Impact of body fat mass and percent fat on metabolic rate and thermogenesis in men

KAREN R. SEGAL, IMELDA LACAYANGA, ANDREA DUNAIF, BERNARD GUTIN, AND F. XAVIER PI-SUNYER
Division of Pediatric Cardiology, Department of Pediatrics, Mount Sinai School of Medicine, New York 10029; and Department of Medicine, College of Physicians and Surgeons, Columbia University at St. Luke's-Roosevelt Hospital Center, New York, New York 10025

SEGAL, KAREN R., IMELDA LACAYANGA, ANDREA DUNAIF, BERNARD GUTIN, AND F. XAVIER PI-SUNYER. *Impact of body fat mass and percent fat on metabolic rate and thermogenesis in men.* Am. J. Physiol. 256 (Endocrinol. Metab. 19): E573–E579, 1989.—To clarify further the independent relationships of body composition parameters to energy expenditure, resting metabolic rate (RMR) and postprandial thermogenesis were studied in four groups who were matched for absolute fat mass (*study 1*) and relative fatness (*study 2*). In *study 1*, five lean [*group A*, 15.4 ± 0.6% (±SE) body fat] and five obese men (*group B*, 25.0 ± 0.9% fat) were matched on body fat mass (13.0 ± 0.9 vs. 14.4 ± 0.8 kg, respectively). Fat-free mass (FFM) and total weight were greater for *group A* than *B*. RMR was measured for 3 h in the fasted state and after a 720-kcal mixed meal. RMR was greater for *group A* than *B* (1.38 ± 0.08 vs. 1.14 ± 0.04 kcal/min, $P < 0.05$). The thermic effect of food, calculated as 3 h postprandial minus fasting RMR, was greater for *group A* than *B* (65 ± 6 vs. 23 ± 9 kcal/3 h; $P < 0.05$). In *study 2*, two groups ($n = 6$ men/group) were matched for percent body fat (33 ± 1% fat for both) but differed in lean, fat, and total weights: 50.8 ± 3.1 kg FFM for the lighter (*group C*) vs. 68.0 ± 2.8 kg FFM for the heavier (*group D*) group, $P < 0.05$. RMR was lower for *group C* than *D* (1.17 ± 0.06 vs. 1.33 ± 0.04 kcal/min, $P < 0.05$), but the thermic effect of food was not significantly different (31 ± 3 vs. 20 ± 6 kcal/3 h). After adjustment for differences in FFM among the four groups, no significant differences in RMR were observed. These results demonstrate that the putative impaired thermogenesis in obesity is specifically a function of relative fatness rather than fat mass and confirm the idea that RMR is determined by FFM and is not independently related to obesity.

obesity; energy expenditure; thermic effect of food; fat-free mass; oxygen consumption

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THE POSSIBILITY that a defect in energy metabolism underlies some human obesity has received considerable investigative attention. A number of studies have demonstrated an association between obesity and impaired postprandial thermogenesis, which is a blunted increase in energy expenditure in response to infused or ingested nutrients (14, 15, 27). However, other investigations have not observed any differences in thermogenesis between lean and obese individuals (5, 7, 25). The importance of defective thermogenesis in obesity has been questioned because absolute energy expenditure at rest and under a variety of conditions is greater in obese than nonobese subjects (2) and because a defect in the postprandial thermogenic compartment of total energy expenditure is not great enough to compensate for the generally higher metabolic rate of the obese (13). As well as having more body fat, obese individuals usually have more fat-free mass (FFM) and greater total body weight (8). The intercorrelations among body composition parameters (8) make it difficult to discern the determinants and significance of blunted thermic responses in obese compared with lean people. Thus the existence and significance of a defect in energy expenditure in obesity is a matter of considerable controversy.

