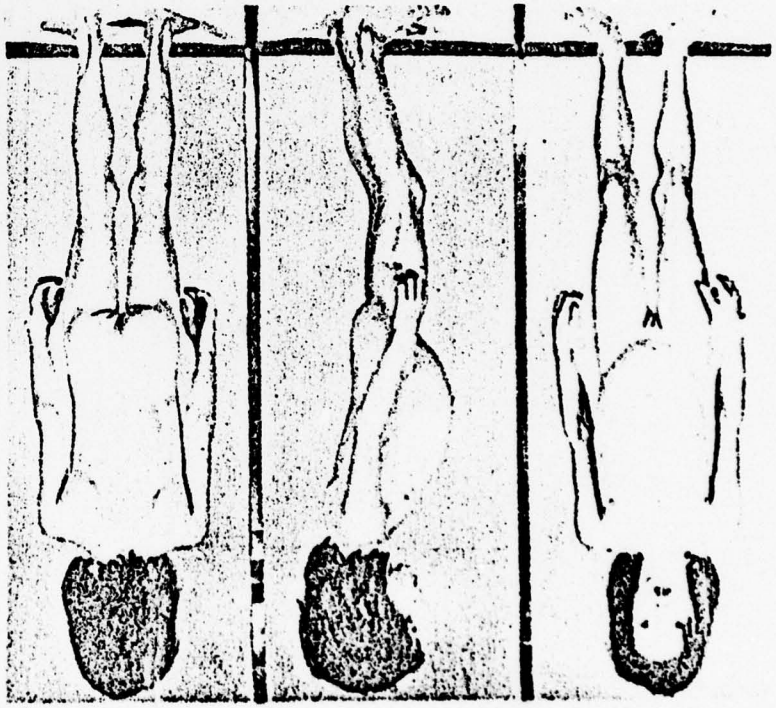
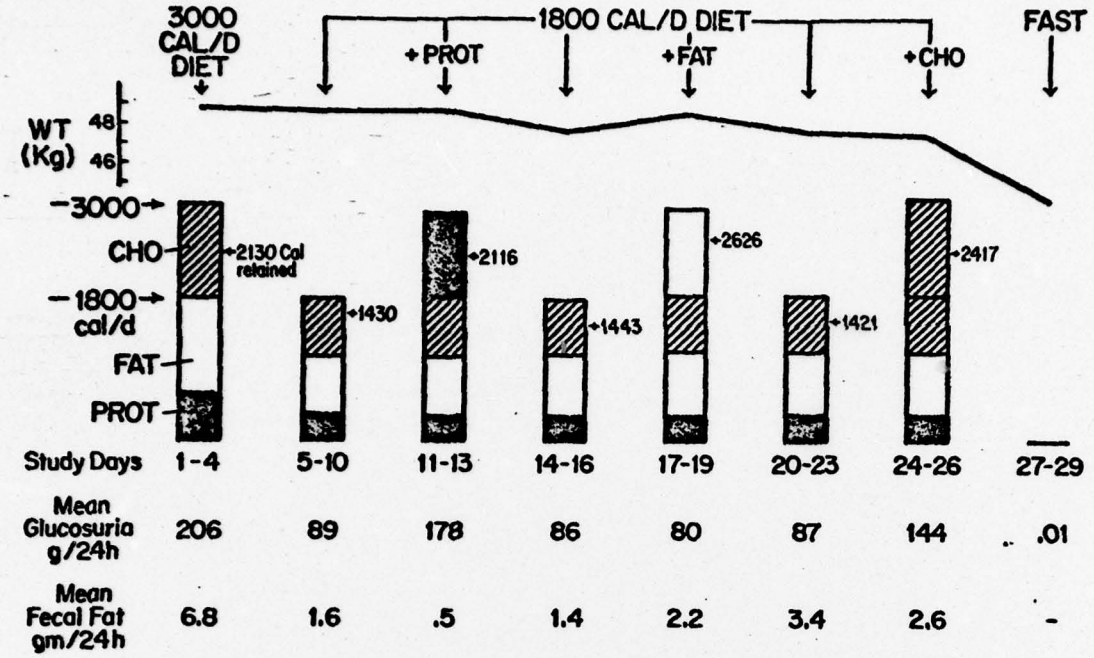
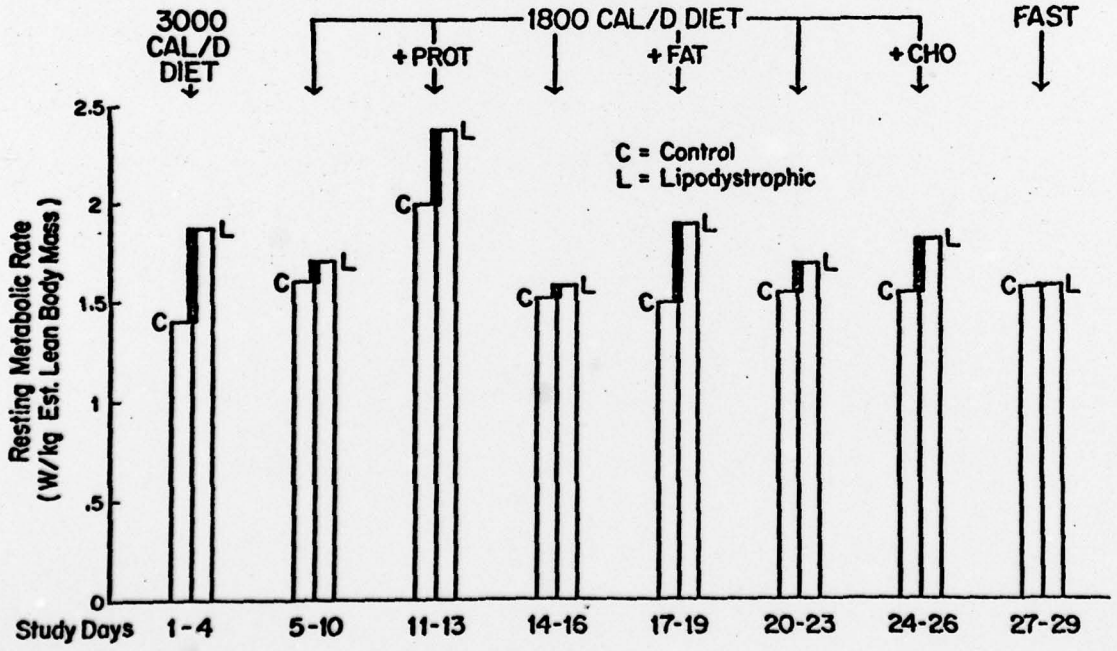