The colinearity of body weight, FFM, and body fat mass poses a problem in human obesity research regarding the impact of individual body composition compartments on metabolism. One approach to the investigation of the determinants of energy expenditure is to study sufficient numbers of subjects who vary widely with respect to energy expenditure and body composition and apply multiple regression analyses to determine the individual relationships of fat mass and lean mass to energy expenditure. However, the interpretation of such data is difficult, owing to the problems associated with interrelated independent variables, as discussed by Pedhazur (19). Another approach is to make use of experimental models in which the naturally occurring intercorrelations among body composition compartments are uncoupled. We have previously shown that, when lean and obese men are matched with respect to total body weight such that the lean men were overweight but overly muscular, thermogenesis is blunted in the obese (26). In another investigation, we matched lean and obese groups with respect to their FFM and found that, whereas fasting resting metabolic rate (RMR) was similar for the two groups, the thermic effect of a meal was significantly lower in the obese than the lean men (24). Although the results of these studies indicated that neither body weight per se nor FFM per se was independently associated with a defect in thermogenesis, it still remained unclear whether the capacity for thermogenesis is negatively associated with body fat mass itself or whether it is qualitatively related to the obese state per se, regardless of absolute fat weight.

The objective of the present studies was to clarify further the independent relationships of body composi-

tion parameters to thermogenesis by imposing a model in which parameters of body fat (fat mass and percent fat) were controlled experimentally; lean and obese men matched with respect to absolute fat mass were compared (*study 1*), and two groups of obese men of similar percent fat and degree of obesity but significantly different absolute body fat mass were compared (*study 2*).

METHODS

Subjects

Study 1. Five lean (*group A*) and five obese men (*group B*) between the ages of 20 and 35 participated in this study. The two groups were matched with respect to age and absolute body fat mass. Body composition was determined by underwater weighing (see below). The lean men were <16% body fat, with no personal or family history of obesity, and the obese men were >24% body fat. All of the subjects were healthy with no personal or family history of diabetes mellitus, or other metabolic disease, or cardiovascular disease. An oral glucose tolerance test (OGTT) was administered (see below) to ensure that all subjects were nondiabetic and had normal glucose tolerance, according to the criteria of the National Diabetes Data Group (17). The men were nonsmokers and were not taking any medications. Highly aerobically trained men or men who exercised regularly were not accepted into the study to eliminate possible confounding due to differences between the two groups in level of cardiorespiratory fitness. All subjects were weight stable at the time of the study with no more than a 2-kg weight loss or gain over the 6 mo prior to the study. The subjects consumed a weight maintenance diet containing at least 250 g carbohydrate/day several days prior to and throughout the duration of their participation in the study. Body weight was measured on each test day to confirm weight maintenance.

Study 2. Two groups of six men were recruited who were matched with respect to percent body fat but differed significantly in absolute body fat mass. The groups were similar in body composition and degree of obesity but differed with regard to total body weight, body fat mass, and FFM; i.e., although the two groups had similar proportional body composition, one group (*group C*) weighed less and had less fat mass and FFM than the other group (*group D*).

The same criteria as those described above for *study 1* for acceptance into this study were applied. The written informed consent of all subjects was obtained, and the protocol was approved by the Institutional Review Board of the Mount Sinai School of Medicine.

Densitometry

Body fat content and FFM were determined by densitometry. The subjects were tested in the morning after a 12-h fast. Body density was determined by hydrostatic weighing in a stainless steel tank in which a swing seat was suspended from a Chatillon 15-kg scale. The subjects submerged beneath the surface of the water while expiring maximally and remained as motionless as possible at the point of maximal expiration for roughly 5 s while underwater weight was recorded. After several practice trials to familiarize the subjects with the test procedure, 10 trials were performed. The estimated underwater weight was the highest value that was reproduced three times (1). Residual lung volume was estimated by means of the closed-circuit O_2 dilution method of Wilmore (32), with use of a 9-liter spirometer (Warren E. Collins, Braintree, MA) and a Med-Science nitrogen analyzer (Fiske Med-Science, St. Louis, MO). Two trials were performed while the subjects assumed a sitting position that duplicated body position in the tank during underwater weighing. Body density was calculated from the formula of Goldman and Buskirk (10), and percent body fat was derived from body density by use of the Siri equation (28): percent body fat equals 4.95/density minus 4.5. FFM is the difference between total body weight and fat weight, where fat weight equals total body weight times percent body fat. Body fat mass is the difference between total body weight and FFM.

OGTT

An OGTT was performed after an overnight (12 h) fast. After a fasting blood sample was drawn from an antecubital vein, a 75-g glucose load (Koladex, Custom Laboratories, Baltimore, MD) was given, and venous blood samples were drawn at 30-min intervals for 2 h. The plasma was separated and analyzed for glucose and insulin. A Beckman glucose analyzer (Beckman Instruments, Fullerton, CA) was used for measuring plasma glucose (12). Plasma insulin was measured by radioimmunoassay with charcoal absorption with use of a human insulin standard (11). The integrated areas under the glucose and insulin curves were calculated.

Graded Exercise Test

Maximal [maximum O_2 uptake ($\dot{V}O_{2\,max}$)] and submaximal aerobic fitness were determined by a continuous multistage exercise test on a Monark cycle ergometer (Monark-Crescent AB, Varbeg, Sweden). Prior to the test, the subjects were familiarized with cycling on an ergometer at a constant pedaling rate and to breathing through the apparatus used for metabolic measurements. The subjects began cycling at a rate of 50 rpm with zero external resistance (unloaded cycling). A metronome was used to assist the subject in maintaining the proper pedaling rate. The work rate was increased in 25-W increments every 2 min until volitional exhaustion was reached and the subject refused to continue despite vocal encouragement or until he was unable to maintain the pedaling rate. Ventilatory measurements were made continuously by open-circuit respirometry with use of a Sensormedics Horizon metabolic measurement cart (Sensormedics, Anaheim, CA), which includes a turbine volume transducer, a Beckman OM-11 polarographic O_2 analyzer, and a Beckman LB-2 nondispersive infrared CO_2 analyzer. The subjects breathed through a Hans Rudolf nonrebreathing valve (Hans Rudolph, Kansas City, MO) and used a mouthpiece and noseclips. The gas analyzers were calibrated before and after each test with 100% nitrogen, room air, and a gas mixture containing

4% CO_2 and 16% O_2. For each measurement, the fractional concentrations of O_2 and CO_2 (FEO_2 and $FECO_2$), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation (VE), and the ventilatory equivalent for O_2 ($VE/\dot{V}O_2$) were obtained.

Submaximum aerobic fitness was determined from the test data by estimation of the ventilatory breakpoint. The ventilatory breakpoint is the highest work rate or $\dot{V}O_2$ before VE increases out of proportion to $\dot{V}O_2$ (30) and provides another index of cardiorespiratory fitness.

Thermogenesis Tests

The subjects refrained from any vigorous physical activity for 3 days before each trial. On at least two occasions before the thermogenesis tests, the subjects visited the laboratory to become familiarized with all procedures and to become accustomed to the measurement of metabolic rate. For the thermogenesis tests the subjects reported to the laboratory at 9:00 A.M. in the postabsorptive state after a 12-h fast on 2 nonconsecutive days, to avoid any carryover effects between treatments. The laboratory was maintained at 24°C throughout the study. Base-line postabsorptive metabolic rate was measured on each day, after a 30-min rest period. Three 5-min measurements were made within a 30-min period (at 5–10, 15–20, and 25–30 min) to avoid discomfort from continuous use of the mouthpiece. The three measures were averaged, and the coefficient of variation across the three measurements was <2%. We have recently demonstrated that, in healthy subjects, similar results are obtained when metabolic rate is measured continuously with use of a ventilated hood, or intermittently with use of a mouthpiece and noseclips, or a breathing mask (23).

The order of the two experimental treatments was randomized independently for each man. On one day, postabsorptive RMR was measured for the last 6 min of every half hour for 3 h while the subjects sat quietly. The gas analyzers were recalibrated (see above) every half hour to correct for drift in the analyzers. The men were allowed to read or listen to music throughout the measurement period. On the other test day, postprandial RMR was measured for the last 6 min of every half hour for 3 h after the subjects consumed a 720-kcal liquid mixed meal (Sustacal, Mead Johnson Nutrition Division, Evansville, IN), which contained 43.5 g protein, 16.5 g fat, and 99.3 g carbohydrate. The test meal was consumed within 5 min.