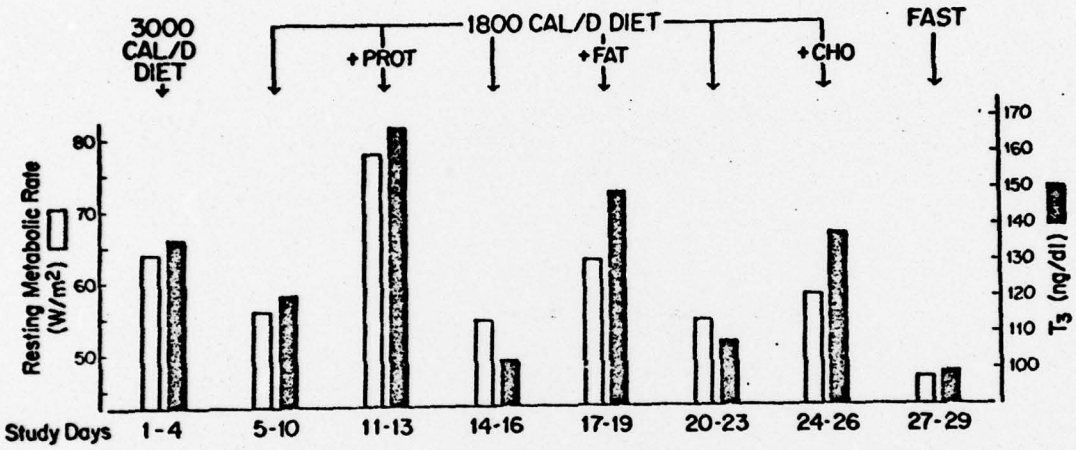






Study Days	1-4	5-10	11-13	14-16	17-19	20-23	24-26	27-29
Mean Glucosuria g/24h	206	89	178	86	80	87	144	.01
Mean Fecal Fat gm/24h	6.8	1.6	.5	1.4	2.2	3.4	2.6	-




3000 CAL/D DIET
1800 CAL/D DIET
+PROT
+FAT
+CHO
FAST
Resting Metabolic Rate (W/m²)
80
70
60
50
170
160
150
140
130
120
110
100
T3 (ng/dl)
Study Days
1-4
5-10
11-13
14-16
17-19
20-23
24-26
27-29