For each metabolic measurement the respiratory quotient ($RQ = \dot{V}CO_2/\dot{V}O_2$) was calculated, and results were converted to kilocalories by use of the Weir equation (31): $kcal = [(1.1 \times RQ) + 3.9] \times \dot{V}O_2$.

Analysis of Data

The same statistical analyses were applied to the data from *studys 1* and 2. The thermic effect of food was compared in the two groups by applying a $2 \times 2 \times 6$ four-way analysis of variance with repeated measures (33) to the RMR from 0 to 180 min on the 2 days using group (*group A* or *B* for *study 1*; *group C* or *D* for *study 2*), food (meal or no meal trials), and time as the factors. Metabolic rate was expressed both as $\dot{V}O_2$ and as caloric expenditure. Significant F ratios from the analyses of variance were followed by post hoc comparisons using the appropriate error terms from the analyses of variance (33).

A one-way analysis of variance was applied to the calculated thermic effect of food, which was derived by subtracting the 3-h energy expenditure during the postabsorptive trial from the postprandial trial.

An analysis of variance with repeated measures was applied to the base-line RMR values obtained on the 2 days to determine whether there was significant day-to-day variation in fasting RMR. The reliability of repeated base-line RMR measurements was tested by the intraclass correlation method (33).

Analysis of covariance was applied to compare the fasting RMR data among the groups, using FFM as the covariate. It is well known that FFM is the major determinant of RMR (4, 22). Because the subjects in each group for each of the studies were selected in such a way that would require them to differ significantly with respect to FFM, a simple comparison of RMR expressed in absolute form (kcal/min) is biased. Frequently, differences in FFM among subjects or between groups are handled by expressing RMR per kilogram of FFM, i.e., by dividing RMR by FFM (16). However, use of such ratios (RMR/FFM) is only truly appropriate when the correlation between RMR and FFM is perfect ($r = 1.0$) and when the mathematical equation relating the two parameters is one in which RMR is in constant proportion to FFM with an intercept equal to zero (16, 29). Another more accurate approach to the assessment of RMR is to derive adjusted RMR values according to the specific relationship between RMR and FFM. This is accomplished by analysis of covariance (19). This analysis was also applied to the thermic effect of food data, to determine whether differences between groups were significant after adjustment for differences in FFM.

Comparisons of maximal and submaximal aerobic fitness, RMR, and the results of the OGTT in the two groups were made by applying one-way analyses of variance to each of these variables. Additional analyses are described in the RESULTS section. For all statistical analyses, the 0.05 level of significance was used.

RESULTS

Study 1

As shown in Table 1, body fat mass was similar for the two groups. However, the lean men (*group A*) had significantly more FFM and total weight than the obese men (*group B*). Aerobic fitness, determined by a graded cycle ergometer exercise test, was significantly lower for *group B* expressed in absolute form but expressed as a maximum power output or as milliliter per kilogram per minute; $\dot{V}O_{2\,max}$ was not significantly different for the two groups. Fasting plasma glucose was not significantly different between the two groups, but fasting plasma insulin and the area under the insulin curves was significantly lower for *group A* than *B*. Plasma insulin levels were strongly correlated with percent body fat ($r = 0.867$).

TABLE 1. *Characteristics of lean (group A) and obese (group B) men matched on body fat mass*

	Group A	Group B	P
Age	27.0±2.4	25.8±1.9	NS
Height, cm	181.7±3.3	167.7±2.4	<0.01
Weight, kg	84.3±7.4	58.0±2.3	<0.01
Percent fat	15.4±0.6	25.8±0.9	<0.001
FFM, kg	71.3±6.6	43.6±2.3	<0.01
Fat mass, kg	13.0±0.9	14.4±0.8	NS
Maximum aerobic fitness			
$\dot{V}O_{2\,max}$			
ml/min	3,118±198	2,199±164	<0.05
$ml \cdot kg^{-1} \cdot min^{-1}$	37.6±2.6	37.9±3.3	NS
Work load, W	215±12	201±11	NS
Ventilatory breakpoint			
$\dot{V}O_2$, ml/min	1,510±75	1,401±61	NS
Work load, W	99±11	92±14	NS
Fasting insulin, μU/ml*	11.8±1.3	21.4±1.4	<0.01
Fasting glucose, mg/dl*	86.2±2.5	91.6±4.1	NS
Insulin area, μU/ml†	221±46	383±47	<0.05
Glucose area, mg/dl†	394±31	448±20	NS
RMR, kcal/min	1.38±0.08	1.14±0.06	<0.05
Adjusted RMR, kcal/min‡	1.29±0.07	1.24±0.97	NS

Values are mean ± SE; $n = 5$ for both *group A* and *B*. See text for definition of abbreviations. * To convert insulin to picomoles per liter multiply by 7.175; to convert glucose values to millimoles per liter multiply by 0.0625. † Integrated over 2 h after a 75-g oral glucose load. ‡ Adjusted by analysis of covariance, using FFM as covariate.

The reliability of the base-line RMR measures was $r = 0.997$, and the day-to-day variation in RMR was <3%. Fasting RMR, measured over 3 h in the fasted state, was greater for the lean than the obese men, 1.38 ± 0.08 vs. 1.14 ± 0.04 kcal/min; $P < 0.05$. When adjusted for differences in FFM by analysis of covariance, RMR was not significantly different for the two groups (1.29 ± 0.07 vs. 1.24 ± 0.07 kcal/min; NS), indicating that the lower resting energy expenditure in *group B* is a function of the lower FFM of the obese group used in this model.

Figure 1 illustrates the thermic effect of food for the two groups. There was a significant group by meal interaction, indicating a difference between groups in the thermic response to the meal. The group by time and group by meal by time interaction were not significant, indicating a similar time course in the thermic response to the meal for the two groups. The same results were obtained whether the analysis was applied to the $\dot{V}O_2$ or to the caloric expenditure data. The increment in caloric expenditure over 3 h above the fasting level was 65 ± 6 kcal for *group A* compared with 23 ± 6 kcal for *group B* ($P < 0.01$). The thermic effect of food (kcal/3 h), adjusted for FFM by analysis of covariance was 66 ± 6 kcal/3 h for *group A* vs. 22 ± 6 kcal/3 h for *group B* ($P < 0.01$). The elevation in metabolic rate at the end of the 3rd h postprandially was extremely small and was not significantly different between the lean and obese groups, thus eliminating the possibility that a delayed thermic response for *group B* accounted for their smaller 3-h thermic response to the meal. The thermic effect of food was significantly correlated both with percent body fat ($r = -0.804$) and plasma insulin levels ($r = -0.859$).

Study 2

Percent body fat was similar for the two groups. However, as shown in Table 2, the lighter group (*group C*) had significantly less body fat mass and less FFM than the heavier group (*group D*). Thus, whereas the body composition was proportionally similar for the two groups, the absolute weights of each of the compartments differed significantly between groups. $\dot{V}O_{2\,max}$ was similar for the two groups expressed as milliliter per kilogram per minute but greater for *group D* when expressed in absolute form. The reliability of the base-line RMR values on the 2 test days was $r = 0.994$ and the day-to-day variation in base-line RMR was <3%. Fasting RMR was lower for *group C* than *D* (1.17 ± 0.06 vs. 1.33 ± 0.04 kcal/min, $P < 0.05$) but not significantly different when adjusted for differences in FFM (1.22 ± 0.05 vs. 1.26 ± 0.05 kcal/min; NS). Fasting plasma insulin and glucose and the areas under the glucose and insulin curves were not significantly different for the two groups (see Table 2). This suggests that the insulin resistance associated with obesity is more strongly related to proportional degree of obesity than to an elevated fat mass per se.

The analysis of variance of the $\dot{V}O_2$ and energy expended over 3 h under the fasting and fed conditions yielded no significant interaction effects for group. This indicates that the effect of the meal on energy expendi-

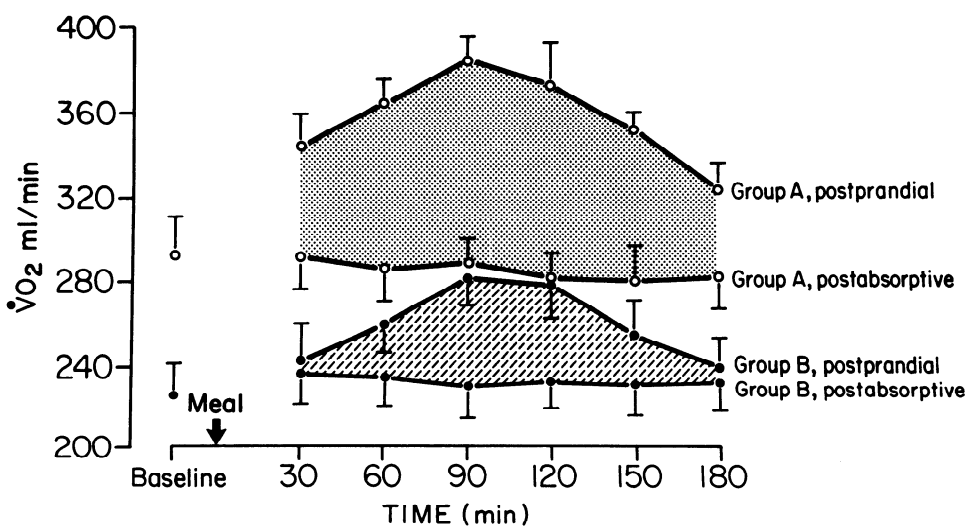

FIG. 1. Resting metabolic rates of lean (*group A*) and obese men (*group B*) over 3 h in postabsorptive state and after a 720-kcal mixed meal. Shaded areas, thermic effect of meal for each group. Values are means ± SE.

TABLE 2. *Characteristics of lighter (group C) and heavier (group D) obese men matched for percent body fat*

	Group C	Group D	P
Age	24.8±1.4	28.5±1.6	NS
Height, cm	173.2±3.6	179.4±1.9	NS
Weight, kg	75.1±4.0	101.7±3.9	<0.001
Percent fat	32.5±1.0	33.1±0.07	NS
FFM, kg	50.8±3.1	68.0±2.8	<0.01
Body fat mass, kg	24.3±1.2	33.7±1.3	<0.01
Maximum aerobic fitness			
$\dot{V}O_{2\,max}$			
ml/min	2,165±232	2,955±213	<0.05
ml·kg·min	28.8±1.7	29.1±2.1	NS
Work load, W	184±9	203±21	NS
Ventilatory breakpoint			
$\dot{V}O_2$, ml/min	1,181±140	1,560±125	NS
Work load, W	83±6	84±13	NS
Fasting insulin, μU/ml*	16.7±1.5	26.9±5.5	NS
Fasting glucose, mg/dl*	80.8±1.8	92.3±5.8	NS
Insulin area, μU/ml†	485.2±69.9	520.2±57.9	NS
Glucose area, mg/dl†	475.1±26.1	476.3±47.5	NS
RMR, kcal/min	1.17±0.06	1.33±0.04	<0.05
Adjusted RMR, kcal/min‡	1.22±0.05	1.26±0.05	NS

Values are mean ± SE. See text for definition of abbreviations. * To convert insulin to picomoles per liter multiply by 7.175; to convert glucose values to millimoles per liter multiply by 0.0625. † Integrated over 2 h after a 75-g oral glucose load. ‡ Adjusted by analysis of covariance, using FFM as covariate.

ture was not significantly different between these two groups of obese subjects (see Fig. 2). Expressed as the increase in caloric expenditure over 3 h due to ingestion of the meal, the thermic effect of food was 31 ± 3 and 20 ± 6 kcal/3 h for *groups C* and *D*, respectively (NS). The statistical power to detect a difference of this magnitude, given the sample size, was calculated to be 0.84. The thermic effect of food, adjusted for FFM by analysis of covariance, was 30 ± 3 and 21 ± 3 kcal/3 h for *groups C* and *D* (NS). Thus, when body composition is held constant, proportionally, the thermic effect of food does not differ significantly in groups who differ with respect to fat mass, lean mass, and total body weight.

DISCUSSION

The role of blunted energy expenditure in obesity has been questioned because, despite smaller increases in metabolic rate in response to thermogenic stimuli, obese people generally have higher total absolute energy expenditure than lean people, owing to their elevated FFM (8, 13). In the present study we made use of two unique models in which *1*) the factor of body fat mass was held constant by matching lean and obese groups with respect to their absolute fat mass, and *2*) the factor of degree of obesity was held constant, whereas the absolute fat, lean, and total body weights were extremely different between groups by matching larger and smaller groups of obese men with respect to percent body fat. In a previous study (26) we demonstrated that body weight itself was not a determinant of postprandial thermogenesis. In another investigation we demonstrated that FFM itself was not a determinant of thermogenesis (24) because, when lean and obese groups were matched with respect to FFM, postprandial thermogenesis was significantly blunted in the obese compared with the lean group, despite the fact that fasting RMR was similar for the two groups. In the present study, the thermic effect of a 720-kcal mixed liquid meal was significantly smaller for the obese than the lean men who were matched with regard to their absolute body fat weight. This finding indicates convincingly that impaired thermogenesis is specifically related to the obese state itself. Thus, when lean and obese men are matched with respect to their fat mass, obesity is associated with a diminished capacity for thermogenesis but not a reduced resting energy expenditure.

After adjustment was made, by analysis of covariance, for the marked differences among groups in FFM, no significant differences in RMR were observed among any of the groups. As Owen et al. (18) have shown, weight, body surface area, FFM, and fat mass are usually highly intercorrelated, and each of these parameters correlates with RMR. In the present investigation, the generally observed intercorrelations among body composition parameters were uncoupled, and FFM correlated statistically better with RMR ($r = 0.752$) than any of the other parameters, alone or in combination. Neither body fat mass, percent fat, nor total body weight increased the amount of explained variance in RMR after FFM entered into the prediction of RMR. This supports the finding

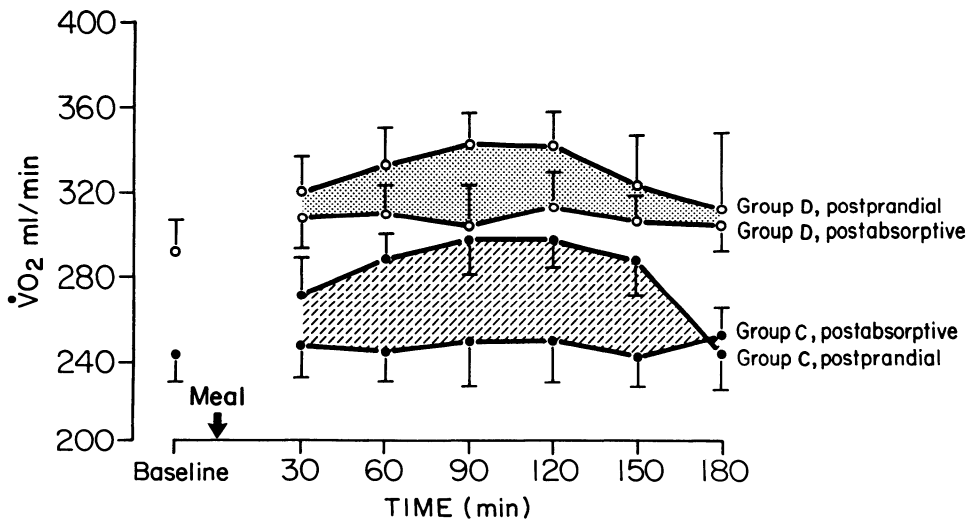

FIG. 2. Resting metabolic rates of lighter (*group C*) and heavier (*group D*) obese men, matched for percent body fat but differing with respect to lean and fat weights, over 3 h in postabsorptive state and after a 720-kcal mixed meal. Shaded areas, thermic effect of meal for each group. Values are means ± SE.

of Ravussin et al. (22) that after adjustment for differences in FFM, 24-h energy expenditure was uncorrelated with other body composition parameters. It is important to note that the experimental models used in the present study were employed to identify further the independent contributions of individual body composition parameters on energy metabolism and probably do not reflect the usual body weight and composition of obese and lean people. For example, the obese men in *study 1* (*group B*) were obese despite the fact that they were not overweight for height. These men were recruited to meet the body fat mass requirement for matching to the lean men on this parameter, but their body habitus may be unrepresentative of most obese men.

The adjustment of the thermic effect of food values for FFM had very little impact because under the conditions of these two experiments, the thermic effect of food was only minimally correlated to FFM ($r = 0.261$, NS). On the other hand, in the combined samples, the thermic effect of food was most strongly related to percent body fat ($r = -0.712$, $P < 0.01$). This supports our previous finding that the thermic effect of food is significantly lower in obese men who were matched to lean men with respect to FFM.

Recent studies have suggested that blunted thermogenesis is related to insulin resistance and impaired glucose tolerance (9, 20, 21), which are frequent complications of obesity (6). In the present study, all subjects had normal glucose tolerance, according to the criteria of the National Diabetes Control Group (17). However, the obese men in *study 1* were hyperinsulinemic compared with the lean men, and plasma insulin was correlated with percent body fat. The thermic effect of food was also significantly correlated with both percent body fat ($r = -0.804$) and plasma insulin levels ($r = -0.859$). Ravussin et al. (21) demonstrated that the blunted thermic effect of infused glucose in obese subjects during the euglycemic insulin clamp was related to reduced rates of glucose disposal and glucose storage. When the rate of glucose uptake was held constant and the rate of insulin infusion varied to achieve the same rate of glucose uptake, the thermic effect of glucose was similar for lean and obese subjects (20).

Under the conditions of *study 2* in which all of the subjects were obese and the usual correlation between percent body fat and body fat mass was uncoupled, fat mass was not significantly related to the thermic effect of food or to insulin and glucose levels, either fasting levels or the integrated response areas after an oral glucose load. The results of *study 1* and *2* suggest that degree of obesity (percent body fat) is a determinant of the thermic effect of food. However, these experimental models do not indicate whether blunted thermogenesis in the obese is specifically a function of degree of obesity per se or of the insulin resistance, which is colinear with degree of obesity. Bogardus et al. (3) demonstrated that between 10 and 28% body fat there was a strong negative correlation between degree of adiposity and insulin sensitivity, determined by the euglycemic, hyperinsulinemic clamp. However, above this threshold of 28% body fat, there was no correlation between degree of obesity and in vivo insulin action (3). If thermogenesis is related to insulin-mediated glucose disposal, as several studies have suggested, then the results of the present study are consistent with those of Bogardus et al. The present study was designed to compare groups of subjects who differed distinctly with respect to masses or proportions of various body composition compartments and thus did not examine the relationship between obesity and thermogenesis throughout the entire continuum from leanness to obesity. In the first experiment, distinctly lean men were compared with clearly obese men even though the two groups of subjects were matched with regard to their absolute body fat mass. In the second experiment, the two groups of subjects varied significantly with regard to lean mass and fat mass, but proportionally, the two groups had the same body composition. By this novel experimental approach we have been able to demonstrate that body fat mass per se is not independently related to thermogenesis. The determinant of the defect in the thermic response to a meal is the relative degree of adiposity. Similarly, fasting plasma insulin levels and the magnitude of the insulin response to an oral glucose load are not related to body fat mass in itself but are elevated in the obese state regardless of absolute body fat mass.

When lean and obese men are matched with respect to their fat mass, obesity is associated with a diminished capacity for thermogenesis. However, thermogenesis is not significantly different between obese groups that are matched on degree of obesity (percent body fat) but differ in absolute fat mass. Therefore, it is the obese state itself rather than the specific amount of body fat itself that is associated with blunted thermogenesis. Further investigation is needed to determine whether impaired thermogenesis precedes or follows the onset of obesity, which would require longitudinal studies of obesity in evolution.

In conclusion, the results of this study, taken together with our other investigations, demonstrate that the putative impaired thermogenesis in obesity is specifically a function of relative fatness (percent body fat) and not of fat mass per se, nor FFM, nor total body weight.

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Address for reprint requests: K. R. Segal, Box 1201, Division of Pediatric Cardiology, Mount Sinai School of Medicine, 1 Gustave Levy Place, New York, NY 10029.

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